CONFIDENTIAL

Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
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1330 Rixensart, Belgium

1. PASS INFORMATION

Title:	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01$_E$ vaccine in young children in sub-Saharan Africa.
Protocol version identifier:	115056 (EPI-MALARIA-003 VS AME)
Date of last version of the protocol:	Amendment 2 Final: 15 October 2020
EU PAS Register No:	EUPAS28541
Active substance:	RTS,S antigen and AS01$_E$ adjuvant
Medicinal product(s):	Mosquirix™
Product reference:	EMEA/H/W/002300
Procedure number:	Not Allocated
Opinion Holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives: **(Amended 15 October 2020)**	Co-primary objectives: • To estimate the incidence of adverse events of special interest (AESI) in children vaccinated with RTS,S/AS01$_E$. • To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$. Objectives related to malaria are considered as secondary objectives.
Countries of study:	Sites in sub-Saharan African (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system.

	In October 2015, the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended the pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme, referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GlaxoSmithKline (GSK) Phase IV studies have been selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 should become study sites in study EPI-MAL-003 which will be exposed clusters.
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2. OPINION HOLDER

Opinion holder:	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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List of Abbreviations

ADEM	Acute Disseminated Encephalo-Myelitis
AE	Adverse Event
AESI	Adverse Event Of Special Interest
AIC	Akaike's Information Criterion
AMP	Agence de Médecine Préventive
AS01	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome
ATP	According-To-Protocol
BOD	Burden Of Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLS	Clinical Laboratory Services
CRP	C-Reactive Protein
CS	Circumsporozoite
CSF	Cerebrospinal fluid
DTP	Diphtheria, Tetanus, Pertussis
DTPa	Diphtheria, Tetanus, Pertussis (acellular) vaccine
DTPw	Diphtheria, Tetanus, Pertussis (whole cell) vaccine
DTPwHepB/Hib	Diphtheria-tetanus- pertussis (whole cell)-hepatitis B-Haemophilus influenza type b pentavalent vaccine
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPI	Expanded Programme on Immunisation
ESR	Erythrocyte Sedimentation Rate

EU PAS	European Union Post-Authorisation Studies
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface Antigen
HDSS	Health and Demographic Surveillance System
HHE	Hypotonic Hyporesponsive Episode
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
MPL	3-O-desacyl-4'- monophosphoryl lipid A (produced by GSK)
MTI	Malaria Transmission Intensity
MVIP	Malaria Vaccine Implementation Programme
NRA	National Regulatory Authority
OPV	Oral Poliovirus Vaccine
P. falciparum	*Plasmodium falciparum*
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction

PCV	Pneumococcal Conjugate Vaccine
pIMD	Potential immune-mediated disorder
PT	Preferred Term
PY	Person-Years
QS-21	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc, a Delaware, USA corporation)
RAFT	Réseau en Afrique Francophone pour la Télémédecine
RDT	Rapid Diagnostic Test
RMP	Risk Management Plan
RR	Relative Risk
RTS	Hybrid protein comprising HBs (hepatitis B surface antibody) and CS protein portions
RTS,S	Particulate antigen, containing both RTS and HBs antigen (S) proteins
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAP	Statistical Analysis Plan
SBC	Schwarz Bayesian Criterion
SCCS	Self-Controlled Case-Series
SDV	Source Document Verification
SOC	System Organ Class
SPM	Study Procedures Manual
SPRT	Sequential Probability Ratio Tests
SSA	Sub-Saharan Africa
VS	Vaccine Safety
WHO	World Health Organization

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

PPD ***(PhD; Epidemiology Lead – Malaria)*** and PPD (MD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.

(Amended 15 October 2020)

4. ABSTRACT

Title	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01$_E$ vaccine in young children in sub-Saharan Africa. 115056 (EPI-MALARIA-003 VS AME), Amendment 2 Final: 15 October 2020
Main authors	PPD (Senior Epidemiology Lead - Malaria) and PPD PPD (Epidemiology Lead - Malaria)
Rationale and background **(Amended 15 October 2020)**	GlaxoSmithKline (GSK) Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01$_E$, for routine immunisation of children living in malaria-endemic countries of sub-Saharan Africa (SSA). RTS,S/AS01$_E$ is the first vaccine to be implemented for the prevention of malaria and it is the first AS01-adjuvanted vaccine to be implemented in the paediatric population. The vaccine antigen, RTS,S, consists of sequences of the *P. falciparum* circumsporozoite (CS) protein and hepatitis B surface antigen (HBsAg). The antigen is adjuvanted with the AS01$_E$ Adjuvant System, which consists of two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (Quillaja saponaria Molina, fraction 21), in a liposomes suspension. The World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended pilot implementations of RTS,S/AS01$_E$ in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5–9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through a WHO-coordinated pilot implementation programme**,** referred to as the Malaria Vaccine Implementation Programme (MVIP) in the remaining sections of this document. In order to align with the MVIP, the study sites for the GSK Phase IV studies have been selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 are exposed clusters in EPI-MAL-003. The first vaccine introduction ***started in April*** 2019 ***in Malawi and Ghana***. The RTS,S/AS01$_E$ vaccine contains new components, including a novel adjuvant that is not present in currently licensed vaccines. If recommended for use, it would be launched solely in malaria-endemic countries in SSA.

The safety and efficacy of RTS,S/AS01$_E$ have been evaluated during pre-authorisation clinical trials conducted mainly in SSA. Study EPI-MALARIA-003 VS AME (115056) (referred to as EPI-MAL-003 in the remainder of the protocol) will further evaluate the safety, effectiveness and impact of the vaccine during initial implementation.

A pre-implementation (i.e. before vaccine implementation) surveillance study, EPI-MALARIA-002 VS AME (115055) (referred to as EPI-MAL-002 in the remainder of the protocol), will measure the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated.

EPI-MAL-003 is intended primarily as a post-implementation safety study, as reflected in the co-primary and secondary objectives. Additionally, vaccine effectiveness and impact estimations are included as secondary objectives.

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MALARIA-005 BOD AME [116682], referred to as EPI-MAL-005 in the remainder of the protocol) is conducted to measure malaria transmission intensity and other malaria control interventions as confounding factors in the study site areas.

The three studies ***are*** conducted in similar if not identical settings and with the same methodology for identification and characterisation of the events of interest. A strong capacity development component is included in the baseline study EPI-MAL-002.

Research question and objectives

(Amended 15 October 2020)

Co-primary objectives

- To estimate the incidence of AESI[1] in children vaccinated with RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$.

[1] Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, Hypotonic Hyporesponsive Episode (HHE), generalised convulsive seizure
Intussusception, hepatic failure or renal insufficiency
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

Secondary objectives

Safety

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01$_E$ or not vaccinated with RTS,S/AS01$_E$):

- To estimate the incidence of aetiology-confirmed and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.
- ***To estimate the incidence of other AEs leading to hospitalisation.***
- To describe risk factors for AESI, meningitis, and malaria.
- To describe the causes of hospitalisation (including AESI, meningitis and malaria).
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following each dose of RTS,S/AS01$_E$.

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01$_E$ or not vaccinated with RTS,S/AS01$_E$):

- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.

- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and AESI, by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- ***To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.***

Effectiveness and impact

- To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01$_E$ on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria diagnosed by RDT and/or microscopy.
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01$_E$ on:
  - the prevalence of anaemia among hospitalised children.
  - the incidence of hospitalisations attributed to malaria (including *P. falciparum*).
  - the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]) overall and by gender.

Study design

(Amended 15 October 2020)

- A disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002) and concurrent (cluster design

comparison of exposed and unexposed clusters)[2] comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01$_E$ vaccination for those living in the exposed clusters.

- The design will include active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities) and enhanced hospitalisation surveillance (continuous monitoring of hospitalisations) in both exposed and unexposed clusters.
- The study targets enrolling at least 45,000 children in active surveillance, including 22,500 in exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants will receive three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.
- The diseases under surveillance for safety include AESI, other AE leading to hospitalisation meningitis, and severe malaria including cerebral malaria. They will be monitored among the vaccinated and unvaccinated children, enrolled in active surveillance and in enhanced hospitalisation surveillance. The mortality rate, overall and by gender, will be estimated. The potential association, overall and by gender, between vaccination and death will also be assessed. The effectiveness (direct effect) of the RTS,S/AS01$_E$ vaccine will be investigated by monitoring all malaria (including severe and cerebral malaria) related events in the vaccinated and unvaccinated children of the exposed clusters, enrolled in active surveillance. The impact (indirect, total and overall effect) of the vaccine will be investigated, in the active surveillance, firstly by comparing the incidence of all malaria (including severe and cerebral malaria) events in EPI-MAL-002 to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the

[2] **Exposed clusters :** Study sites where the RTS,S/AS01$_E$ vaccine will be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.

Unexposed clusters: Study sites where the RTS,S/AS01$_E$ vaccine will not be implemented ***at the beginning of*** the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI. **(Amended 15 October 2020)**

exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect). Secondly, the impact will also be investigated in the active surveillance, by comparing the incidence of all malaria (including severe and cerebral malaria) events in children of the unexposed clusters in EPI-MAL-003 to the incidence of all malaria (including severe and cerebral malaria) events in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect).

- The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months. Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01$_E$ (or equal point in time for unvaccinated children).

Population, including the setting and study population

The study population is defined as study participants < 5 years of age living in a geographically limited area with a demographic surveillance system in place, and a well--developed infrastructure to monitor population health and vaccination programmes. All EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005 studies sites have been identified.

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria have enrolled for EPI-MAL-002 (Ghana [Kintampo and Navrongo], Kenya [Kombewa], and Burkina Faso [Sapone, Nouna]).

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. In order to align with the MVIP, the study sites for the GSK Phase IV studies have been selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented. Sites from Ghana and Kenya that were part of study EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.

Variables

(Amended 15 October 2020)

Co-primary endpoints

In children in active or enhanced hospitalisation surveillance:

- Occurrence of AESI.
- Occurrence of aetiology-confirmed meningitis.

Secondary endpoints

Safety endpoints

In children in active or enhanced hospitalisation surveillance:

- Occurrence of probable meningitis (final classification).
- Occurrence of clinically suspected meningitis (final classification).
- Occurrence of meningitis cases identified at site level (first line laboratory).
- Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- Occurrence of hospitalisation (including those attributed to an AESI, meningitis or malaria), or death.
- ***Occurrence of other AE leading to hospitalisation***
- Occurrence of febrile convulsions during the 7-day period (Days 0-6) and 1-month period (Days 0-29) following each dose of RTS,S/AS01$_E$.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation.

Effectiveness and impact endpoints

In children in active surveillance:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
  - Any malaria (including *P. falciparum* malaria);
  - Severe malaria (including *P. falciparum* malaria);
  - Cerebral malaria.
- Occurrence of anaemia at hospital entry among hospitalised children.

- Occurrence of hospitalisation
  - All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.
- Occurrence of death
  - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death).
  - AE attributed deaths

Data sources

HDSS (or equivalent surveillance system)

- Listings of all children living in the study area based on the demographic census;
- Total number of children < 5 years of age (according to year and gender) recorded at the beginning of the study, at least once a year during the study duration and at the end of the study;
- Other demographic data (cause and date of deaths, migrations), if available;
- Information related to vaccination, if available.

Active surveillance (enrolment)

- Socio-demographic data;
- Active participation in any trial with an investigational product.

Active surveillance (home visits)

- Vaccination types and dates;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;
- Verbal autopsy report.

Active surveillance (outpatient visits and hospitalisations at all health care facilities)

- Data on visits at primary health care facilities and hospitals since enrolment or last home visit.

Enhanced hospitalisation surveillance (hospitalisations)

- Socio-demographic data;
- Active participation in any trial with an investigational product;
- Health history;
- Malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards;
- Type of health care facility;
- Final diagnosis for the hospitalisation visit on discharge for all children;
- Data relevant to the diagnosis of AESI, other AE leading to hospitalisation, meningitis and malaria (including cerebral malaria);
- Vaccination types and dates;
- Autopsy report.

Study conclusion (home visit)

- Vital status;
- Verbal autopsy report;
- Vaccination types and dates;
- Health history since last visit.

Baseline study EPI-MAL-002

- Baseline incidence rates of AESI, other AE leading to hospitalisation, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality.

Malaria Transmission Intensity Study EPI-MAL-005

- Estimation of annual parasite prevalence;
- Changes in diagnostic practices;
- Malaria control and prevention measures at the community and individual level.

Study size

(Amended 15 October 2020)

- The study targets enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children are estimated to be enrolled in active surveillance, assuming that the distribution according to the administration of RTS,S/AS01$_E$ in the exposed clusters will be 10% without any dose (2,250 unvaccinated children), 10% with an incomplete primary schedule (i.e. 1 or 2 doses; 2,250 partially vaccinated children), 80% with the full primary schedule (i.e. 3 doses; 18,000 vaccinated children).
- For some of the AESI, the incidence could be very rare (around 1/100,000 person-years [PY]) and the period at risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis. The 95% confidence interval (CI) around the observed incidence of 15.5 per 100,000 PY (1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], with 50% of the study participants receiving the 4th dose, based on 20,250 study participants) will be [0.4, 86.1].
- With the before-after design, assuming 10 as the cumulative number of meningitis cases in EPI-MAL-002, based on cohort size and period of follow-up of 1 year following dose 3, a true relative risk (RR) = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters in a follow-up time corresponding to an observed RR equal to 3.
- With the before-after design, and depending on the follow-up, the total effect for severe malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, ranges from ***16***% to ***23***%, and the direct effect, from 23% to 33%.
- With the before-after design, and depending on the follow-up, the total effect for cerebral malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, expressed as RR ranges from ***1.51*** to ***1.82***, and the direct effect, from ***1.55*** to ***1.88***.

Data analysis

(Amended 15 October 2020)

Analysis of the co-primary objectives:

- The incidence rate of each AESI will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable.
- The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first RTS,S/AS01$_E$ vaccination for the vaccinated study participants and virtual vaccination corresponding to the week before first visit for the unvaccinated study participants) and the end of the at-risk period or the earliest of the followings:
  - Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis);
  - Date of end of study period;
  - Date when child reaches 5 years;
  - Date of last contact (lost-to follow-up, defined as two unsuccessful attempts to visit the child at home within the month of the scheduled visit);
  - Date of death.
- Each AESI will be grouped after case ascertainment (for both confirmed and non-confirmed cases).
- The incidence rate of aetiology-confirmed meningitis and of cerebral malaria will be computed with 95% CI using the same approach as described above.

For the analysis of the secondary objectives, all comparisons will be performed separately for each of the two designs (i.e. before-after design and cluster design). As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters; and the cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters.

Milestones

The milestones will be adapted based on the timing of vaccine introduction in the intended study sites in the target SSA countries.

Progress reports will be generated every 6 months. An interim epoch analysis is planned to be performed one year after the 3rd dose of RTS,S/AS01$_E$ in the last study participant from exposed clusters.

5. AMENDMENTS AND UPDATES

Amendment 1 Final: 24 April 2019.

Amendment 2 Final: 15 October 2020

The rationales for protocol amendment 1 & ***protocol amendment 2, are*** provided in Annex 7.

(Amended 15 October 2020)

6. MILESTONES

The target population for the introduction of the RTS,S/AS01$_E$ vaccine are children living in sub-Saharan Africa (SSA). The age group in which the vaccine will be administered is 5 to 17 months of age.

The milestones below will be adapted based on the timing of vaccine introduction in the intended study sites in the target SSA countries and the selected immunisation schedule (3-doses primary with a 4th dose). The World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) recommended pilot implementations of RTS,S/AS01$_E$ in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose [WHO, 2015(a)]. In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through the MVIP. This programme initially planned to make the RTS,S/AS01$_E$ vaccine available in selected areas, starting in 2018 [WHO, 2017], ***but the RTS,S/AS01$_E$ vaccine was implemented in selected areas/clusters of 3 SSA countries in 2019***.

The study targets enrolling at least 45,000 children in active surveillance, including 22,500 in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact assuming that 80% of the 22,500 study participants will receive three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose), and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact (see Annex 2 for definitions of exposed and unexposed clusters). The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. In the participating sites, the vaccine coverage is not expected to be low. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children in the exposed clusters is reached. The length of recruitment in active surveillance is assumed to be approximately 18 months from first study participant first visit to last study participant first visit at each site.

The protocol might be adapted according to feedback from the European Medicines Agency (EMA) and the National Regulatory Authorities (NRAs), and the Institutional Review Boards (IRBs) in the countries of the study; the WHO recommendations will also be taken under consideration.

The milestones for dates in the future in the following table are therefore tentative.

Milestone	Planned date
Draft 1 protocol submitted to EMA as part of an EU "Article 58 procedure"	June 2014
Draft 2 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the consolidated list of questions	March 2015
Draft 3 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the list of outstanding issues	June 2015
Draft 4 protocol submitted to EMA as part of an EU "Article 58 procedure" to answer the list of outstanding issues	July 2015
Draft 5 protocol prepared with updates to enable synergy with WHO Pilot Implementation, and submitted as part of a Type II variation	February 2017
Draft 6 protocol prepared with updates to answer the request for supplementary information, and submitted as part of a Type II variation	July 2017
Final protocol submitted to NRAs in the first country of the study, as applicable according to local regulatory guidance, either as part of the marketing authorisation applications or after granting of marketing authorisation	Q4 2017
Start of data collection	Q1 2019
End of data collection	***Q1 2025****
Study progress reports	1 progress report every 6 months
Interim epoch analysis	***Q2 2023**** and ad-hoc (if triggered by a safety signal)
Registration in the EU PAS register	***EUPAS28541***
NCT Number	***NCT03855995***
Statistical analysis completed	***Q4*** 2025*
Final report of study results	***Q1 2026****

*Tentative date; depending on recruitment timelines and implementation of vaccination by the Ministries of Health

(Amended 15 October 2020)

7. RATIONALE AND BACKGROUND

7.1. Background

GSK Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01$_E$, for routine immunisation of children living in malaria-endemic countries of SSA. RTS,S/AS01$_E$ is the first vaccine to be implemented for the prevention of malaria and it ***is*** the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

The vaccine antigen, RTS,S, consists of sequences of the *P. falciparum* circumsporozoite (CS) protein and hepatitis B surface antigen (HBsAg). The antigen is adjuvanted with the AS01$_E$ Adjuvant System, which consists of two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (Quillaja saponaria Molina, fraction 21), in a liposomes suspension.

The pre-authorisation clinical development has been conducted mainly in SSA countries. The main clinical study supporting efficacy and safety is the large Phase III study, MALARIA-055, conducted at 11 study sites in 7 countries across SSA, which enrolled 15,459 children. This clinical trial was conducted in two age categories: infants aged 6-12 weeks at first dose and children aged 5-17 months at first dose. Infants aged 6-12 weeks at first dose received RTS,S/AS01$_E$, in co-administration with other childhood vaccinations (diphtheria-tetanus-whole-cell pertussis-hepatitis B- *Haemophilus influenza* type b pentavalent vaccine [DTPwHepB/Hib] and oral poliovirus vaccine [OPV]), within the context of the Expanded Programme on Immunization (EPI). The comparator group received meningococcal C conjugate vaccine in co-administration with the same EPI vaccines. At Month 20, infants vaccinated with RTS,S/AS01$_E$ in co-administration with other childhood vaccinations received either a fourth dose of RTS,S/AS01$_E$ with OPV, or meningococcal C conjugate vaccine with OPV. Infants in the comparator group received meningococcal C conjugate vaccine with OPV. Children aged 5-17 months at first dose received RTS,S/AS01$_E$ without co-administration of other vaccines. The comparator group received human diploid-cell rabies vaccine. At Month 20, children vaccinated with RTS,S/AS01$_E$ received either a fourth dose of RTS,S/AS01$_E$ or meningococcal C conjugate vaccine. Children in the comparator group received meningococcal C conjugate vaccine at the time of the fourth dose. Children aged 5 to 17 months at first dose were followed for approximately 48 months after Dose 1 and infants aged 6 to 12 weeks at first dose for approximately 38 months after Dose 1.

In most SSA countries endemic for malaria, pharmacovigilance reporting systems are either in development phase, poorly functional or non-existent. As RTS,S/AS01$_E$ will be distributed in SSA countries, GSK Biologicals deems crucial to expand the data on vaccine safety without relying solely on a passive reporting system once the vaccination will be implemented. Therefore, GSK Biologicals has developed a Post Approval Plan comprised of a set of complementary prospective studies that will be conducted in similar if not identical settings.

The pre-implementation (i.e. before vaccine implementation) surveillance study EPI-MAL-002, will measure the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated. The events measured in EPI-MAL-002 are based on data generated from MALARIA-055 described below (see Section 7.2 and Section 7.3), or are events that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines. The EPI-MAL-002 study has started in Q4 2015. The RTS,S/AS01E vaccine ***was*** implemented in selected areas/clusters of 3 SSA countries (Ghana, Kenya and Malawi) in 2019. As the vaccine becomes available in the study sites that are exposed clusters, EPI-MAL-003 will be initiated. EPI-MAL-002 and EPI-MAL-003 ***are*** partly run concomitantly in the same study sites.

EPI-MAL-003 is intended primarily as a post-implementation safety study as reflected in the co-primary and secondary objectives. Additionally, vaccine effectiveness and impact estimations are included as secondary objectives. EPI-MAL-002 and -003 will be conducted with the same methodology for identification and characterisation of the events of interest. A strong capacity development component is included in the baseline study EPI-MAL-002.

In parallel with both EPI-MAL-002 and EPI-MAL-003, a third study (EPI-MAL-005) is conducted to measure malaria transmission intensity (MTI) and other malaria control interventions as confounding factors in the study site areas. This study began in Q4 2014, at the first malaria transmission peak season, in the West African sites with peak in the second half of the year, and will run until the completion of EPI-MAL-003.

The three studies ***are*** conducted in similar if not identical settings. Sites selection has been done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO [WHO, 2017] (refer also to Section 9.2.1), in order to ensure synergy between the latter and those three studies. The MVIP encompasses all aspects of the pilot implementation of the malaria vaccine:

1. The implementation of the RTS,S/AS01$_E$ malaria vaccine in selected areas in each of the participating countries (Ghana, Kenya and Malawi),
2. The WHO-led evaluations of feasibility, impact and safety of the malaria vaccine, as described in the Malaria Vaccine Pilot Evaluation protocol (*An evaluation of the cluster-randomised pilot implementation of RTS,S/AS01$_E$ through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa*) and the Program for Appropriate Technology in Health (PATH)-led health utilization study and economic analyses.
3. The GSK-led evaluation of the malaria vaccine consisting of the EPI-MAL-002 baseline study in the MVIP pilot countries prior to vaccine implementation and the EPI-MAL-003 Phase 4 study conducted in a sub-set of vaccination and comparator areas of the three MVIP pilot countries following vaccine implementation.

Through this programme, the malaria vaccine will be routinely delivered in sub-national areas of the pilot implementation countries by Ministries of Health (MoH) using an expanded schedule of their routine EPI contacts, building on the national immunization programmes which routinely deliver vaccines to young children living in SSA countries. According to the MVIP, the RTS,S/AS01$_E$ vaccine will be given as a four dose schedule with the first dose administered as soon after 5 months of age as possible, followed by doses two and three at approximately one month intervals, and a fourth dose 15-18 months after dose three. Vaccine implementation will be conducted based on a cluster-randomized design, in which some areas (clusters) introduce RTS,S/AS01$_E$ at the beginning of the programme and other clusters, initially without RTS,S/AS01$_E$, act as comparison areas. In terms of vaccine evaluation, GSK will monitor vaccine safety, effectiveness and impact in some of those clusters while the WHO will monitor vaccine safety, effectiveness/impact and programmatic feasibility in the remaining ones (see Malaria Vaccine Pilot Evaluation protocol sections 7.6.5, 9.1, 9.5, 10.1 and 10.10 for more details regarding number and distribution of clusters for vaccine evaluation component). The division of clusters into intervention or comparison areas will be randomized; with the exception of sites where the EPI-MAL-002 and EPI-MAL-003 are/will be running, which will be purposely selected by the MoHs according to WHO guidance. ***From*** each pilot country, about 256,000 children ***are expected to be*** included into the pilot implementation programme (about 128,000 children in the RTS,S/AS01$_E$ clusters [exposed clusters] and about 128,000 in the comparison arm [unexposed clusters]). Identical monitoring systems will be set up to record the outcomes of interest in both intervention and comparison areas.

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7.2. Safety results of the clinical development of RTS,S/AS01$_E$

In the large, pivotal Phase III study (MALARIA-055), serious adverse events (SAEs) were collected throughout the trial in all study participants regardless of causal relationship. Seizures occurring within 7 days after vaccination were collected proactively and were analysed according to Brighton Collaboration Guidelines. Potential immune-mediated disorders (pIMDs) were collected as SAEs throughout the trial. Information was collected on all unsolicited reports of AEs that occurred within 30 days after vaccination and on reactogenicity within 7 days after vaccination among the first 200 children in both age categories at each study site. This study was overseen by an Independent Data Monitoring Committee. Safety results are shown below for the intention-to-treat population.

In the 5-17 month old group at Month 20 post Dose 1, at least one SAE was reported in 1,108 children out of 5,949 vaccinated with RTS,S/AS01$_E$ (18.6%; 95% confidence interval [CI]: 17.6, 19.6) and in 676 children out of 2,974 who received the rabies vaccine (control group) (22.7%; 95% CI: 21.1, 24.3) [The RTS,S Clinical Trials Partnership, 2014]. At least one SAE related to vaccination (judged by the study investigator) was reported in 10 children (0.2%) vaccinated with RTS,S/AS01$_E$ and in one child (0.0%) receiving the rabies vaccine.

Over the same surveillance period in the 6-12 week old group, at least one SAE was reported in 959 infants among 4,358 who were vaccinated with RTS,S/AS01$_E$ (22.0%; 95% CI: 20.8, 23.3) and in 503 infants among 2,179 who received the meningococcal C conjugate vaccine (control group) (23.1%; 95% CI: 21.3, 24.9) [The RTS,S Clinical Trials Partnership, 2014]. SAEs were judged to be related to vaccination by the study investigator for 4 children (0.1%) vaccinated with RTS,S/AS01$_E$ and 3 infants (0.1%) receiving the meningococcal C conjugate (control group).

Pneumonia, gastroenteritis, malaria, anaemia and febrile convulsions were the most frequently reported SAEs in both study groups.

Up to study end, in the 5-17 month old group, at least one SAE was reported in 720 children out of 2,976 vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (24.2%; 95% CI: 22.7, 25.8), in 752 children out of 2,972 vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (25.3%; 95% CI: 23.7, 26.9) and in 846 children among 2,974 who received the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (control group) (28.4%; 95% CI: 26.8, 30.1). At least one SAE related to vaccination was reported in 8 children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, in 4 children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and in one child receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015].

In the 6-12 week old group, over the same surveillance period, at least one SAE was reported in 580 infants among 2,180 who were vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (26.6%; 95% CI: 24.8, 28.5), in 602 children among 2,178 who were vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (27.6%; 95% CI: 25.8, 29.6), and in 619 infants among 2,179 who received meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose (control group) (28.4%; 95% CI: 26.5, 30.4). At least one SAE related to vaccination was reported in 6 infants vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, in one infant vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and in 3 infants receiving the meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015].

Potential immune-mediated disorders (pIMDs)

In the 5-17 month old group and up to Month 20 post Dose 1, 3 cases of pIMDs were reported among children vaccinated with RTS,S/AS01$_E$ (2 cases of encephalitis, one case of erythema multiforme) and 2 cases among children receiving the rabies vaccine (2 cases of encephalitis). In the 6-12 week old group, 3 cases were reported among infants vaccinated with RTS,S/AS01$_E$ (encephalitis, glomerulonephritis acute, Langerhans' cell histiocytosis) and 2 cases among children receiving the meningococcal C conjugate vaccine (encephalitis, glomerulonephritis).

Post 4th dose of RTS,S/AS01$_E$/ meningococcal C conjugate vaccine, no case of pIMD was reported in the 6-12 week old group, and 6 cases were reported in the 5-17 month old group: 3 cases among children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (2 cases of encephalitis and one case of encephalomyelitis), 1 case among children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose (encephalitis), and 2 cases among children receiving the rabies vaccine followed by meningococcal C conjugate vaccine at the time of the 4th dose (vitiligo, Stevens-Johnson syndrome).

Meningitis

An imbalance was observed for meningitis in the 5-17 months category (Table 1). During the 20 months period post Dose 1, in children aged 5-17 months, 16 meningitis cases (9 no aetiology, 4 meningococcal meningitis, 1 meningitis viral, 1 meningitis pneumococcal, 1 *Haemophilus influenza* meningitis) occurred in the RTS,S/AS01$_E$ group and 1 (no aetiology) in the control vaccine group (Relative Risk [RR] = 8.0 [95% CI: 1.1, 60.3]). Among infants aged 6-12 weeks, 9 meningitis cases (3 no aetiology, 3 meningitis pneumococcal, 3 meningitis due to salmonella) occurred in the RTS,S/AS01$_E$ group and 3 (2 no aetiology, 1 meningitis pneumococcal) in the control group (RR = 1.5 [95% CI: 0.4, 5.5]) [The RTS,S Clinical Trials Partnership, 2014]. Most of the meningitis cases were observed during the 12 months period post-Dose 3 (23 out of 29 cases, 79.3%), no clear risk window was identified in study MALARIA-055. The meningitis cases were mainly observed in 2 trial sites, Lilongwe in Malawi and Kombewa in Kenya.

Table 1 Meningitis cases observed in MALARIA-055 over 20 months post first dose (MedDRA preferred terms including meningitis and meningitis with any aetiologies)

Analysis available	Follow up (post dose 3)	Age category	Number of cases in RTS,S/AS01$_E$ group (Number of RTS,S/AS01$_E$ study participants)	Number of cases in control group (Number of control study participants)	RR	95% CI
June 2014	18 months	6-12w	9 (4358)	3 (2179)	1.5	0.4-5.5
		5-17m	16 (5949)	1 (2974)	8.0	1.1-60.3

Between administration of the 4th dose of RTS,S/AS01$_E$/ meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 2 meningitis cases occurred among children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, and 3 cases among children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No case occurred in the control vaccine group (rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose). In infants aged 6-12 weeks, 2 meningitis cases occurred among infants vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 3 cases among infants receiving meningococcal C conjugate vaccine for primary vaccination and at the time of the 4th dose [The RTS,S Clinical Trials Partnership, 2015]. Therefore, meningitis was considered as a potential risk.

Febrile convulsions

Among children aged 5-17 months, the occurrence of generalised convulsive seizures with fever within 7 days following primary vaccination in RTS,S/AS01$_E$ recipients was 1.04 case/1000 doses compared to recipients of control vaccine (0.57 case/1000 doses). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 0.16 case/1000 doses of RTS,S/AS01$_E$ vaccine versus 0.47 case/1000 doses of control vaccine. Although the increase in febrile convulsions was observed within 7 days of vaccination in children, the overall rate of febrile convulsions reported as a SAE was not increased in the RTS,S/AS01$_E$ group compared to the control group over 30 days post vaccination (0.8% in RTS,S/AS01$_E$ versus 0.8% in control) and over 18 months of follow-up (3.8% in RTS,S/AS01$_E$ versus 3.8% in controls) [The RTS,S Clinical Trials Partnership, 2011]. The incidence of febrile convulsions after administration of the 4th dose of RTS,S/AS01$_E$/ meningococcal C conjugate vaccine was 2.5 cases/1000 doses in children aged 5-17 months, vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, 1.2 case/1000 doses in children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 0.4 case/1000 doses in the control vaccine group (rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose). Among infants aged 6-12 weeks, the incidence of febrile convulsions was 2.2 cases/1000 doses in infants vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$, no case/1000 doses in infants vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose and 0.5 case/1000 doses in the control vaccine group [The RTS,S Clinical Trials Partnership, 2015]. Therefore, febrile convulsions were considered as an identified risk.

Severe malaria including cerebral malaria

In the MALARIA-055 study there was a higher susceptibility to severe malaria in 5-17 months child recipients of a primary course of RTS,S/AS01$_E$ without a 4th dose (R3C) relative to the control group (C3C) after Month 20. This finding was considered to be related to a potential rebound effect and has been included in the Risk Management Plan (RMP) as a potential risk. In order to further investigate this finding, an additional analysis was conducted in MALARIA-055 to examine clinical syndromes and outcomes of cases of severe malaria.

The cases of severe malaria disease according to the secondary case definition 1 (*P. falciparum* > 5000 parasites per µL AND with one or more marker(s) of disease severity including co-morbidities: pneumonia, meningitis, sepsis, gastroenteritis) were classified by syndrome using the markers of severe malaria disease. GSK Biologicals has considered the definition for cerebral malaria cases as: parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL. It should be noted that whereas this is a commonly used definition, low coma score can be the outcome of many diseases processes and is not pathognomic of sequestration of parasitized red cells in the cerebral microvasculature.

In a post-hoc analysis of the Phase III study MALARIA-055, the distribution of the markers of severity used in the case definition of severe malaria were analysed by study group. Of the 1038 severe malaria cases according to the secondary case definition 1, 73 cases met the definition of cerebral malaria (parasitaemia > 5000 per µL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL) in both age categories over the entire study period. An imbalance was observed for cerebral malaria in the 5-17 month category (Table 2).

Table 2 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; from MALARIA-055 study)

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
	Missing	1	0	0	0	1	0

R3C group: 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 at study Month 20
R3R group: children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a 4th dose of RTS,S/AS01$_E$ at study Month 20
C3C group: 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. ***Note that it is only for the 5-17 months age category***
SE = Study end (Month 48)
All cases: Secondary case definition 1 (> 5000 parasites/µL and at least 1 marker of severe disease, including comorbidities)
Cerebral: > 5000 parasites/µL and BCS ≤ 2 and a haemoglobin level of ≥ 5 g/dL
Anaemia: > 5000 parasites/µL and BCS > 2 and a haemoglobin level of < 5 g/dL
Cerebral+Anaemia: > 5000 parasites/µL and BCS ≤ 2 and a haemoglobin level of < 5 g/dL
Other severe disease: >5000 parasites/µL, a BCS >2, a haemoglobin level of ≥ 5 g/dL and another marker of severe disease (prostration, respiratory distress, seizures, hypoglycemia [< 2.2 mmol/L], acidosis [BE ≤ -10.0 mmol/L], lactate ≥ 5.0 mmol/L)
Missing: Haemoglobin or BCS unavailable so syndrome classification could not be determined

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- During the 20 months period post Dose 1, in children aged 5-17 months, 16 cerebral malaria cases (parasitaemia > 5000 per μL, Blantyre Coma Score ≤ 2 and haemoglobin level of ≥ 5 g/dL) occurred in the RTS,S/AS01$_E$ group, among 5948 children, and 5 cerebral malaria cases occurred in the control vaccine group, among 2974 children. In addition, cerebral malaria and anaemia (parasitaemia > 5000 per μL, Blantyre Coma Score ≤ 2 and haemoglobin level of < 5 g/dL) were observed for 6 subjects in the RTS,S/AS01$_E$ group and 1 subject in the control vaccine group.
- Between administration of the 4th dose of RTS,S/AS01$_E$ / meningococcal C conjugate vaccine and study end, in children aged 5-17 months, 9 cerebral malaria cases occurred among 2719 children vaccinated with RTS,S/AS01$_E$ and receiving meningococcal C conjugate vaccine at the time of the 4th dose. No cerebral malaria with anaemia was observed in this group. 11 cerebral malaria cases occurred among 2681 children vaccinated with RTS,S/AS01$_E$ and receiving a 4th dose of RTS,S/AS01$_E$ (plus one case of cerebral malaria with anaemia), and 2 cerebral malaria cases occurred among 2702 children receiving rabies vaccine for primary and meningococcal C conjugate vaccine at the time of the 4th dose (plus 2 cases of cerebral malaria with anaemia).

Taking into consideration the fact that the numbers were small, that no clinical diagnosis was performed by the investigators (no clinical case definition used), that there is no known biological plausibility of a pre-erythrocytic vaccine to directly cause cerebral malaria, the most likely explanation of the imbalance is a possible rebound effect and/or shift of age linked to the efficacy of the intervention. Therefore, GSK Biologicals considers cerebral malaria as a safety concern that requires further evaluation, and has therefore categorized it as an important potential risk in the RMP.

Overall mortality by gender

Ad-hoc analysis of mortality by gender based on the completed Phase III study MALARIA-055 data was performed at the request of WHO, in the context of their policy making pertaining to the potential use of *Mosquirix* in SSA [WHO, 2016(a); WHO, 2016(b)].

In this analysis all-cause mortality in the girls who received RTS,S/AS01$_E$ was ≈2-fold higher than in the girls who received the control vaccine (123/5091 [2.4%] versus 33/2603 [1.3%]; for both age categories pooled); while in boys, all-cause mortality was slightly lower in the group that received RTS,S/AS01$_E$ compared to the boys in the control group (95/5215 [1.8%] versus 55/2550 [2.2%]).

It is GSK's position that this should not be considered a safety signal because:

- Low fatality rate overall in study MALARIA-055 compared to what could be expected: 1 to 2% in each group, while in real-life setting mortality under 5 ***years old*** in SSA is estimated to be 5% (World bank);
- An investigator-initiated case control study in one site showed a 70% reduction in all-cause mortality in children enrolled in the study, as compared to children living in the same area but not enrolled in MALARIA-055;

- Background mortality rates per gender vary significantly across SSA countries. Under circumstances where boys and girls have the same access to resources such as food and medical care, boys have higher mortality rates than girls during childhood. Western Africa had the most countries (five) with evidence of excess female child mortality in the 2000s as well as several countries of Eastern Africa and Middle Africa [United Nations, 2011].
- The overall trend for differences in mortality rates in girls between the RTS,S/AS01$_E$ and control groups is also observed in the subgroup analyses of the potential confounding factors including administration of recommended EPI vaccines (measles, yellow fever, etc), human immunodeficiency virus (HIV) status and different access to medical care and/or proper nutrition. These differences are in-line with the observed imbalance in overall mortality and it is difficult to understand whether they actually contributed to the overall mortality differences between girls in the RTS,S/AS01$_E$ treatment groups and girls in the control group. Therefore, these additional analyses only seem to support the hypothesis that the observed imbalance in mortality in girls (i.e. active versus control) is likely to be a chance finding (given the small numbers involved and the fact that clinical trials are not designed to evaluate impact on mortality, especially for a disease like malaria that is perfectly treatable).

However, GSK Biologicals considers that gender-specific mortality requires further evaluation, and has therefore categorized it as missing information in the RMP.

In summary, meningitis is considered/reported as a potential risk in the RMP of RTS,S/AS01$_E$. The occurrence of febrile convulsions is considered/reported as an identified risk associated during the 7 days following vaccination with RTS,S/AS01$_E$. The imbalance observed for cerebral malaria following a post-hoc analysis of the MALARIA-055 study is considered as a safety concern that requires further evaluation and is therefore categorized as an important potential risk in the RMP. At present, GSK Biologicals does not consider excess/increased mortality in females as a potential risk. Additional data need to be generated; for now it has been categorized in the RMP as missing information.

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7.3. Efficacy results of the clinical development of RTS,S/AS01$_E$

Efficacy results of the Phase III study, MALARIA-055, are shown below for the intention-to-treat population. Efficacy against all episodes of clinical malaria in children aged 5 to 17 months over 12 months after Dose 3 was estimated to be 55.1% (95% CI: S50.5, 59.3) [The RTS,S Clinical Trials Partnership, 2011]. Over 18 months after Dose 3 it was estimated to be 45.1% (95% CI: 41.4, 48.7) [The RTS,S Clinical Trials Partnership, 2014]. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 12 months was 32.9% (95% CI: 26.3, 38.8) [The RTS,S Clinical Trials Partnership, 2012] and over 18 months was 27.0% (95% CI: 21.1, 32.5) [The RTS,S Clinical Trials Partnership, 2014].

In both age groups, vaccine efficacy for clinical malaria waned over time (Schoenfeld residuals p<0. 001). In children 5-17 months, the reduction in malaria by 6 month time intervals following Dose 3 was reported as: 68% (95% CI: 64, 72) over the first 6 months of follow-up; 41% (95% CI: 36, 46) over the subsequent 6 months of follow-up; and 26% (95% CI: 19, 33) over the last 6 months of follow-up [The RTS,S Clinical Trials Partnership, 2014]. In infants 6-12 weeks, the corresponding reduction was reported to be 47% (95% CI: 39, 54), 23% (95% CI: 15, 31), and 12% (95% CI: 1, 21), respectively [The RTS,S Clinical Trials Partnership, 2014].

Long-term follow-up efficacy data and data following administration of a 4th dose of RTS,S/AS01$_E$ 18 months post Dose 3 show a decline in efficacy against clinical and severe malaria with time in both children and infants who did not receive a 4th dose of the RTS,S/AS01$_E$ vaccine. Administration of a 4th dose of RTS,S/AS01$_E$ enhanced protection against clinical malaria in infants and children as well as the efficacy against severe malaria in children. In children aged 5 to 17 months who did not receive a 4th dose of RTS,S/AS01$_E$, efficacy against all episodes of clinical malaria over 30 months post Dose 3 was estimated to be 35.2% (95% CI: 30.5, 39.5). In children who were administered a 4th dose of RTS,S/AS01$_E$, efficacy against all episodes of clinical malaria over 30 months was 43.9% (95% CI: 39.7, 47.8). For severe malaria, efficacy over 30 months in children aged 5 to 17 months was 4.5% (95% CI: -20.6, 24.5) when no 4th dose of RTS,S/AS01$_E$ was administered and 34.9% (95% CI: 15.6, 50.0) when a 4th dose of RTS,S/AS01$_E$ was administered. In infants aged 6-12 weeks, efficacy against all episodes of clinical malaria over 30 months was 20.3% (95% CI: 13.6, 26.5) without administration of a 4th dose of RTS,S/AS01$_E$ and 27.8% (95% CI: 21.7, 33.4) with administration of a 4th dose of RTS,S/AS01$_E$. Efficacy against severe malaria over 30 months was 7.9% (95% CI: -23.3, 31.2) without administration of a 4th dose of RTS,S/AS01$_E$ and 11.9% (95% CI: -18.3, 34.5) with administration of a 4th dose of RTS,S/AS01$_E$ [The RTS,S Clinical Trials Partnership, 2015]. These data support the benefit of a 4th dose of RTS,S/AS01$_E$ administered 18 months post Dose 3.

A potential rebound effect was observed in children aged 5-17 months. Throughout the period 18 months post Dose 3 to study end, an increased incidence of severe malaria was observed in children who did not receive a 4th dose of RTS,S/AS01$_E$, compared to controls: efficacy was -41.0% (95% CI: -98.5, -0.8). Among children who were administered a 4th dose of RTS,S/AS01$_E$, efficacy against severe malaria throughout the same period was -4.0% (95% CI: -50.0, 27.8). In infants aged 6-12 weeks, efficacy against severe malaria during the period 18 months post Dose 3 to study end was 11.2% (95% CI: -31.3, 40.2) when no 4th dose of RTS,S/AS01$_E$ was administered and 32.4% (95% CI: -3.2, 56.2) when a 4th dose of RTS,S/AS01$_E$ was administered. In contrast, clinical malaria disease showed no period of increased incidence compared to controls. The impact of RTS,S/AS01$_E$ against clinical malaria and severe malaria varied substantially by study site and the rebound effect was mainly observed in medium and high transmission settings [The RTS,S Clinical Trials Partnership, 2015].

In three trial sites (Korogwe, Tanzania; Nanoro, Burkina Faso and Kombewa, Kenya) of the MALARIA-055 study, children were followed for 3 additional years to further document the long-term incidence of severe malaria in RTS,S/AS01$_E$ and control groups (study MALARIA-076). Secondary objectives included evaluation of the incidence of clinical malaria, parasite prevalence, and serious adverse events of special interest.

The incidence of severe malaria was very low in each of the three study sites and was consistent with the epidemiology of the disease in high transmission areas – showing a decreased incidence of severe malaria with increasing age during childhood. There was no indication of rebound of severe malaria during the three additional years of follow-up in children who received either 3, or 4 doses of RTS,S/AS01$_E$.

In Nanoro (Burkina Faso), the site with highly seasonal malaria transmission, an increased susceptibility to uncomplicated malaria was observed. This increase did however not outweighing the initial benefit offered by the RTS,S/AS01$_E$ vaccine, and most importantly did not appear to result in an increase of severe malaria cases.

In all three sites vaccine efficacy estimates against clinical malaria and the impact in terms of clinical cases averted remained positive over the six- to seven-year period, starting from the first vaccine dose in study MALARIA-055 until the end of follow-up in study MALARIA -076

Overall vaccine efficacy over the 7-year follow-up period was:

- ***against clinical malaria: 4 doses: 24% (95% CI: 16, 31); 3 doses: 19% (95% CI: 11, 27)***
- ***against severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32) [Tinto, 2019].***

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7.4. Summary of the study rationale

In July 2015, the EMA issued a positive opinion for the RTS,S/AS01$_E$ vaccine [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)], and in October 2015 recommendations about RTS,S/AS01$_E$ were issued by the WHO's SAGE and the MPAC [WHO, 2015(a)] (see Section 9.2.1).

The EMA issued a positive opinion for the RTS,S/AS01$_E$ vaccine with the following indication: "*Mosquirix* is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *P. falciparum* and against hepatitis B. The use of *Mosquirix* should be based on official recommendations considering *P. falciparum* malaria epidemiology in different geographical areas" [European Medicines Agency, 2015(a); European Medicines Agency, 2015(b)]. These policy recommendations will be defined by the WHO and public health authorities in the malaria endemic SSA countries where the vaccine would be used.

The WHO's SAGE and MPAC recommended pilot implementations of RTS,S/AS01$_E$ in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. They did not recommend the use of the malaria vaccine in the 6–12 weeks age group [WHO, 2015(a)]. The first vaccine introduction ***occurred*** in 2019 ***after*** approv***al*** and recommend***ation*** by local health authorities. ***The RTS,S/AS01$_E$ vaccine was implemented in selected areas/clusters of 3 SSA countries and plan to expand the RTS,S/AS01$_E$ vaccination programme to the unexposed areas/clusters from 2023 is under discussion***. In this post-implementation safety study EPI-MAL-003, only the 5-17 months age group will be kept.

The safety profile of RTS,S/AS01$_E$ has been evaluated during pre-authorisation clinical trials conducted mainly in SSA. The EPI-MAL-003 study will further evaluate the safety of the vaccine during initial implementation by monitoring for rare AE such as protocol -defined AESI (potentially associated with RTS,S/AS01$_E$, historically associated with vaccines other than RTS,S/AS01$_E$, or which may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines), other AE leading to hospitalisation and meningitis (potential risk) among a minimum of 20,250 vaccinated study participants from exposed clusters.

In addition to the efficacy data provided by the MALARIA-055 pre-authorisation clinical trial, evidence on the impact and effectiveness of RTS,S/AS01$_E$ when administered post-implementation most close to routine medical practice is needed. Although primarily designed as a post-implementation safety study to detect potential rare and uncommon AE following vaccination with RTS,S/AS01$_E$, the secondary objectives of EPI-MAL-003 also aim to evaluate the effectiveness (direct effect) and impact (indirect, total and overall effects) of RTS,S/AS01$_E$ when administered post-implementation most close to routine medical practice in SSA. Estimation of effectiveness and impact will be done by comparison of a vaccinated cohort and an unvaccinated cohort (see Section 9.7.7.1 for diagrams of vaccine effects [direct, indirect, total and overall]).

It is important to note that background data on AE are limited for malaria-endemic countries in SSA. This makes the assessment of risks potentially associated with the new vaccine following its implementation challenging. More specifically, the incidence and onset of autoimmune diseases and some of the other AESI are not known for African populations. Thus, an epidemiological study (EPI-MAL-002) to collect AESI data has been initiated in Q4 2015 in the same study sites. The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation), of approximately 30,000 children in several sites in SSA countries (with at least 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented), will measure the baseline incidence of AESI, other AE leading to hospitalisation, meningitis and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated. In addition, EPI-MAL-005 will be conducted in parallel to EPI-MAL-002 and EPI-MAL-003, to measure MTI and record malaria control interventions at community level in the study site areas on a yearly basis.

As much as possible, sites have been selected for EPI-MAL-002 and EPI-MAL-005 based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system. The capacity of the study sites to detect AESI and meningitis will be strengthened early in EPI-MAL-002. This should ensure improved sensitivity and specificity of case detection and should also enable standardised calculation of incidence rates. EPI-MAL-003 ***is*** conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005.

GSK Biologicals intends to enrol 30,000 unvaccinated study participants in EPI-MAL-002 (with at least 20,000 in sites where the RTS,S/AS01$_E$ vaccine will be implemented). The EPI-MAL-003 study targets enrolling at least 45,000 children in active surveillance, including 22,500 children in the exposed clusters; with a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ for evaluation of the vaccine safety, and a minimum of 2,250 unvaccinated children for evaluation of effectiveness and impact (assuming that 80% of the 22,500 study participants in the exposed clusters will receive three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose; see Section 9.2.7.1.1 for details of procedures if a child selected to be unvaccinated receives RTS,S/AS01$_E$ vaccine); and 22,500 in the unexposed clusters for evaluation of the vaccine safety, effectiveness and impact.

Considering the limited number of sites where the safety study may be performed and following feasibility assessment with respect to recruitment target and practical conduct of the study, GSK considers that a sample size of around 45,000 study participants is the highest possible.

GSK acknowledges the limitations of these studies in terms of sample size, the difficulties to diagnose and characterise rare diseases such as auto-immune diseases in young children, the potential biases introduced by the sequential generation of data between EPI-MAL-002 and EPI-MAL-003 studies, as well as the unpredictable occurrence of meningitis cases and paucity of data on other rare diseases of special interest in those settings. GSK also acknowledges the uncertainties of vaccine uptake and coverage at each of these studies sites, and therefore the feasibility of recruiting and following unvaccinated children in the exposed clusters. However, the proposed approach is believed to be the best possible taking into account ethical considerations and practical limitations of the SSA setting. The potential biases and limitations are detailed in Section 9.9.

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8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To estimate the incidence of AESI[3] in children vaccinated with RTS,S/AS01$_E$.
- To estimate the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$.

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8.2. Secondary objectives

8.2.1. Safety

In children enrolled in EPI-MAL-003 study (vaccinated with RTS,S/AS01$_E$ or not vaccinated with RTS,S/AS01$_E$):

- To estimate the incidence of aetiology-confirmed and/or probable meningitis (final classification).
- To estimate the incidence of probable meningitis (final classification).
- To estimate the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification).
- To estimate the incidence of cerebral malaria (malaria diagnosed by rapid diagnostic test [RDT] and/or microscopy).
- ***To estimate the incidence of other AE leading to hospitalisation***
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.
- To describe risk factors for AESI, other AE leading to hospitalisation, meningitis, and malaria.
- To describe the causes of hospitalisation (including AESI, other AE, meningitis and malaria).
- To describe the causes of death, overall and by gender.
- To assess the risk of febrile convulsions during the 7-day period and 1-month period following each dose of RTS,S/AS01$_E$.

[3] Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode (HHE), generalised convulsive seizure
Intussusception, hepatic failure or renal insufficiency
Juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease
Diabetes mellitus type I, thrombocytopenia, anaphylaxis

In children enrolled in EPI-MAL-002 or EPI-MAL-003 studies (vaccinated with RTS,S/AS01$_E$ or not vaccinated with RTS,S/AS01$_E$):

- To monitor trends over time of meningitis cases identified at site level (first line laboratory).
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed and/or probable meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and meningitis by comparing the incidence of aetiology-confirmed, probable and/or clinically suspected meningitis in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and AESI by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association between vaccination and cerebral malaria by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- To assess the potential association, overall and by gender, between vaccination and death by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- ***To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.***

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8.2.2. Effectiveness and impact

- To estimate the vaccine effectiveness (direct effect) and the impact (indirect, total and overall effects) of vaccination with RTS,S/AS01$_E$ on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria diagnosed by RDT and/or microscopy.
- To estimate the vaccine effectiveness (direct effect) and impact (indirect, total and overall effects) of vaccination with RTS,S/AS01$_E$ on:
  - the prevalence of anaemia among hospitalised children.

- the incidence of all-cause hospitalisations and hospitalisations attributed to malaria (including *P. falciparum*).
- the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]) overall and by gender

9. RESEARCH METHODS

9.1. Study design

The EPI-MAL-003 study is a disease surveillance study with prospective cohort event monitoring including both temporal (before-after comparison with EPI-MAL-002) and concurrent (cluster design comparison of exposed and unexposed clusters) comparisons of the occurrence of adverse and malaria events between vaccinated and unvaccinated subjects living in exposed or unexposed clusters located in SSA countries, and eligible for RTS,S/AS01$_E$ vaccination for those living in the exposed clusters. The design will include active surveillance ***(corresponds to a prospective cohort monitoring)*** and enhanced hospitalisation surveillance (Figure 1) in both exposed and unexposed clusters (see Annex 2 for definitions).

Active surveillance: First, a cohort of at least 22,500 children including a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ and a minimum of 2,250 unvaccinated children, will be recruited in the exposed clusters (assuming that 80% of the 22,500 vaccinated study participants will receive three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose). Second, a cohort of at least 22,500 children will be recruited in the unexposed clusters. In both exposed and unexposed clusters, the children will be actively followed-up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Parents/ legally acceptable representative(s) (LARs) (according to local requirements) will be invited to enrol their child into the active surveillance as follows:

- **DTP group:** Children identified at any administration of DTP/HepB/Hib (usually given at 6, 10 and 14 weeks of age) or at hospitalisation before administration of 3rd dose of DTP/HepB/Hib and vaccinated with at least one dose of DTP/HepB/Hib. That group will include both RTS,S/AS01$_E$ vaccinated and unvaccinated children (from exposed or unexposed clusters);
- **Catch-up group:** Children identified at 1st RTS,S/AS01$_E$ dose administration (schedule depend***s*** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start. This group will include only RTS,S/AS01$_E$ vaccinated children from exposed clusters. Indeed, the objective of this catch-up is to include all the children who will receive the RTS,S/AS01$_E$ vaccine and who could not be recruited at the time of DTP/HepB/Hib administration because the study had not yet started.

There is no predefined number of study participants to be enrolled in each group. All children meeting the inclusion criteria are expected to be enrolled in the study within the recruitment period.

All children enrolled in the active surveillance will be followed-up through home visits (Figure 1, see also Section 9.2.7.1). Children receiving at least one dose of RTS,S/AS01$_E$ will be defined as the vaccinated study participants. For these children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01$_E$ vaccine, up to 2 years after the last dose. For children not vaccinated with RTS,S/AS01$_E$, visits will be scheduled at equal points in time. Note that, in practice, it is possible to find RTS,S/AS01$_E$ vaccinated children in an unexposed cluster (e.g., parents/LARs from an unexposed cluster can decide to have their child vaccinated in another cluster where the vaccine is available) or RTS,S/AS01$_E$ unvaccinated children in an exposed cluster (e.g. parents/LARs from an exposed cluster can decide not to have their child vaccinated). A last home visit will be conducted at study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). In addition to the home visits, in children enrolled in the active surveillance, all visits to health care facilities (primary health care and hospital level) for any diseases, signs and symptoms will be reported to the study staff up to the end of the active follow-up period for each individual child (2 years after the last RTS,S/AS01$_E$ dose or equal point in time for unvaccinated) (Figure 1, see also Section 9.2.7.1). Thereafter there will be continuous monitoring of hospitalisations only, up to study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Enhanced hospitalisation surveillance: All children ***who are at least 6 weeks and*** <5 years ***of age***, within the study areas in both exposed and unexposed clusters, not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance ***at the time of hospitalisation***, are eligible for enrolment in enhanced hospitalisation surveillance (Figure 1, see also Section 9.2.7.2). A home visit will be conducted at study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Since the MoHs of the countries participating in the MVIP according to the SAGE/MAPC recommendation plan to expand the RTS,S/AS01$_E$ vaccine implementation to the unexposed clusters from 2023, clusters that were initially unexposed will become exposed with regards to RTS,S/AS01$_E$ vaccination. This change in vaccine implementation directly impacts the current study plan. Therefore, the enrolment of subjects in the enhanced hospitalisation surveillance will be stopped in clusters that were not involved in the EPI-MAL-002 study (i.e. all clusters in Malawi; unexposed clusters in Ghana and 1 exposed and 2 unexposed clusters in Kenya) as from 01 January 2023. Subjects already enrolled in EHS will continue to be followed until study conclusion, in order to capture information on their subsequent hospitalisations. Study conclusion will be conducted in a timely manner from 01 January 2023. As initially planned, the enrolment of subjects in EHS will be pursued until the end of study in clusters involved in the EPI-MAL-002 study because this will provide relevant information for the before/after comparison.

Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months (see Section 9.2.5; i.e. 24 months after the 4th dose of RTS,S/AS01$_E$).

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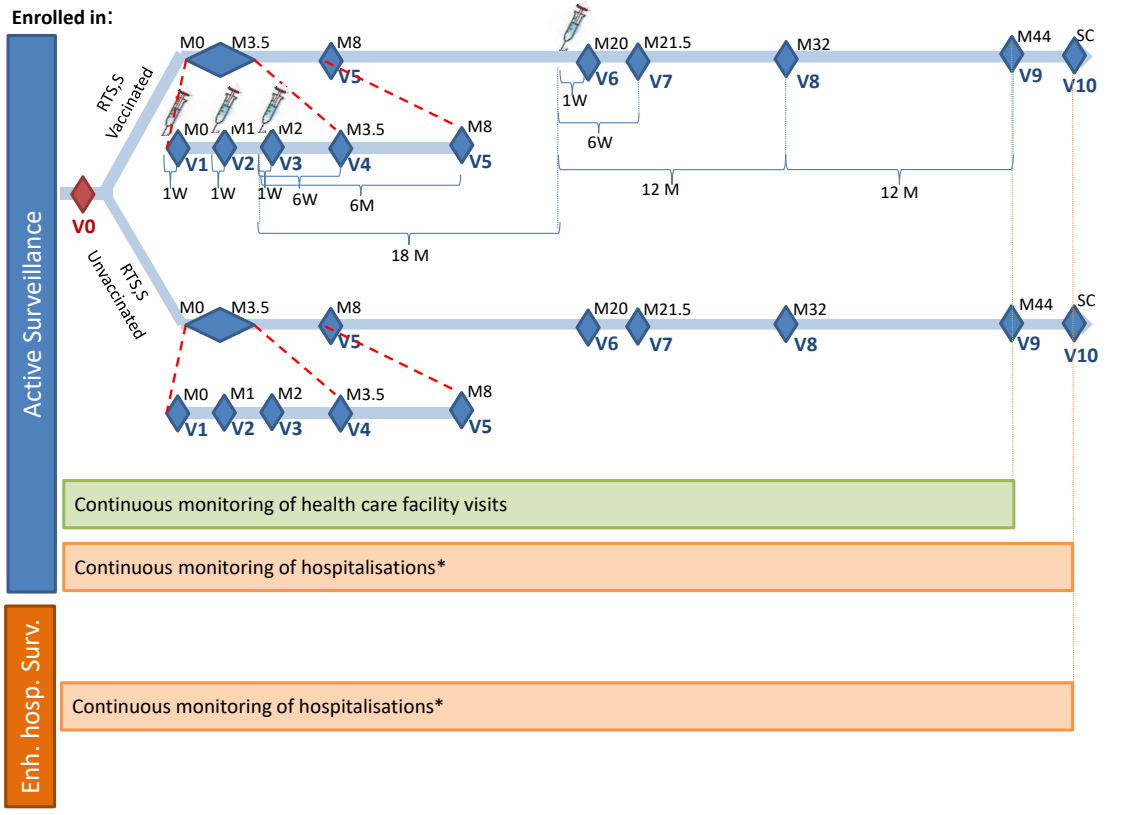
Figure 1 Study design overview

Distribution of vaccinated and unvaccinated children among the clusters		
Study groups *in active surveillance*	**RTS,S/AS01$_E$ exposed clusters**	**RTS,S/AS01$_E$ unexposed clusters**
DTP	RTS,S/ AS01$_E$ vaccinated and unvaccinated children	RTS,S/ AS01$_E$ vaccinated and unvaccinated children
Catch-up	RTS,S/ AS01$_E$ vaccinated children	-



* Hospitalisation is defined as spending at least one night at a health care facility
V0 = 1st dose of RTS,S/AS01$_E$ vaccine for catch-up group; 1st identification of the child at any DTP/HepB/Hib, or during hospitalisation before 3rd dose of DTP/HepB/Hib (for children who already received at least 1 dose of DTP/HepB/Hib) for DTP group.
V = visit; W = week(s); M = month(s); SC = study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first).
The RTS,S/AS01$_E$ vaccinated children will be either included in the DTP group (exposed or unexposed clusters) or in the catch-up group (exposed clusters) according to the abovementioned active surveillance study group characteristics.

The unvaccinated children will be included in the DTP group only and will be from either the exposed or the unexposed clusters.

For the children enrolled in active surveillance in the DTP group, enrolment is at any administration of DTP/HepB/Hib vaccine or at hospitalisation before 3rd administration of DTP/HepB/Hib vaccine and vaccinated with at least one dose of DTP/HepB/Hib. This group includes both RTS,S/AS01$_E$ vaccinated and unvaccinated children from exposed or unexposed clusters.

The catch-up group of the active surveillance will include a group of children identified at 1st RTS,S/AS01$_E$ dose administration (schedule depend***s*** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start**.** This group includes RTS,S/AS01$_E$ vaccinated children from exposed clusters.

For the children vaccinated with RTS,S/AS01$_E$, the home visits will take place approximately 1 week after administration of each dose of primary schedule of RTS,S/AS01$_E$ (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose; and 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after administration of the 4th dose of RTS,S/AS01$_E$.

For the children not vaccinated with RTS,S/AS01$_E$, the home visits will be scheduled at equal points in time.

A last home visit (V10) will be conducted at study conclusion.

Continuous monitoring of outpatient visits at health care facilities will be done up to the end of active follow-up for children enrolled in active surveillance.

For active surveillance, continuous monitoring of hospitalisations will be done throughout the whole study period.

For EHS, the continuous monitoring of hospitalisations will be done throughout the whole study period for clusters involved in EPI-MAL-002 study. For the other clusters not involved in EPI-MAL-002 study, enrolment into EHS will be stopped and study conclusion will be conducted in a timely manner from 01 January 2023.

(Amended 15 October 2020)

The diseases under surveillance for safety include AESI, other AE leading to hospitalisation, meningitis, and severe malaria including cerebral malaria. They will be monitored among the vaccinated and unvaccinated children, enrolled in active surveillance and in enhanced hospitalisation surveillance. The potential association, overall and by gender, between vaccination and death will also be assessed.

The effectiveness (direct effect) of the RTS,S/AS01$_E$ vaccine will be investigated by monitoring all malaria (including severe and cerebral malaria) related events in the vaccinated and unvaccinated children of the exposed clusters, enrolled in active surveillance. This will be achieved by collecting data on any malaria and severe malaria (including cerebral malaria) from all health care facilities, including outpatient visits and hospitalisations. The impact (indirect, total and overall effect) of the vaccine will be investigated, in the active surveillance, firstly by comparing the incidence of all malaria (including severe and cerebral malaria) cases in EPI-MAL-002 to the incidence of all malaria (including severe and cerebral malaria) cases in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect). Secondly, the impact will also be investigated in the active surveillance, by comparing the incidence of all malaria (including severe and cerebral malaria) cases in children of the unexposed clusters in EPI-MAL-003 to the incidence of all malaria (including severe and cerebral malaria) cases in unvaccinated children of the exposed clusters in EPI-MAL-003 (indirect effect), in vaccinated children in EPI-MAL-003 (total effect), or in all children of the exposed clusters in EPI-MAL-003 (overall effect) (see also Section 9.7.7 and Figure 3, Figure 4 and Figure 5).

(Amended 15 October 2020)

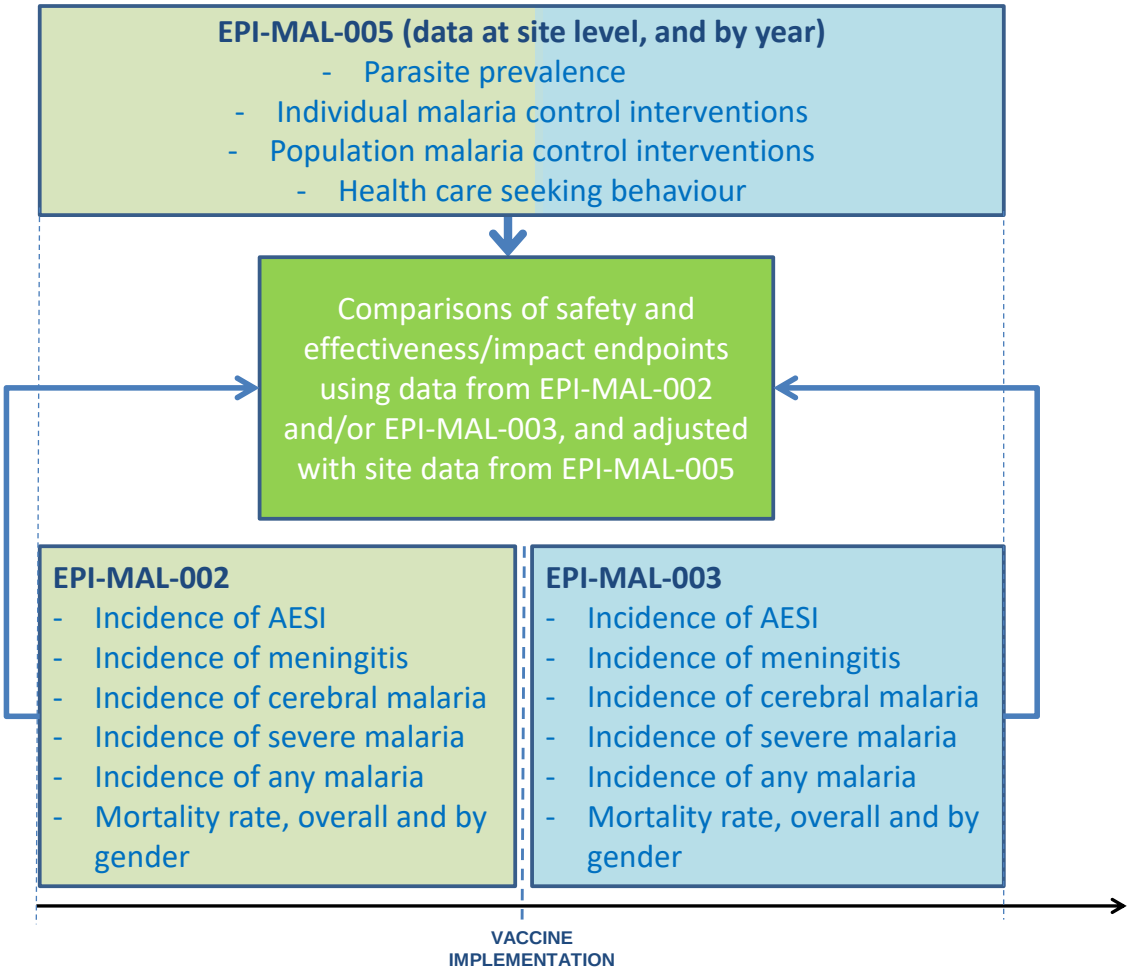
9.1.1. Rationale for the study design

The RTS,S/AS01$_E$ vaccine will be implemented only in part of malaria endemic countries of SSA. Most of these countries have no baseline incidence data on rare diseases such as those that may be reported in temporal association with vaccination. Therefore assessment of causality between adverse events and RTS,S/AS01$_E$ may be difficult. As there are no baseline incidence rates for the AESI in the target population and in order to respond to potential safety concerns emerging during the introduction of the RTS,S/AS01$_E$ vaccine, baseline incidence rates must be generated before vaccination. Additionally, many countries do not have standardised malaria surveillance systems in place. Both of these are required to evaluate the safety of the RTS,S/AS01$_E$ vaccine.

GSK Biologicals has developed a set of studies to address the paucity of data regarding AE following vaccination with RTS,S/AS01$_E$, and to evaluate effectiveness and impact (Figure 2). Study EPI-MAL-003 ***is*** conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005 studies. The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation) measures the baseline incidence of AESI, other AE leading to hospitalisation, meningitis, and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated. Studies EPI-MAL-002 and EPI-MAL-003 will collect data in a similar manner to ensure their comparability. Capacity building of sites will be provided before start of EPI-MAL-002 and throughout the studies, to strengthen early case finding and diagnosis of the events of interest. EPI-MAL-005 will run in parallel with EPI-MAL-002 and EPI-MAL-003, and aims to estimate the annual parasite prevalence and record malaria control measures, providing information on potential confounding factors relevant to interpreting EPI-MAL-002/003 malaria outcome measures. In addition, as the vaccine will be implemented using a cluster design (sites in Kenya and Ghana where the EPI-MAL-002 is running should become part of the intervention areas, and new sites have been selected to be part of the comparison areas of the EPI-MAL-003), a concurrent unvaccinated cohort may be added as a comparator. For study sites of EPI-MAL-003 which are unexposed clusters of EPI-MAL-003 and where the EPI-MAL-002 was not conducted, the same capacity building will be provided before start of EPI-MAL-003 and throughout the study.

(Amended 15 October 2020)

Figure 2 Evaluation of safety, effectiveness and impact using data collected in studies EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005



Active surveillance

In order to detect the events of interest within a wide range of time to onset intervals after RTS,S/AS01$_E$ vaccination (from a few hours to several weeks or months), active surveillance of the enrolled children will be conducted through home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities. See Section 9.1 for details of home visits for vaccinated children receiving at least one dose of RTS,S/AS01$_E$ and visits for children who do not receive RTS,S/AS01$_E$ vaccine. The home visits will take place approximately 1 week after administration of each dose of the primary schedule of RTS,S/AS01$_E$ (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose, and 1 week (V6), 6 weeks (V7), 12 months (V8) and 24 months (V9) after the 4th dose of RTS,S/AS01$_E$ (see details in Section 9.2.7.1). These home visits at 12 months and 24 months after the last dose will help to capture protocol-defined diseases that may have long risk window periods and that may not have been identified if the study participant did not visit a health care facility, and to monitor the occurrence of malaria episodes for evaluation of vaccine effect. In case the 4th dose of RTS,S/AS01$_E$ was missed, a visit will be conducted approximately 24 months after the last dose received.

In addition to the home visits, any diseases, signs and symptoms in children enrolled in the active surveillance will also be reported to the study staff by all health care facilities (primary health care and hospital level) up to the end of the active follow-up period for each individual child.

If no SAE is detected in the enrolled child, active follow-up will cease and any diseases, signs and symptoms in children enrolled in the active surveillance will be reported to the study staff through monitoring of hospitalisations only, up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). If a SAE ***(AESI or meningitis or severe malaria including cerebral malaria*** is detected in the child, he or she will be followed for an additional 12 months to further characterise the event. A last home visit (V10) will be conducted at study conclusion. Follow-up for the SAE disposition is described in Section 11.5.

An important function of the active surveillance component is to ensure referral of sick children to the health care facilities. Due to EPI-MAL-002 activities, the active surveillance processes should already be effective when EPI-MAL-003 begins enrolment, allowing for identification of AE at an early stage of this study. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building will be provided before start of EPI-MAL-003 and throughout the study.

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Enhanced hospitalisation surveillance

For the purpose of this study, enhanced hospitalisation surveillance corresponds to case detection during hospitalisation through monitoring of medical records and registries. Enhanced hospitalisation surveillance is included to supplement the active surveillance for several reasons: 1) it may capture AESI, other AE leading to hospitalisation, meningitis, and severe malaria including cerebral malaria in children who may have been vaccinated but declined enrolment in active surveillance, or who were not enrolled in active surveillance as recruitment had been completed or were not eligible for active surveillance; 2) it will provide supplemental information regarding these events in unvaccinated children (from either the exposed or the unexposed clusters) not enrolled in active surveillance, complementing data generated from EPI-MAL-002. Including those unvaccinated children ensures continuity with EPI-MAL-002 and captures events that may be occurring in the community (see Section 9.9 for the potential biases and limitations). All hospitalised children ***who are at least 6 weeks and*** <5 years ***of age*** within the study areas who are not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance, are eligible for enrolment in enhanced hospitalisation surveillance, to allow for data collection regarding that hospital visit and any subsequent ***hospitalisations*** until study conclusion. Children already enrolled in active surveillance will have hospitalisations monitored as part of the procedures related to the active surveillance and will therefore not be enrolled in enhanced hospitalisation surveillance.

To assess the operational conduct of both active surveillance and enhanced hospitalisation surveillance, two control outcomes have been included in the study protocol, as for EPI-MAL-002. Abscess at injection site (after any vaccination) is included as a positive control and positional foot deformation is included as a negative control (see case definitions in Section 9.2.6.10). These conditions are relatively easy to diagnose and will be used to assess changes in the performance of health care systems to diagnose disease.

Selected study sites are expected to have a HDSS or equivalent surveillance system in place. If a site does not have a HDSS in place, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites. In addition, being part of the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) (or seeking membership to INDEPTH) is an asset to ensure standard health and demographic surveillance practices, thereby enabling standardised calculation of incidence rates.

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9.2. Setting

9.2.1. Study population

The three studies EPI-MAL-002, -003 and -005 are planned to be anchored when possible on the INDEPTH health and demographic survey platform (http://www.indepth-network.org) or equivalent surveillance system to provide both population and health facility linkage [INDEPTH]. For this study, the HDSS (or equivalent surveillance system) provides the population and its characteristics, from which a cohort may be identified. The cohort will be a subset of the total eligible population of children specified within the geographic catchment area of the study sites. The cohort is considered dynamic, as ***infants*** and immigrants are included in the cohort and the birth or in-migration date is recorded. Similarly, deaths and outmigrations- are recorded.

The process begins with a census of the population and proceeds with regularly scheduled (at least once a year) monitoring of vital events (births, deaths), migration, selected health outcomes, and other demographic and lifestyle variables. The census serves as the source document for the initial screening for study population eligibility.

Note: If a site is not part of the INDEPTH network, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

Initially, seven sites in five SSA countries were chosen to participate in the EPI-MAL-002 study. Following SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria [WHO, 2015(a)], some of the initially chosen sites located in low-endemicity settings had to be terminated. For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01$_E$ vaccine is planned to be implemented according to MVIP, were added to the already defined study sites for EPI-MAL-002 as described below.

In April 2017, the WHO Regional Office for Africa announced that the RTS,S/AS01$_E$ vaccine will be first introduced in 3 countries (Ghana, Kenya and Malawi) through MVIP. The 3 countries were selected to participate in the pilot programme based on the following criteria: high coverage of long-lasting insecticidal-treated nets; well-functioning malaria and immunisation programmes, a high malaria burden even after scale-up of long-lasting insecticidal-treated nets, and participation in the Phase III RTS,S/AS01$_E$ malaria vaccine trial. Each of the 3 countries will decide on the districts and regions to be included in the MVIP. High malaria burden areas will be prioritized [WHO, 2017]. In order to align with the MVIP, the study sites for the GSK's baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) have been selected as follows:

- Sites have been selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented in the framework of the MVIP. Burkina Faso sites that started EPI-MAL-002 have early terminated the study activities on 06 June 2018 (with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI). Burkina Faso sites will not be included in EPI-MAL-003 because the MVIP will not take place in the country. Their data will therefore not be included neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies**,** nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study (e.g. background incidence of meningitis for study sample size and the exposure to other vaccines). Considering the RTS,S/AS01$_E$ vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site.
- As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.
- Currently, as per MVIP and WHO guidance, 4 study sites (corresponding to 4 clusters of the MVIP) in each of the 3 countries selected for the RTS,S/AS01$_E$ pilot implementation programme (12 study sites/clusters in total) are planned to be part of EPI-MAL-003: 2 of them should become exposed clusters and 2 of them should become unexposed clusters. Phase IV vaccine evaluation being fully embedded in the MVIP, selection of the unexposed clusters that will be included in study EPI-MAL-003 depends on the cluster identification process led by the MoH in collaboration with the WHO. Of note, the clusters, once pre-identified by the MoHs are submitted to a comprehensive scientific and operational study site assessment conducted by GSK, which will determine study feasibility in those sites. Exposed and unexposed clusters will be comparable in terms of malaria transmission, health facilities level, geographical region and population size.

  - As per WHO guidance, study sites from Ghana and Kenya included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.
  - Selection of the remaining study sites/clusters that will be included in the EPI-MAL-003 study is completed and is fully embedded in the MVIP.

- In summary: currently, a total of 3 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa]) ***have enrolled*** study participants in the EPI-MAL-002 study. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 sites ***have*** become exposed study sites/clusters in EPI-MAL-003. Selection of the remaining study sites/clusters that will be included in the EPI-MAL-003 study is completed and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.

Taking into account a global birth cohort of 23,000 children ***at the time of EPI-MAL-002 study preparation***, and the refusal rate of parents for their children to join the study, an expected number of at least 45,000 children, including 22,500 children in the exposed clusters (with minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ and a minimum of 2,250 unvaccinated children) and 22,500 children in the unexposed clusters will be part of the active surveillance of the study. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children in the exposed clusters is reached. The number of children enrolled per site will depend on the birth cohort at each site.

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9.2.2. Eligible population

The eligible study population is defined as those children living in the study areas.

The WHO's SAGE on Immunization and the MPAC recommended pilot implementations of RTS,S/AS01$_E$ in children of 5–17 months of age, in parts of 3-5 SSA countries, administering 3 doses of the vaccine to children 5-9 months of age in areas of moderate-to-high transmission of malaria with a fourth dose administered 15-18 months following the third dose. At the start of the malaria vaccine implementation, children aged 5-12 months will be eligible for dose 1 of RTS,S/AS01$_E$. In some countries a large number of children aged 5-12 months may therefore be vaccinated at the start of the pilot implementation programme. Once the malaria vaccine implementation is in steady state, the majority of children receiving dose 1 will have only recently grown into the eligible age range. Co-administration could happen such as measles or yellow fever vaccines, scheduled in older infants at 9 months of age.

For the active surveillance, children from both exposed and unexposed clusters will be enrolled. At least 22,500 children in the exposed clusters, including a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$, and a minimum of 2,250 unvaccinated children, are targeted to be enrolled (assuming that 80% of study participants will receive at least three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not

have any dose). At least 22,500 children in the unexposed clusters will be enrolled into the active surveillance when presenting for administration of DTP/HepB/Hib vaccine. Parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine (DTP group), regardless whether they subsequently decide to vaccinate their child with RTS,S/AS01$_E$ or not. In addition, parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for 1st administration of RTS,S/AS01$_E$ vaccine and who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are, older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start (catch-up group).

For enhanced hospitalisation surveillance, parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are ***at least 6 weeks and*** <5 years ***of age*** and who can be linked to the HDSS or equivalent surveillance system, will be approached to enrol their child into this study:

- If a child, who is first identified during hospitalization by study staff, fulfills the eligibility criteria for enrolment in active surveillance (within the recruitment period), enrolment in active surveillance will be proposed. If the parents/LARs decline enrolment in active surveillance ***and if the child fulfills the eligibility criteria for enrolment in enhanced hospitalisation surveillance***, enrolment in enhanced hospitalisation surveillance will be proposed.
- If a child, who is first identified during hospitalization by study staff, is not eligible for enrolment in active surveillance but fulfills the eligibility criteria for enrolment in enhanced hospitalisation surveillance, enrolment in enhanced hospitalisation surveillance will be proposed.

  Note: 'first identified during hospitalization by study staff' means 'not already enrolled in the study'.

Hospitalisation is defined as spending at least one night at a health care facility. Some primary care facilities have beds available for overnight monitoring; these stays are considered to be "hospitalisations" for protocol purposes. Additionally, some tertiary hospitals may offer primary health care services. So the more general term, "health care facility" is used in the protocol to include the spectrum of health care service access points, from primary health care clinics to tertiary hospitals. There may be a difference in the degree of severity of cases admitted in the hospital and those hospitalised at primary health care facilities as the latter may include children with non-severe disease who live too far to be sent home on the same day. On the other hand, hospitalisations in primary health care facilities may also include cases that under European conditions would normally be referred to the hospital, such as: parental refusal to refer the child to a hospital, difficulties of transport or local standard practice. This issue will be addressed by identifying the type of health care facility (either hospital or primary health care facility) in case of hospitalisation. The type of health care facility will be included as covariate in the analyses, where appropriate.

There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003. Children enrolled in active surveillance of EPI-MAL-002, and not eligible for RTS,S/AS01$_E$ vaccination or declining RTS,S/AS01$_E$ vaccination will continue to be followed up to the

study conclusion visit in EPI-MAL-002. Children enrolled in active surveillance of EPI-MAL-002, and becoming vaccinated with RTS,S/AS01$_E$, will have their study conclusion of EPI-MAL-002. Thereafter, these children can be enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

For children enrolled in enhanced hospitalisation surveillance of EPI-MAL-002, study conclusion of EPI-MAL-002 will be done at start of study EPI-MAL-003 (as the vaccine becomes available in the study sites that are exposed clusters). Thereafter, these children can be eligible and enrolled in active surveillance or in enhanced hospitalisation surveillance of EPI-MAL-003 according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

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9.2.3. Inclusion criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or study participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All study participants must satisfy ALL the following criteria at study entry:

- Study participants' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written informed consent provided from either the parent(s) or LAR of the study participant.
- Study participant living in the HDSS or equivalent surveillance system area.
- For enrolment in the active surveillance – DTP group: children must be aged < 18 months, identified at any administration of DTP/HepB/Hib (or at hospitalisation before 3rd dose of DTP/HepB/Hib in case of hospitalisation and vaccinated with at least one dose of DTP/HepB/Hib). (This group will include children from exposed and unexposed clusters.)

  OR

  For enrolment in the active surveillance – Catch-up group: children must be aged < 18 months, received at least one dose of DTP/HepB/Hib vaccine, whose age corresponds to the age after the 3rd dose of DTP/HepB/Hib vaccine, (=who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start) and identified at 1st RTS,S/AS01$_E$ dose administration (This group will include children from exposed clusters only).

  OR

  For enrolment in the enhanced hospitalisation surveillance: children must be aged ***at least 6 weeks and*** <5 years ***at the time of hospitalisation*** at any time during the study. (This group will include children from exposed and unexposed clusters.)

Parents/LARs of children meeting all eligibility criteria for active surveillance, not having completed the visits for DTP/HepB/Hib, and first identified during hospitalisation, must first be proposed enrolment in active surveillance (if recruitment is not completed).

Children already enrolled in active surveillance will have hospitalisation monitored as part of the procedures related to the active surveillance and can therefore not be enrolled in enhanced hospitalisation surveillance.

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9.2.4. Exclusion criteria

The following criterion should be checked at the time of study entry. If the exclusion criterion applies, the study participant must not be included in the study:

- Child in care

  Please refer to Annex 2 for the definition of child in care.

9.2.5. Study period

Taking into account a global birth cohort of 23,000 children ***at the time of EPI-MAL-002 study preparation*** (11,500 children in the exposed clusters, and 11,500 children in the unexposed clusters), a period of approximately 18 months is assumed to be sufficient to enrol at least 45,000 children in active surveillance of EPI-MAL-003, including 22,500 children in the exposed clusters (with a minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ and a minimum of 2,250 unvaccinated children assuming that 80% will receive three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose) and 22,500 in the unexposed clusters. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. In the participating sites, the vaccine coverage is not expected to be low. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children is reached.

The recruitment period will be adapted according to the birth cohorts of the different sites at the time of study start. The duration of the recruitment will also be adjusted according to the recommended schedule of the vaccine and the vaccine coverage in the exposed clusters, the time the participating countries start implementing the vaccine (which may be different between countries), and potential unanticipated logistical issues.

The total study duration per site will be approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months. Study end per site will occur when the last child enrolled in active surveillance has accrued a total follow-up period of 24 months after the 4th dose of RTS,S/AS01$_E$ (or equal point in time for unvaccinated children). (Children reporting a SAE ***due to study procedure might*** have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months).

Note: There might be an overlap of studies EPI-MAL-002 and EPI-MAL-003, some children enrolled in EPI-MAL-002 will have the possibility to be part of EPI-MAL-003. First, the study conclusion of EPI-MAL-002 for children enrolled in enhanced hospitalisation surveillance will be done at the start of study EPI-MAL-003 (as the RTS,S/AS01$_E$ vaccine becomes available in the sites that are exposed clusters; See Section 9.2.2). In addition, children enrolled in active surveillance of EPI-MAL-002, and becoming vaccinated with RTS,S/AS01$_E$, will have their study conclusion of EPI-MAL-002. Thereafter, these children can be enrolled in EPI-MAL-003 (active surveillance or enhanced hospitalisation surveillance if hospitalised) according to the inclusion/ exclusion criteria and the EPI-MAL-003 recruitment procedures.

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9.2.6. Case definitions

9.2.6.1. AESI

Adverse events of special interest (AESI) are protocol-defined diseases corresponding to AEs that are potentially associated with RTS,S/AS01$_E$, that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines.

The list of AESI has been developed in collaboration with a group of paediatricians working in SSA. This group of paediatricians has been consulted following an opportunity to receive scientific advice with the EMA in 2011. Indeed, the Committee for Medicinal Products for Human Use (CHMP) suggested seeking advice from relevant paediatric clinicians on which additional AESI (particularly autoimmune disorders) may be of most relevance for SSA countries as well as the surveillance indicators. In addition, GSK had considered four diseases which have been identified as potential AE with other vaccines and has added these to this list (Intussusception, Kawasaki diseases, Henoch-Schonlein Purpura and Hypotonic Hyporesponsive Episode [HHE]).

When available, the Brighton Collaboration Working Groups case definitions are used. These aim to define levels of diagnostic certainty of reported events following immunisation. Their global use enhances data comparability within and across clinical trials and surveillance systems and allows the adaption of the diagnosis based on the health facility's settings. Each case definition is structured in two or three levels of diagnostic certainty, each level being defined by a set of clinical and/or additional diagnostic criteria.

- Level 1 of diagnostic certainty: most specific and least sensitive level
- Level 2 of diagnostic certainty: intermediate level of specificity and sensitivity
- Level 3 of diagnostic certainty: most sensitive but lowest level of specificity.

Job Aids are field guides that act as a reference tool for study staff. For this study, Job Aids have been developed to standardise the definition of each AESI during a collaborative initiative between GSK, Agence de Médecine Préventive (AMP) and Réseau en Afrique Francophone pour la Télémédecine (RAFT). RAFT physicians will provide support for case diagnosis through virtual consultation infrastructure.

The predefined list of AESI and associated clinical information is provided in Table 3 and case definitions are provided in Annex 5.

Table 3 Summary of AESI by body system

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
Nerves and Central Nervous System				
ADEM	0.6 to 0.8/100,000 PY [Karussis, 2014]; 0.2/100,000 PY (in < 18 yr olds, Canada) [Banwell, 2009]; 0.40, 0.27 and 0.30/100,000 PY (10-14 yr olds, 15-19 yr olds, 20-29 yr olds, respectively, China) [Xiong, 2014]; 0.03/100,000 PY (10-16 yr olds, Germany) [Pohl, 2007]; 0.2/100,000 PY (< 18 yr olds, The Netherlands) [Ketelslegers, 2012]; 0.34/100,000 PY (1-15 yr olds, UK) [Absoud, 2012]; 0.3/100,000 PY (≤18 yr olds, US) [Langer-Gould, 2011]; 0.4/100,000 PY (< 20 yr olds, US) [VanLandingham, 2010]	1-2 per million following vaccination against measles, 0.2 per 100,000 following vaccination against Japanese encephalitis, 1 per 300 to 1 per 7,000 following administration of neural vaccine against rabies [Tenembaum, 2007]	NA	BC
Encephalitis	11.1 (95% CI: 10.1, 12.1) and 4.7 (95% CI: 4.3, 5.1) encephalitis-associated hospitalisations /100,000 PY (in <1 yr and 1-4 yr olds, US, respectively) [Vora, 2014]	1396 cases (mean age 23.4 yrs, range 0-89 yrs) in the US from 1990 to 2010 [Al Qudah, 2012]	Onset within 6 wks and 2 wks after vaccination: 65.2% and 50.7% of patients, respectively [Al Qudah, 2012]	BC
Guillain-Barré Syndrome	0.7/100,000 PY (in 12-29 yr olds, Tanzania) [Howlett, 1996]; 0.38/100,000 PY (in 0-4 yr olds, China) [Chen, 2014]; 0.62/100,000 PY (95% CI: 0.52, 0.75) in 0-9 yr olds in a meta-analysis from studies in North America and Europe [Sejvar, 2011]	1 additional case per 10^6 doses with influenza vaccination in US, 1992-1994 [Lasky, 1998] Calculated RR in different studies on influenza vaccination from 1978 to 2005 produced RR values ranging from 0.4 to 1.7 [Sejvar, 2011]	Ranges from 3-5 days to 6-10 wks, and up to a few months and even years [Sejvar, 2011]	BC
Generalised convulsive seizure	Unknown	1.04 per 1,000 (95% CI: 0.62, 1.64) after primary vaccination with RTS,S/AS01 in children 5-17 months at first dose [The RTS,S Clinical Trials Partnership, 2012]; 2.5 per	0-7 days after RTS,S/AS01	BC

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
		1,000 and 2.2 per 1,000 after 4th dose of RTS,S/AS01 in children 5-17 months at first dose, and in children aged 6-12 weeks at first dose, respectively [The RTS,S Clinical Trials Partnership, 2015]		
Hypotonic Hypo-responsive syndrome	NA	Reported rates following whole-cell and acellular pertussis component combination vaccines range from 21 to 71 episodes and 7 to 36 episodes per 100,000 doses and 36 to 250 episodes and 4 to 140 episodes per 100,000 children, respectively [Buettcher, 2007]	3–4h but ranges from immediately to 48h post vaccination	BC
Hepato-Gastrointestinal and Renal System				
Intussuscep-tion	Average rate 1 case per 3,300; yearly variations 1:2,500 to 1:5,000 (<1 yr old, Panama) [Sáez-Llorens, 2004]; <5/100,000 PY (<9 wks), 62/100,000 PY (26-29 wks), 26/100,000 PY (52 wks) (US) [Tate, 2008]; 8.1/100,000 PY (<1 yr Australia) [Justice, 2005]	Overall estimate of risk of IS ***within 7 days is estimated at 5.4 (95% CI: 3.9-7.4) after 1st dose Rotarix and 5.5 (95% CI:3.3-9.3) after 1st dose RotaTeq.*** Small increase after dose 2 for both vaccines [Carlin, 2013; Rosillon, 2015] **(Amended 15 October 2020)**	1 to 7 days after 1st and 2nd doses of *Rotarix* and *RotaTeq* vaccines	BC
Hepatic insufficiency	Unknown	NA	1-10 days	BC
Renal insufficiency	Unknown	NA	1-10 days	BC
Skin and Mucous Membrane & Bone and Joints				
Juvenile chronic arthritis	18/100,000 PY (in ≤16 yr olds, Canada) [Feldman, 2009]; 7/100,000 PY (Germany); 24/100,000 PY (Australia) [Begg, 2007]	NA	≤ 6 months	P
SJS and TEN	SJS:1-6 per million PY [Roujeau, 1995]; TEN: 0.4-1.2 per million PY [Roujeau, 1995]	NA	1-3 weeks	P
Henoch Schonlein purpura	Peak at 70/100,000 PY (in 4-6 yr olds, UK) [Gardner-Medwin, 2002]	NA	NA	P
Kawasaki disease	About 215/100,000 PY (in <5 yr olds, Japan) [Nakamura, 2010];	Reporting to VAERS in the US, from 1990 through mid-October 2007: Hib (31 cases of Kawasaki disease), PVC-	1 month after vaccination	P

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
	20/100,000 PY (in <5 yr olds, US); 17/100,000 PY (in <5 yr olds, African Americans) [Holman, 2010]; 6.4/100,000 PY (in <5 yr olds, Israel) [Bar-Meir, 2011]	7 (29 cases), MMR (22 cases), diphtheria and tetanus toxoids and acelluar pertussis (21 cases), inactivated polio (17 cases), rotavirus (16 cases), diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated polio combined (16 cases), hepatitis B (13 cases). 0.65 and 0.37 reports /100,000 PY for *RotaTeq* and *Pediarix*, respectively, before label revision of *RotaTeq*, and 2.78 and 2.44/100,000 PY for *RotaTeq* and *Pediarix* , respectively, after label revision [Hua, 2009] PCV-7: 4.6 per 100,000 doses, PCV-13: 5.4 per 100,000 doses [Tseng, 2013] PCV-13: 1 case in 233 vaccinated children, considered not to be related to vaccination [Gutierrez Brito, 2013] Electronically captured health insurance claims in the US, from 2006 to 2007: *RotaTeq*: 1 case within 30 days, 2 cases between 31 and 60 days after vaccination in North Wales. DTaP: 1 case [Loughlin, 2012]		
Systemic Disease and Haematology				
Diabetes mellitus type 1	0.06/100,000 PY (0.0, 0.13) (in 0-4 yr olds, Tanzania) [Swai, 1993]; 0.9/100,000 PY (in 0-4 yr olds, Sudan) [Karvonen, 2000]; 2.3 to 6.3/100,000 PY (in 0-4 yr olds, Tunisia) [Karvonen, 2000]; 9.06/100,000 PY (0-4 yr olds, Cyprus), 14.15/100,000 PY (5-9 yr olds, Cyprus) [Skordis, 2012];	NA	≤6 months	P

Body System/ AESI	Expected incidence (per 100 000 person-years)	Risk of AE	Risk period identified (for other licensed vaccines)	Brighton Case (BC) definition/ Protocol (P) definition
	3.1/100,000 PY (in <18 yr olds, Egypt) [El-Ziny, 2014]; 12.9/100,000 PY (0-5 yr olds, Germany), 18.7/100,000 PY (5-10 yr olds, Germany) [Galler, 2010]; 8.59/100,000 PY (0-4 yr olds, Israel), 13.29/100,000 PY (5-9 yr olds, Israel) [Sella, 2011]; 17.1/100,000 PY (0-4 yr olds, Saudi Arabia), 10.9/100,000 PY (5-9 yr olds, Saudi Arabia) [Habeb, 2011]; 4.3/100,000 PY (0-4 yr olds, Turkey), 9.1/100,000 PY (5-9 yr olds, Turkey) [Demirbilek, 2013]			
Thrombo-cytopenia	2.2/100,000 PY (in <16 yr olds, Germany) [Sutor, 2001]	NA	12-25 days median (range 1-83 days)	BC
Anaphylaxis	70/100,000 PY (in 0-19 yr olds, Minnesota, US) [Decker, 2008]	Monovalent measles (12 per 100,000 doses), MMR (1 per 100,000 doses), HPV bivalent (1.4 per million doses) or HPV quadrivalent (from 2.6 per 100,000 to 1.7 per million doses) [Vanlander, 2014] 0.65 (95% CI: 0.21, 1.53) per million doses for the most common vaccines for children and adolescents [Bohlke, 2003]	0-48 hours [Bohlke, 2003]	BC

ADEM= Acute Disseminated Encephalo-Myelitis; AE = adverse event; Hib = *Haemophilus influenzae* type B; HPV = human papilloma virus; MMR = measles, mumps, rubella; PCV = pneumococcal conjugate vaccine; SJS= Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis; NA = not available; PY = person years; RR = relative risk; VAERS = Vaccine Adverse Event Reporting System.

9.2.6.2. AE/SAE

Refer to Section 11.1 for the definition of AE and SAE.

9.2.6.3. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria)

These include all hospitalisations reported by the physician not due to an AESI (see Section 9.2.6.1) or to meningitis (Section 9.2.6.4) or to any malaria or to severe malaria (including cerebral malaria) (Section 9.2.6.6).

Collection of hospitalisations for an AE other than AESI or meningitis or any malaria or severe malaria (including cerebral malaria) will be stopped as of 01 January 2023 in subjects previously enrolled in EHS in sites not involved in EPI-MAL-002 study. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria) will continue to be collected as part of continuous monitoring for subjects enrolled in AS in all sites or EHS in sites involved in EPI-MAL-002 study.

(Amended 15 October 2020)

9.2.6.4. Meningitis

Of note, because meningitis was identified as a potential risk during RTS,S/AS01$_E$ clinical development (see Section 7.2), the disease is identified separately from the other AESI.

- At the site level, a suspected meningitis case based on clinical symptoms and/or signs is defined as [adapted from WHO, 2003]:
  - A child with sudden onset of fever (> 38.0°C rectal or 37.5°C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

  Lumbar puncture will be performed according to routine medical practice for examination of cerebrospinal fluid (CSF). Children with symptoms and/or signs of meningitis will be classified as follows based on first line laboratory results (for monitoring trends over time):
  - If a CSF sample is available and a bacterial agent has been identified, as bacterial confirmed meningitis case;
  - If a CSF sample is available, no bacterial agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels) or positive blood culture to a bacterial agent, as probable meningitis case;
  - If a CSF sample is available and all examinations are normal at first line laboratory level, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.
- Based on second line laboratory results (see Section 9.2.7.3.1 and 9.2.7.3.2) and after external panel of experts review (see Section 9.2.7.4.1), final classification of meningitis cases will be as follows (for the statistical analyses):
  - If a CSF sample is available and any known aetiologic agent (bacterial or not) has been identified, as aetiology-confirmed meningitis case;
  - If a CSF sample is available, no aetiologic agent has been identified in the CSF, but some abnormalities in the CSF have been detected (such as turbid macroscopic aspect, positive Gram, positive antigen test, pleiocytosis, abnormal glucose or protein levels), or positive blood culture to a bacterial agent as probable meningitis case;

– If a CSF sample is available and all laboratory results are normal after second line laboratory results, or if no CSF sample is available and no alternative diagnosis, as clinically suspected meningitis case.

If none of the criteria (no specific clinical symptoms and/or signs or laboratory results) are fulfilled, after review by the external panel of experts, the case will be classified as a no meningitis case.

9.2.6.5. Febrile convulsions

- Adapted from Brighton case definition for generalised seizures (see Annex 5): generalised seizures with measured fever ≥ 37.5 °C (axillary) or reported history of fever.

9.2.6.6. Malaria

Case definitions according to the WHO will be used [WHO, 2015(b)]. Any malaria will include uncomplicated and severe malaria cases, including cerebral malaria.

- Uncomplicated malaria [WHO, 2015(b)]

  Plasmodium parasitaemia > 0 detected by microscopy and/or RDT

  AND

  Presence of fever (temperature ≥ 37.5°C), as reported by the parent(s)/LAR(s) or recorded at the time of presentation

  OR

  Occurring in a child who is unwell and brought for treatment to a health care facility

  AND

  Without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

- Severe falciparum malaria [adapted from WHO, 2015(b)]

  P. falciparum parasitaemia > 0 detected by microscopy and/or RDT

  AND

  One or more of the following, occurring in the absence of an identified alternative cause:

  – Impaired consciousness: a Glasgow coma score < 11 in children ≥ 2 years of age or a Blantyre coma score < 3 in children < 2 years of age;

  – Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;

  – Multiple convulsions: more than two episodes within 24 h;

  – Acidosis: a base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).

- Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);
- Severe malarial anaemia: haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤15% in children < 12 years of age with a parasite count > 10,000/µL;
- Renal impairment: plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L;
- Jaundice: plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL;
- Pulmonary oedema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation;
- Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena;
- Shock: compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill);
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/µL).

- Severe vivax malaria is defined as for severe *falciparum* malaria but with no parasite density thresholds [WHO, 2015(b)].
- Cerebral malaria [adapted from WHO, 2015(b)]:

  Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age);

  AND

  If malaria with seizure: coma persisting for > 30 min after the seizure.

  Other treatable causes of coma should be excluded before diagnosing cerebral malaria (e.g. hypoglycaemia, bacterial meningitis).

Note: Suspected malaria cases routinely tested using RDT will have a blood smear for reading by microscopy in parallel, in order to measure sensitivity and specificity. This will be done for all suspected cases presenting at primary health care facilities one day per month during the first year of the study.

9.2.6.7. Anaemia

- All anaemia: haemoglobin <11g/dL [Stoltzfus, 1993].
- Severe anaemia: haemoglobin <7g/dL [Stoltzfus, 1993].

9.2.6.8. Hospitalisation

- Hospitalisation (all causes)

  A study participant requiring overnight stay in hospital/inpatient facility.

- Hospitalisation for malaria (including *P. falciparum* malaria)

  A hospitalised study participant with malaria (including *P. falciparum* malaria) and for whom malaria is the primary cause of hospitalisation.

9.2.6.9. Death

- Death – all cause

  A fatality (of any cause).

- Malaria attributed death (including *P. falciparum* malaria)

  A fatality for which malaria (including *P. falciparum* malaria) is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.

- Deaths attributed to an AE

  A fatality for which an AE is listed as a contributing cause of death, based on either verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* [INDEPTH, 2003] for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital.

* If a site is not part of the INDEPTH network, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

Deaths, including malaria attributed deaths with an uncertain diagnosis after review by the GSK safety physician, will be reviewed by the expert panel to confirm the primary/secondary cause of death (see Section 9.2.7.4.3).

9.2.6.10. Surveillance quality indicators

To ensure the quality of the surveillance that will be performed in the study sites, two surveillance quality indicators have been added based on discussion with African paediatricians (see also Section 9.9): abscess at injection site during the 7-day period (Days 0-6) after any vaccination and foot positional deformations.

Abscess at injection site after vaccination

The diagnosis and monitoring of abscess at the injection site will be used as a positive control, as this is an AE that is relatively frequently observed after routine vaccination in Africa, and is defined as:

- A localised collection of material in subcutaneous tissue, fat, fascia or muscle at the site of immunisation confirmed in spontaneous or surgical drainage of material from the mass or by presence of palpable fluctuance (defined as a wavelike motion on palpation due to liquid content). The abscess may be further classified as due to infectious aetiology, a sterile abscess or not-determined. Abscesses of infectious aetiology may be accompanied by fever/regional lymphadenopathy. Sterile abscesses are not accompanied by fever/regional lymphadenopathy.

Foot positional deformations

The diagnosis and monitoring of foot positional deformations as a birth defect will be used as a negative control (to assess changes in the performance of health care systems to diagnose disease), and is defined as:

- Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot

  OR

- Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg

  OR

- Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.

9.2.7. Study procedures

Supplementary study conduct information not mandated to be present in this protocol is provided in the Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the study participants.

In the event that a parent/LAR does not give consent for their child to participate in EPI-MAL-003, this decision will not influence their ability to access future vaccinations, including RTS,S/AS01$_E$.

9.2.7.1. Active surveillance

For the purposes of this study, study participants enrolled into active surveillance will be followed up through home visits and through continuous monitoring of outpatient visits and hospitalisations at all health care facilities. Study procedures to be conducted at scheduled study contacts/visits and during hospitalisations are detailed in Table 4 and Table 5. Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

9.2.7.1.1. Enrolment and follow-up

- Parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine (V0) (any visit for DTP/HepB/Hib vaccine) or 1st RTS,S/AS01$_E$ dose during the catch-up group enrolment period (Section 9.2.3). In case the child is first seen during hospitalisation, meeting the inclusion criteria for active surveillance (DTP group), and not having completed the visits for DTP/HepB/Hib, the child can be enrolled in active surveillance during hospitalisation – See Section 9.2.3. The parent(s)/LARs will be informed about the study and the study procedures will be explained to them. They will be asked to provide signed or witnessed and thumbprinted informed consent, according to local requirements. Reasons for non-participating will be recorded**.**

  Information on the cluster (exposed or unexposed), on the study participants' socio-demographic characteristics (e.g. date of birth and gender, the number of persons in the household) and active participation in any trial with an investigational product will be recorded at enrolment visit.

  Each enrolled study participant will be assigned a study participant study number (study participant number) and will be provided with a study ID card and study specific stickers. The stickers can be used on the health care facility's registers if no other system is in place to indicate a study participants' visit and facilitate identification of data from enrolled study participants from the facility's register.

- Each child enrolled in active surveillance will be followed-up longitudinally through community based home visits.
  - For children receiving at least one dose of RTS,S/AS01$_E$ (vaccinated children), these visits will take place approximately 1 week after administration of each dose of the primary schedule of RTS,S/AS01$_E$ (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after administration of the third dose. V6 will take place approximately 1 week after administration of the fourth dose of RTS,S/AS01$_E$ (administered approximately 18 months after the third dose). This visit will be followed by visits approximately 6 weeks (V7), 12 months (V8) and 24 months (V9) after the fourth dose as described in Table 4. A last visit (V10) will take place at study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first). If a child does not receive the complete primary schedule, V2 and/or V3 will not take place, but V4 will be done 6 weeks after the recommended scheduled visit for the third dose of RTS,S/AS01$_E$. If the child finally receives a delayed dose of the vaccine, the 1 week post vaccination visit (V2 and/or V3) will take place and V4 may take place again. If a child does not receive the 4th dose, a visit will take place approximately 24 months after the last dose received, and a last visit (V10) will take place at study conclusion.
  - For unvaccinated children (i.e. children in the exposed clusters whose parents/LARs elect not to have them vaccinated with RTS,S/AS01$_E$ or children in the unexposed clusters), visits will be scheduled at equal points in time. The visits will take place 1 week (V1, V2, V3), 6 weeks (V4) and 6 months (V5) after the recommended scheduled visit for the primary series of RTS,S/AS01$_E$. Additional visits will be conducted at 1 week (V6), 6 weeks (V7), 12 months

(V8) and 24 months (V9) after the recommended scheduled visit for the 4th dose of RTS,S/AS01$_E$. A last visit (V10) will take place at study conclusion.

– If a child has been initially followed according to the schedule for the unvaccinated group, and finally receives a dose of RTS,S/AS01$_E$, the child will start the active follow-up of the vaccinated group as of V1, limited to a time period up to study end (which could be less than 2 years of follow-up after the last dose of RTS,S/AS01$_E$). This child will be considered unvaccinated until he/she receives the first dose of RTS,S/AS01$_E$.

Two attempts should be made to visit the child at home within the month of the scheduled follow-up visit/study conclusion visit before it is abandoned.

Information on dates of vaccine administered (RTS,S/AS01$_E$) and other vaccines as part of routine immunisation (administered concomitantly, or any time before, or prior to RTS,S/AS01$_E$ during the study period) will be recorded at each home visit (see also Section 9.3.3.1 for ascertainment of vaccine history).

Surveillance of AESI, other AE leading to hospitalisation, meningitis and malaria will be performed as described below.

Data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms (whether prescribed or self-medicated), and exposure to environmental hazards such as chemicals will be recorded at each visit. In addition, information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, and information on medication administered in anticipation of a reaction to the vaccination will be recorded (see Section 9.3.3).

- All health care facilities (primary health care and hospital level) will report to the study staff any diseases, signs and symptoms in children enrolled in the active surveillance, up to the end of the active follow-up period for each individual child. After the home visit 2 years after last dose (or equal point in time for unvaccinated), there will still be continuous reporting of hospitalisations up to study conclusion. If a child is diagnosed with a SAE, the child will be followed for an additional 12 months to further characterise the event. Follow-up for the SAE disposition is described in Section 11.5.

(Amended 15 October 2020)

9.2.7.1.2. Surveillance of AESI, meningitis and malaria during follow-up

The surveillance of AESI, meningitis and measures of malaria burden will be done at different levels in line with the surveillance strategy implemented for the EPI-MAL-002 study:

- **Scheduled home visits**

  Active surveillance will be performed by trained community health workers through home visits. Medical history (e.g. chronic co-morbidities, such as known HIV

infection, or congenital disease, such as known hemoglobinopathies) will be recorded at the first visit (V1) and a basic physical examination will be performed at each visit. Community health workers will use visual aids and other training materials to detect any potential signs and symptoms indicating that the child is sick (such as change in food/milk intake, crying, identification of dehydration, bleeding, oedema, jaundice, neck stiffness). They will also be trained to recognise symptoms and signs of AESI and meningitis and be instructed to measure body temperature systematically of all children. Any signs and symptoms detected during examination or in the past 48 hours preceding the visit will be recorded in the electronic case report form (eCRF). Children who are sick, have an acute condition or with disabilities will be referred to health facilities for further assessment and care that will be dispensed according to routine medical practice, including consultation, laboratory tests and treatment. Any child with fever (≥ 37.5°C) and symptoms suggestive of malaria will be referred to the primary health care facility or hospital where diagnosis of malaria will be ensured using RDT and/or microscopy. Referral will be recorded in the eCRF.

At follow-up visits 1 and 3, and at study conclusion, the parent/LAR will be asked for any noticed or previously diagnosed abnormalities while checking for developmental milestone delays and presence of physical disability using the study specific guidance document (see Annex 6).

In the event of death occurring at home, the cause of death will be systematically obtained through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] as is routinely done in the study area.

If a site is not part of the INDEPTH network, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

- **Reporting by primary health care facilities and hospitals**

  Health care staff serving paediatric patients in all the primary health care facilities and hospitals in the study area will inform the study staff about any diseases, signs and symptoms among children enrolled in active surveillance, up to the home visit 2 years after the last dose of RTS,S/AS01$_E$, or equal point in time for unvaccinated. Thereafter there will still be continuous reporting of hospitalisations until the child reaches 5 years of age, or study end, whichever comes first. Children reporting a SAE ***due to study procedure might*** have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months.

  To maximise the possibility of capturing an AESI, meningitis, or malaria, an active search will be performed by the study staff through hospital rounds and by regular (at least 3 times a week) review of patient records at primary health care facilities.

  The eCRFs for the reporting of AESI, meningitis, or malaria will allow timely reporting of the first signs and symptoms detected by the community health workers and health care staff and completion of diagnostic information, as more results from examination in hospitals with specialised care become available. Clinicians in charge of the patients may seek consultation with RAFT study physicians for case confirmation. Data entry is described in Section 9.6.

The maximum intensity (mild, moderate, severe) of each AESI, and meningitis recorded in the eCRFs will be assigned to categories.

In case a child enrolled in the active surveillance is hospitalised at any time during the study, then procedures should be followed as for hospitalisations of the children enrolled in the enhanced hospitalisation surveillance (see Section 9.2.7.2).

(Amended 15 October 2020)

9.2.7.1.3. Surveillance of other AE leading to hospitalisation during follow-up

The surveillance of other AE leading to hospitalisatin will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.

(Amended 15 October 2020)

9.2.7.1.4. Surveillance for death

The surveillance of death will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.
(Amended 15 October 2020)

9.2.7.1.5. Study conclusion

Study participants will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit), a record will be taken of any vaccinations received and of the study participants' health and vital status and any disability.

The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

9.2.7.1.6. Outline of study procedures

Table 4 List of study procedures for participants in active surveillance

Epoch	1											
Type of contact	**Enrolment V0** [1]	**At time of each routine vaccination**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Study conclusion V10** [2]
Visit days			**1W (5-10 D) after 1st RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 2nd RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6W (40-50 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6 M (±2 W) after 3rd RTS,S dose or equal point in time for unvacc.**	**1 W (5-10 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**6 W (40-50 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**12 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**24 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**Study end or child reaches 5 years of age, whichever occurs first *(±2 W)***
Time point (Month) [3]			**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Informed consent	●											
Cluster specification (exposed/unexposed)	●											
Check inclusion/exclusion criteria	●											
Assign study participant study number	●											
Provide study ID card and study-specific stickers	○											
Record socio-demographic characteristics and active participation in any trial with an investigational product	●											
Record administration of RTS,S/AS01$_E$ [4]			●	●	●			●				

Epoch	**1**											
Type of contact	**Enrolment V0** [1]	**At time of each routine vaccination**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Study conclusion V10** [2]
Visit days			**1W (5-10 D) after 1st RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 2nd RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6W (40-50 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6 M (±2 W) after 3rd RTS,S dose or equal point in time for unvacc.**	**1 W (5-10 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**6 W (40-50 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**12 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**24 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**Study end or child reaches 5 years of age, whichever occurs first *(±2 W)***
Time point (Month) [3]			**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Record any other vaccination [5]			●	●	●	●	●	●	●	●	●	●
Record brief medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies)			●									
Record any outpatient visits and hospitalisations at all health care facilities			●	●	●	●	●	●	●	●	●	
Conduct physical examination including systematic measurement of body temperature			●	●	●	●	●	●	●	●	●	

Epoch	**1**											
Type of contact	**Enrolment V0** [1]	**At time of each routine vaccination**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Study conclusion V10** [2]
Visit days			**1W (5-10 D) after 1st RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 2nd RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6W (40-50 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6 M (±2 W) after 3rd RTS,S dose or equal point in time for unvacc.**	**1 W (5-10 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**6 W (40-50 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**12 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**24 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**Study end or child reaches 5 years of age, whichever occurs first *(±2 W)***
Time point (Month) [3]			**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Record any detected signs and symptoms including AESI, other AE, leading to hospitalisation, meningitis, malaria, abscess at injection site, foot positional deformations			●	●	●	●	●	●	●	●	●	
Refer sick children and children with disabilities to outpatient clinic or hospital according to clinical diagnosis			●	●	●	●	●	●	●	●	●	
Record information about malaria control measures, health care seeking behavior, drug use and exposure to environmental hazards			●	●	●	●	●	●	●	●	●	

Epoch	**1**											
Type of contact	**Enrolment V0** [1]	**At time of each routine vaccination**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Study conclusion V10** [2]
Visit days			**1W (5-10 D) after 1st RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 2nd RTS,S dose or equal point in time for unvacc.**	**1W (5-10 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6W (40-50 D) after 3rd RTS,S dose or equal point in time for unvacc.**	**6 M (±2 W) after 3rd RTS,S dose or equal point in time for unvacc.**	**1 W (5-10 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**6 W (40-50 D) after 4th dose of RTS,S or equal point in time for unvacc.**	**12 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**24 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.**	**Study end or child reaches 5 years of age, whichever occurs first *(±2 W)***
Time point (Month) [3]			**M0**	**M1**	**M2**	**M3.5**	**M8**	**M20**	**M21.5**	**M32**	**M44**	
Record any serious delay in developmental milestones or physical disability			●		●							●
If death, record verbal autopsy diagnosis [6]			●	●	●	●	●	●	●	●	●	●
Study conclusion												●

● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF)

○ is used to indicate a study procedure that does not require documentation in the eCRF

1. Enrolment for the DTP group will be done during a visit for administration of DTP/HepB/Hib vaccine – see Figure 1 for definition of V0. Completion of Enrolment visit procedures should be achieved within a maximum of 10 days after the administration of DTP/HepB/Hib vaccine for the DTP group or at Visit 1 for the catch-up group.
2. A last visit will be conducted at study end or when the child reaches 5 years of age, whichever occurs first.
3. Study months may be adapted according to the schedule implemented at each study site.
4. To be administered via EPI system at EPI clinics and/or outreach registers (for children in the vaccinated group).
5. Standard immunisations will be recorded.
6. Using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home and through medical records for children who died at a health care facility. If a site is not part of the INDEPTH network, INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

(Amended 15 October 2020)

9.2.7.2. Enhanced hospitalisation surveillance

For the purposes of this study, study participants from both exposed and unexposed clusters enrolled in enhanced hospitalisation surveillance will have data collected from hospitalisation visits.

Table 5 provides detail on the procedures to be conducted for children enrolled in enhanced hospitalisation surveillance at or around the time of hospitalisation.

Data regarding the hospitalisation will be uniformly collected whether the child is enrolled in active surveillance or in enhanced hospitalisation surveillance.

9.2.7.2.1. Informed consent (for study participants not enrolled previously, i.e. for previous hospitalisation or for active surveillance)

Freely given and written or witnessed and thumbprinted informed consent must be obtained from each study participant's parent(s)/LAR(s), as appropriate, prior to participation in the study. Refer to Section 10.1 for the requirements on how to obtain informed consent.

In case routine procedures are performed before the informed consent form (ICF) signature, collection of those data for the study CRF will be done retrospectively once the ICF is signed or witnessed and thumbprinted. No study specific procedures will be performed before the ICF is signed or witnessed and thumbprinted.

9.2.7.2.2. Check inclusion and exclusion criteria (for study participants not enrolled previously)

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.3 and 9.2.4 before enrolment.

9.2.7.2.3. Assign study participants study number (for study participants not enrolled previously)

Provide study ID cards and assign study participant study number and record in the eCRF for all newly enrolled study participants (for study participants already enrolled - previous hospitalisation or for active surveillance - the same study participant study number applies). A holder will be provided for carrying the study participant's ID card/study stickers together with other records e.g. child growth record, immunisation record to avoid double enrolment.

In the event that a <18 months old child eligible for active surveillance (DTP group) is first detected during hospitalisation before the active surveillance recruitment is completed, parents/ LARs (according to local requirements) will be invited to enrol their child in active surveillance. If consenting, they will be provided with study-specific stickers and a follow-up visit will be scheduled for active surveillance in the DTP group (see Section 9.2.7.1). For all study participants enrolled into active surveillance, study-specific stickers with the study participant's study number should be used at health care facilities to identify any visit of the study participant in the facility register if no other system is in place.

9.2.7.2.4. Collect demographic data (for study participants not enrolled previously)

Record cluster specification (exposed/unexposed), socio-demographic data (e.g. date of birth and gender, the number and age of persons in the household), and active participation in any trial with an investigational product in the study participants' eCRF.

9.2.7.2.5. Record type of health care facility

Record type of health care facility.

9.2.7.2.6. Record any serious delay in developmental milestones or physical disability (for study participants not enrolled previously and at study conclusion)

Perform an assessment of developmental milestones and physical disabilities according to the study specific guidance document (see Annex 6).

9.2.7.2.7. Health history

Record medical history (e.g. chronic co-morbidities, such as known HIV infection, or congenital disease, such as known hemoglobinopathies), and perform a physical examination. Ask the parent/LAR for any noticed or previously diagnosed abnormalities. Record any pre-existing conditions present in a study participant prior to the start of the study.

9.2.7.2.8. Record information about health care seeking behaviour, malaria control measures, drug use and exposure to environmental hazards

Record data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated). Record also information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals (see Section 9.3.3).

9.2.7.2.9. Record standard vaccinations

Record all immunisations received, including type and dates, in the eCRF. Update if needed with vaccinations received since the last visit. See also Section 9.3.3.1 for ascertainment of vaccine history.

9.2.7.2.10. Record diagnosis

Record main diagnosis and any secondary diagnoses made by the physicians in the eCRF.

9.2.7.2.11. Record haemoglobin measurement

For all hospitalised study participants, measurement of haemoglobin concentration, if available, at hospital entry will be recorded in the eCRF.

9.2.7.2.12. Record deaths

In the event of death occurring at the hospital, the cause of death from the medical record or the death certificate will be recorded in the eCRF.

9.2.7.2.13. Record cases of suspected AESI, other AE leading to hospitalisation, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations

For all suspected AESI or any meningitis case, details of risk factors, medication history and results of the clinical examination and diagnostic testing (Annex 6) will be recorded in the eCRF. A blood sample will be taken for storage for all AESIs and meningitis (see Section 9.2.7.3). For all cases suspected of meningitis or neurological AESIs, a part of the CSF sample, collected according to routine practice, will be stored for further confirmatory testing (see Section 9.2.7.3.1). Final diagnosis will be recorded in the eCRF.

Children diagnosed with meningitis, cerebral malaria or with an AESI will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

For all hospitalisations, details of risk factors, medication history and results of the clinical examination as well as the final diagnosis will be recorded in the eCRF.

For suspected malaria, malaria microscopy and/or RDT or other results, such as retinoscopy for cerebral malaria (refer to Section 9.2.7.3.1) will be recorded in the eCRF.

For foot positional deformations and abscess at injection site after vaccination, record in the eCRF.

9.2.7.2.14. Record and report adverse events

Refer to Section 11.2 for the time period for the investigator to record AEs. Refer to Section 11.3 for guidelines on how to record AEs via eCRF.

The study participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the study participants manifest any signs or symptoms they perceive as serious.

9.2.7.2.15. Study conclusion

Study participants will exit the study when they reach 5 years of age or at study end (whichever occurs first), if not earlier due to migration or in the event of death.

At the study conclusion (home visit), a record will be taken of the study participant's health and vital status, any disabilities and all vaccinations received. The investigator will review collected data to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

Note: For subjects enrolled in EHS, data collection of other AE leading to hospitalisation will be stopped as from 01 January 2023 in sites not participating in EPI-MAL-002. For those subjects, a study conclusion visit will be conducted in a timely manner from 01 January 2023. For subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge.

(Amended 15 October 2020)

9.2.7.2.16. Outline of study procedures

Table 5 List of study procedures to be conducted in the event of hospitalisation

Type of contact	Hospitalisation visit	Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) *(±2 W)*
Study participants not enrolled previously (either in active surveillance or in enhanced hospitalisation surveillance)		
Informed consent	●	
Cluster specification (exposed/unexposed)	●	
Check inclusion/exclusion criteria	●	
Assign study participant study number	●	
Provide study ID card (to all study participants not enrolled previously) and study-specific stickers (only to eligible study participants <18 months not enrolled previously in DTP group and enrolled before the active surveillance recruitment is terminated)	○	
Record socio-demographic characteristics and active participation in any trial with an investigational product	●	
All study participants		
Record type of health care facility	●	
Record brief medical history	●	
Record information about malaria control measures, health care seeking behaviour, drug use and exposure to environmental hazards	●	
Record any serious delay in developmental milestones or physical disability	●[4]	●
Record all vaccinations [1]	●	●
Identify if specific signs and symptoms present (standard for AESI screening among all hospitalisations)	●	

Type of contact	**Hospitalisation visit**	**Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) *(±2 W)***
Record diagnosis with major symptoms and test results	●	
Record measurement of haemoglobin concentration	●	
Record any cases of death and cause of death	●	●
Record risk factors	●	
Record medication history	●	
Confirm diagnoses at discharge	●	
Only for study participants with suspected AESI, cerebral malaria or meningitis		
Consult specialised health care professional, if required [2]	○	
Record clinical examination and additional testing according to clinical diagnosis for suspected AESI[3], cerebral malaria or meningitis	●	
For each diagnosis of an AESI[3] or meningitis, collect approx. 5 mL of whole blood and store serum	●	
For each diagnosis of a neurological AESI[3] or meningitis, where a CSF sample has been taken as part of routine practice, store part of the CSF sample (minimum 500 µL)	●	
Record and report AEs	●	
Follow-up children up to study conclusion, by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge	●	
Only for study participants with suspected malaria		
For suspected malaria, record malaria microscopy and/or RDT or other result	●	
Study conclusion		●

● is used to indicate a study procedure that requires documentation in the individual eCRF
○ is used to indicate a study procedure that does not require documentation in the eCRF
[1] Standard immunisations will be recorded.
[2] See Study Procedures Manual (SPM)
[3] See Annex 5
[4] For study participants not enrolled previously

For subjects enrolled in EHS in sites not participating in EPI-MAL-002, a study conclusion visit will be conducted in a timely manner from 01 January 2023.

(Amended 15 October 2020)

9.2.7.3. Biological sample handling and analysis

9.2.7.3.1. Biological samples

All enrolled study participants admitted to the hospital are expected to have routine laboratory tests performed according to good medical practice and routine practice (see Section 9.2.7.6), including, but not limited, to:

- All hospitalised children: haemoglobin concentration or full blood count.
- Malaria suspects: access to diagnosis of malaria using RDT and/or microscopy (according to routine practice) will be ensured for all children clinically suspected of malaria during active surveillance and at any of the health care facilities.

- Meningitis suspects: CSF examination (and blood culture if feasible) according to routine practice (first line testing).
- Neurological diseases such as seizures, encephalitis, Acute Disseminated Encephalo-Myelitis (ADEM), Guillain-Barre syndrome suspects: require neurological investigations (e.g. magnetic resonance imaging if available), eventually CSF analysis and other laboratory testing according to routine practice.
- Some AESI (such as diabetes mellitus, renal failure, hepatic failure, severe thrombocytopenia with bleeding): require laboratory testing for case management.

For all hospitalised children suspected of having an AESI or meningitis, a sample of approximately 5 mL of whole blood will be collected; a sample of at least 500 µL of CSF would be ideally collected for all cases of a suspected neurological AESI (seizures, encephalitis, ADEM, Guillain-Barre syndrome suspected) or meningitis, when a CSF sample is taken as part of routine practice.

Full details for obtaining, storing and shipment of biological samples will be provided in the SPM.

Samples will not be labelled with information that directly identifies the study participants but will be coded with the identification number for the study participant (study participant number).

Collected samples will be used for protocol mandated research. In addition, these samples may be used to perform research related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all study participants in countries where this is allowed will be invited to give another specific consent to allow GSK or a contracted partner to use the samples for future research including development of tests and their quality assurance. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing, in the context of the study, will be done in line with the consent of the individual study participant’s parent(s)/LAR(s).

Refer also to the Investigator Agreement (Annex 9), that notes that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last study participant performed the last study visit/contact), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the study participants consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

9.2.7.3.2. Laboratory assays

Any biological sample evaluation will be limited to the scope of this study and only related to assessment of study endpoints; it could include, for example, serology or deoxyribonucleic acid polymerase chain reaction (PCR) for infectious diseases or confirmatory tests for autoimmune diseases.

For all required biological sample evaluations, details of assay type, assay method, test kit/manufacturer and laboratory used, as applicable for the test conducted, will be recorded.

The principal investigator or designee of each study site/cluster will ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents. In case second line confirmatory testing is required (for instance PCR for meningitis or antibody testing for auto-immune AESI), samples will be sent to a qualified referral second line laboratory in South Africa (Clinical Laboratory Services [CLS]).

9.2.7.4. Case ascertainment

For the purpose of this study, a panel of experts will be set up and a charter will be defined. As much as possible, the same experts will be involved in the case ascertainment process for studies EPI-MAL-002 and EPI-MAL-003, using the same rules and charter.

9.2.7.4.1. Meningitis cases

Meningitis case identification

At the site level, a suspected meningitis case, based on clinical symptoms and/or signs is defined as [adapted from WHO, 2003]:

- A child with sudden onset of fever (> 38.0 °C rectal or 37.5 °C axillary) and one or more of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign such as bulging fontanelle in children under one year of age.

Meningitis case characterisation

Further characterisation of a suspected meningitis case will imply performing a lumbar puncture for examination of CSF (and blood culture if feasible) and etiological (bacterial, viral, protozoal or fungal) search with a two-step laboratory approach.

Lumbar puncture will be performed according to routine medical practice. The diagnosis of bacterial meningitis will first be made on site, based on CSF macroscopic and microscopic examinations and blood culture if feasible (first line laboratory results). CSF tests will include selective culture for *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenza* type b; latex agglutination tests for detection of bacterial antigens (*Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenza* type b), Gram stain, white blood cell counts and cell differentiation and biochemistry testing (protein and glucose). Cryptococcal infection will be diagnosed using Indian ink, for HIV-positive children and those with unknown HIV-status, if feasible.

In addition, an external laboratory based in South Africa (CLS) is contracted to harmonize laboratory procedures, to provide Quality Assessment and Quality Control and to train laboratory technicians in all sites. If needed, in case of stock out, GSK will assess the need of supplementing reagents and consumables.

Based on these first examinations, the diagnosis of bacterial meningitis will be made by the physicians in charge of the children, with support from RAFT upon request from the investigators. Job Aids for medical staff and training on standardised diagnosis are put in place ***as*** in EPI-MAL-002 to improve the sensitivity and specificity of the case diagnosis for all meningitis. Decisions to start treatment of children with suspected meningitis will be based on the medical routine practice and should not be delayed by the second line laboratory investigations.

All collected CSF samples, regardless of first line testing outcome, will be shipped to a referral second line laboratory based in South Africa, CLS (unique for all sites) for identification of bacterial, viral, protozoal and fungal meningitis using molecular testing such as PCR.

Final meningitis case ascertainment

A specific subgroup of two experts will perform case ascertainment following strictly the definitions for meningitis as described in Section 9.2.6.4; the definition of aetiology-confirmed meningitis being highly specific. Two experts will independently review all the cases. The experts will be blinded with regards to RTS,S vaccine exposure as much as possible. They will use all available medical information (including the first line and second line laboratory results) and classify the meningitis cases according to the case definitions (see Section 9.2.6.4). They will also be provided with all the data available in the eCRF (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records)**.** If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

In parallel, monitoring trends over time of meningitis cases identified at site level (first line laboratory) will be done, and if GSK, with the support from the investigators, considers that the number of meningitis cases in vaccinated children is above the expected number (see Section 9.7.6.2.2), authorities will be informed as appropriate. The external panel of experts will be convened to assess the cases (using WHO methodology for case assessment [WHO, 2013]). This might trigger additional investigation on the

potential association between use of the vaccine and onset of meningitis cases using methodology such as case control or self-controlled case series (SCCS). Final decision for further investigation will be also discussed with the local authorities, taking into account any additional surveillance data collected in the countries at the same period.

This section might be adapted according to the preliminary findings for EPI-MAL-002.

9.2.7.4.2. AESI

A panel of experts in the different fields will be established and will assess whether the aetiology of the AESI is confirmed or not and whether the date of first symptoms of the disease falls within the risk period. For events (i.e. onset of the AESI) captured during active surveillance of vaccinated children, the observation period is defined as 1 year after the last dose of RTS,S/AS01$_E$. For events occurring in children enrolled only through enhanced hospitalisation surveillance or in unvaccinated children enrolled in active surveillance, the observation period will be defined as 1 year after the administration of last known dose of any vaccine.

The panel of experts will perform case ascertainment of AESI with an uncertain diagnosis and outcome after review by the GSK safety physician. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. The same procedures will be followed as for meningitis. Two experts will independently review the cases. The experts will be blinded with regards to RTS,S vaccine exposure as much as possible. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.1). Anonymized copies of the medical records including laboratory results might be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification (strictly following the case definitions) will be used for the statistical analyses.

9.2.7.4.3. Death

Death with an uncertain diagnosis after review by the GSK safety physician will be reviewed by the external panel of experts. These cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external expert review. Two selected experts will independently review ***and confirm the possible cause of death***. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases ***according to the cause of death.*** Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

(Amended 15 October 2020)

9.2.7.4.4. Other AE leading to hospitalization

Other AE leading to hospitalisation or with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts as described in Section 9.2.7.4.3.

(Amended 15 October 2020)

9.2.7.4.5. Malaria

Enrolled children presenting at health facilities (outpatient and inpatient) with signs and symptoms of malaria will receive malaria testing (RDT and/or microscopy) as part of standard care in the country (see Section 9.2.7.6). As part of good medical practice, the clinical staff will ensure that all study participants diagnosed with malaria will receive adequate care following national guidelines.

GSK will consider the following definition for cerebral malaria cases: severe *P. falciparum* malaria with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age), and, if malaria with seizure: coma persisting for > 30 min after the seizure (see Section 9.2.6.6 [WHO, 2015(b)]). It should be noted that these coma scores are not specific for malaria and other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis) should be excluded. Therefore, each severe malaria case will be reviewed by GSK medical staff according to standard procedure for signal detection. In addition, a panel of experts will perform case ascertainment. The same procedures will be followed as for meningitis and AESI. Two selected experts will independently review all cerebral malaria cases and severe malaria cases with an uncertain diagnosis and outcome after review by the GSK safety physician. These last cases will be flagged in the eCRF during the manual cleaning by the GSK safety physician, for external experts' review. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.6). Anonymized copies of the medical records including laboratory results and technical examinations may be requested by the experts. If the two experts cannot reach an agreement, then the different clinical opinions of the experts will be listed. This final classification will be used for the statistical analyses.

9.2.7.5. Management of AESI, other AE leading to hospitalisation, meningitis cases, malaria, abscess at injection site and foot positional deformations

Children showing defined signs and symptoms during a follow-up visit will be referred to a health care facility for further assessment if in need of investigation and care.

Children diagnosed with an AESI, meningitis or cerebral malaria will be followed up after hospital discharge up to study conclusion (i.e. study end or child reaches 5 years of age, whichever occurs first) in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge.

Case management will be performed as in EPI-MAL-002. This section might be adapted according to experiences gained during EPI-MAL-002.

(Amended 15 October 2020)

9.2.7.6. Package for standard of care

Any child participating in active surveillance presenting at primary health care level should have access to basic care that can be dispensed at this level, including:

- Consultation, essential medicines, RDT and any laboratory test available, if needed for diagnosis.
- Treatment for common diseases including malaria.

At the hospital level, any child enrolled in the study should have access to care and treatment as available, including:

- Admission and emergency care, diagnostic testing including laboratory and radiological examinations, treatment and care until discharge.
- For protocol-defined AESI and meningitis: diagnostic testing according to the algorithms (see medical Job Aid) and treatment required until the end of the study.

9.2.7.7. Capacity building

Capacity building from the sites conducting EPI-MAL-002 that will also participate in EPI-MAL-003 will be utilized to strengthen early case finding and diagnosis of the events of interest. For study sites of EPI-MAL-003 which are unexposed clusters and where the EPI-MAL-002 was not conducted, the same capacity building will be provided before start of EPI-MAL-003 and throughout the study.

- Training

  The Agence de Médecine Préventive [AMP, http://amp-vaccinology.org] will provide intensive training for the study staff, community health workers and health care professionals working at all health care facilities in the study area on diagnosis of AESI, and meningitis, and on pharmacovigilance. Appropriate training packages and educational material will be developed. The community health workers involved in active surveillance will be trained to recognize clinical symptoms, using simplified visual aids (non-medical Job Aid). Health care professionals will be trained using medical Job Aid, developed to facilitate diagnosis using decision-making algorithms.

  In addition, all sites will have access to online continued medical education, training packages (including training on AESI, meningitis, HIV and hemoglobinopathies) and a telemedicine system established by the Réseau en Afrique Francophone pour la Télémédecine [RAFT, Geneva; http://raft.globalhealthforum.net]. The latter will allow the investigators to discuss cases with their colleagues and with medical experts.

In EPI-MAL-002, health care (including EPI staff) and study staff will be trained in pharmacovigilance procedures. This training will also be provided to any new health care and study staff hired during the course of that study or for study EPI-MAL-003 using the same materials.

- Laboratory support

  GSK will support the first line laboratory testing. First, an external laboratory, CLS, is contracted to assess laboratory quality system and as needed, will provide technical assistance in quality systems as well as laboratory training and support/coaching. Second, the principal investigator or designee of each study site/cluster is requested to ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents such as lumbar puncture kits or malaria RDT for diagnosis of meningitis and malaria, respectively.

  CLS will perform PCR and serology testing on CSF and serum samples in order to complement the diagnosis done by the first line laboratory.

(Amended 15 October 2020)

9.2.8. Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Active safety follow-up through home visits may be replaced by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.***
- ***For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact.***
- ***The study conclusion home visit may be replaced by a telephone call or other means of virtual contact.***
- ***A retrospective data collection of medical events based on medical records may be implemented at any of the health care facilities.***

Note: Certain restrictions might make it impossible for parents/LARs to provide written consent for changes in study procedures during special circumstances. Parents/LARs of subjects already enrolled will provide consent verbally.

(Amended 15 October 2020)

9.3. Variables

Safety and effectiveness/impact endpoints are aligned in EPI-MAL-002 and EPI-MAL-003.

9.3.1. Co-primary endpoints

In children included in active or enhanced hospitalisation surveillance:

- Occurrence of AESI (see Section 9.2.6.1 for definition).
- Occurrence of aetiology-confirmed meningitis (see Section 9.2.6.4 for case definition).

(Amended 15 October 2020)

9.3.2. Secondary endpoints

9.3.2.1. Safety endpoints

In children included in active or enhanced hospitalisation surveillance:

- Occurrence of probable meningitis (final classification) (see Section 9.2.6.4 for case definition).
- Occurrence of clinically suspected meningitis (final classification) (see Section 9.2.6.4 for case definition).
- Occurrence of meningitis cases identified at site level (first line laboratory) (see Section 9.2.6.4 for case definition).
- Occurrence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis or malaria).
- Occurrence of febrile convulsions during the 7-day period (Days 0-6) and 1-month period (Days 0-29) following each dose of RTS,S/AS01$_E$ (see Section 9.2.6.5 for case definition).
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following each vaccination and foot positional deformation (see Section 9.2.6.10 for case definitions).
- ***Occurrence of other AE leading to hospitalisation (see section 9.2.6.3 and section 9.2.6.9 for definitions).***

  (Amended 15 October 2020)

9.3.2.2. Effectiveness and impact endpoints

In children included in active surveillance:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
  - Any malaria (including *P. falciparum* malaria) (see Section 9.2.6.6 for case definitions);
  - Severe malaria (including *P. falciparum* malaria) (see Section 9.2.6.6 for case definitions);
  - Cerebral malaria (see Section 9.2.6.6 for case definitions).

- Occurrence of anaemia at hospital entry among hospitalised children (see Section 9.2.6.7 for case definition).
- Occurrence of hospitalisation
  - All causes and hospitalisations for any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria (see Section 9.2.6.8 for case definition).
- Occurrence of death
  - All causes and malaria attributed deaths (including *P. falciparum* malaria attributed death) (see Section 9.2.6.9 for case definition)

9.3.3. Patient characteristics and potential confounding variables

9.3.3.1. Recorded in EPI-MAL-002 and EPI-MAL-003

For all enrolled study participants, socio-demographic characteristics, data on access to care and health care seeking behaviour, neighbourhood of residence (urban/rural area), distance from health facilities, use of malaria control intervention at individual level (e.g. use of bednets, indoor residual spraying, seasonal malaria chemoprevention), information on medication intake (including curative antimalarial drugs) during the 14 days preceding onset of symptoms, whether recorded (evidence of prescription) or reported (prescribed without any evidence or self-medicated) will be recorded in the eCRF. Information on medication given as treatment of an AESI, meningitis or malaria, information on medication given for chronic therapy, information on medication administered in anticipation of a reaction to the vaccination, and exposure to environmental hazards such as chemicals will be recorded. Data on vaccination, more specifically dates and doses of RTS,S/AS01$_E$ and EPI vaccine administration, as well as data on medical history including co-morbidities (e.g. chronic diseases, such as known HIV infection), or diagnosed congenital diseases, such as known hemoglobinopathies, will also be collected. In case of hospitalisation, type of health care facility will be collected.

For children enrolled in enhanced hospitalisation surveillance or hospitalised children in active surveillance, additional information on co-morbidities will be captured such as malnutrition, chronic disease or diagnosed congenital disease, known HIV infection, known hemoglobinopathies.

Of note, the vaccine history will be ascertained for all enrolled study participants through the following channels: individual vaccination cards, vaccination registers at the health care facilities and vaccination data collected during study area census rounds. If any of the sources described here above confirm vaccination, it will be assumed that vaccination has taken place for the analysis.

9.3.3.2. Recorded in EPI-MAL-005

Malaria transmission intensity (MTI) data will be collected through EPI-MAL-005 (see Section 9.4.4 for more detail). Rainfall and humidity, where available, will be collected at the study area level. Bednet use, seasonal malaria chemoprevention and other malaria control measures will also be collected at the study site population and individual level***s*** (which will be summarized at centre level).

The *P. falciparum* parasite prevalence will be measured as a way to characterise the MTI. The *P. falciparum* parasite prevalence will be computed as the proportion of study participants infected with *P. falciparum* parasitaemia divided by the total number of study participants tested, and will be estimated through annual cross sectional surveys (study start, every 12 months, and study end) during malaria peak transmission, in study participants at least 6 months and less than 10 years of age at the time of survey. These estimates will be calculated for each year and for each site separately.

Considering that the main reservoir of malaria is in the population between 5-20 years old (based on data collected in study EPI-MAL-001 parallel to the pivotal efficacy Phase III trial) and that MTI will be assessed directly following the introduction of the vaccine, it is assumed that there will be negligible herd immunity effect as a small proportion of the study participants will be vaccinated.

Moreover, the parasite prevalence will also be estimated in two different subgroups of the total cohort of the EPI-MAL-005. These two subgroups will consider only vaccine eligible study participants and only vaccine ineligible study participants, respectively. The vaccine ineligible study participants are defined as those study participants that on the basis of age would be ineligible for RTS,S/AS01$_E$ vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the recommendation for RTS,S/AS01$_E$ vaccination in the country.

Therefore, the year- and centre- specific MTI's computed on this vaccine ineligible subgroup (control group) will be included as covariates in the model of the study EPI-MAL-003 to assess annual fluctuations and/or changes due to other malaria control intervention. Note that if there is any herd effect, then the vaccine effect estimated in the EPI-MAL-003 adjusted for annual fluctuation would be an underestimation of the true vaccine effect.

In addition, the malaria control intervention use and health care seeking behaviour will also be included in the model of the study EPI-MAL-003, as centre level covariates estimated in study EPI-MAL-005 per year.

9.4. Data sources

9.4.1. HDSS (or equivalent surveillance system) databases

Each site maintains a demographic database which is updated on a regular basis to include births, deaths, immigrations and emigrations. Data regarding vaccinations may also be included in the study site database. This information is obtained through census rounds (at least once a year) and constantly updated in between the rounds with the help of key-informants living in the community. Cause of deaths is established by trained fieldworkers using the INDEPTH Standard Verbal Autopsy Questionnaire [INDEPTH, 2003] for children who died at home. From this database, the listing of children at the beginning of the study will provide the study site with a basis for recruitment of children <18 months old for active surveillance and for the total number of children < 5 years of age recorded at least once a year during the study duration. During the study, further newborns may be identified by one of several possible mechanisms (depending on the site): by subsequent HDSS or equivalent surveillance system updates, by existing community-based informers who report new births/deaths/other events to the study sites between censuses, at the time of first EPI vaccination (e.g. BCG vaccination or first DTP/HepB/Hib vaccination), or at birth (if born at a health care facility).

If a site is not part of the INDEPTH network, the INDEPTH procedures for demographic census and for verbal autopsy might be implemented to ensure consistency across study sites.

9.4.2. Active surveillance and enhanced hospitalisation surveillance

Study participants enrolled in active surveillance will have data collected during home visits, outpatient visits and hospitalisations at all health care facilities, while study participants enrolled in enhanced hospitalisation surveillance will have data collected during hospitalisation only (see also study procedures in Section 9.2.7).

The first level of screening will be done at the community level during follow-up visits by study community health workers who will be trained to recognise signs and symptoms of AESI and meningitis. Any study participants presenting with specific signs or symptoms, as described by the Job Aid tool, will be referred to the health care facility (usually primary health care facility) where the public health care staff will perform clinical assessment according to routine practice. If a suspected AESI, meningitis or severe malaria case including cerebral malaria is detected at the primary health care facility level, the study participant will be referred to a higher level health care facility (hospital) to confirm the diagnosis based on the highest level of diagnostic certainty available (see Annex 5). If another event is detected at the primary health care facility level, the study participant might be referred to a higher level health care facility according to the routine practice. In the case of a seriously sick child, this child will be referred directly to the hospital by the community health worker.

Training on AESI and meningitis diagnosis, HIV and hemoglobinopathies will be provided and support will be available from specialised health care professionals to confirm diagnosis (see Section 9.2.7.7).

The surveillance system will also be implemented in the study area at each health care level. Health care workers will record all outpatient visits (referral and non-referral) of study participants enrolled in the active surveillance up to the end of the active follow-up on a register allowing for the collection of basic data (e.g. date of visit, clinical diagnoses and rapid testing confirmation, referral or treatment). In case appropriate registers are not available in the facilities, study registers will be developed. At enrolment, study participants participating in active surveillance will be given study specific stickers with the study participant's study number. The stickers can be used on the health care facility's registers if no other system is in place to indicate a study participant's visit and facilitate identification of data from enrolled study participants from the facility's register. The recorded data will be collected retrospectively on a regular basis and encoded in the eCRF.

Every day study staff will perform a round at hospitals and other health care facilities (with hospitalisation facility) to see all newly hospitalised children that could be eligible for the study. Parents/LARs of eligible children not yet enrolled into the study should be asked if they would agree to their child's participation and signed or witnessed and thumbprinted informed consent shall be obtained.

The monthly total number of children < 5 years of age requiring hospitalisation (see Section 9.2.6.8) will be recorded in the logbook monthly for the study duration, for the purpose of the aggregated data analysis.

All enrolled hospitalised children will have their diagnosis recorded with main symptoms and results from routinely performed confirmatory tests. In the case of AESI and meningitis, additional information should be recorded according to clinical and laboratory standard of diagnosis (see Annex 5). Study staff will complete the eCRF containing all relevant information for each enrolled study participant, to include an International Classification of Diseases (ICD) code allocated by a physician. All enrolled hospitalised study participants diagnosed with suspected AESI or meningitis will have a sample of approximately 5 mL of whole blood taken; in the case of neurological AESI or meningitis requiring a CSF sample according to routine practice, where possible, an additional aliquot will be reserved. Admitted study participants are expected to receive care by hospital staff following National guidance. As part of good medical practice, the clinical staff will ensure that sick study participants admitted to hospital will receive adequate care provided by health care facilities (see Section 9.2.7.6).

AESI, other AE leading to hospitalisation meningitis, or malaria will be recorded in the eCRF. Data entry is described in Section 9.6.

The investigator will assess the maximum intensity (mild, moderate, severe) that occurred over the duration of the event for all AESI, other AE leading to hospitalisation or meningitis reported during the study. The assessment will be based on the investigator's clinical judgement.

(Amended 15 October 2020)

9.4.3. Baseline study EPI-MAL-002

The study EPI-MAL-002 is designed to estimate baseline incidence rates of AESI, other AE leading to hospitalisations, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality prior to introduction of RTS,S/AS01$_E$. It will also serve as the platform for capacity building for EPI-MAL-003, with the overall goal to increase the sensitivity and specificity of capturing rare safety events post vaccination.

(Amended 15 October 2020)

9.4.4. Malaria transmission intensity study EPI-MAL-005

Annual fluctuations in malaria incidence occur as a result of changes in transmission intensity, which may be caused by changes in environmental factors such as rainfall or changes in usage of other malaria control interventions (use of bednets for example). Therefore, by taking into account these variations in MTI and malaria control intervention coverage, more accurate estimations of the vaccine impact on malaria disease diagnosed by RDT and/or microscopy during EPI-MAL-003 will be possible. Those estimations will be used as covariates in the models, as described in Sections 9.7.7.2 and 9.7.7.3.

EPI-MAL-005 started in Q4 2014, is planned to run in parallel with EPI-MAL-002 and EPI-MAL-003, in similar if not identical settings, and will assess the following parameters: prevalence of *P. falciparum* parasitaemia, use of malaria control interventions at community level, changes in environmental factors such as rainfall, changes in health care seeking behaviour, within-site geographical heterogeneity in MTI and individual malaria prevention measures and risk factors for malaria. Compliance with DTP-based, measles and RTS,S/AS01$_E$ vaccines will also be collected.

It may happen that study participants enrolled in EPI-MAL-003 are also enrolled in EPI-MAL-005. Cases of malaria detected only during the annual home visits planned for EPI-MAL-005 will not be included in the analysis of EPI-MAL-003. However, if the cases of malaria are detected during an EPI-MAL-005 home visit that coincides with a home visit scheduled in EPI-MAL-003, the events will be captured in EPI-MAL-003.

9.5. Study size

The study targets enrolling at least 22,500 children in the exposed clusters (with at least 20,250 vaccinated children and at least 2,250 unvaccinated children) and 22,500 children in the unexposed clusters. In total, 45,000 children are estimated to be enrolled in active surveillance, assuming that the distribution according to the administration of RTS,S/AS01$_E$ in the exposed clusters will be the following:

- 10% without any dose, corresponding to 2,250 unvaccinated children (in the exposed clusters);
- 10% with an incomplete primary schedule (i.e. 1 or 2 doses), corresponding to 2,250 partially vaccinated children;

- 80% with the full primary schedule (i.e. 3 doses), corresponding to 18,000 vaccinated children. Among those children, two scenarios are considered with regards to the uptake of the 4th dose of RTS,S/AS01$_E$: either 50% (i.e. 9,000 children), or 75% (i.e. 13,500 children).

Note that the size of each exposed/unexposed cluster is assumed to be around 4,000 children, leading to a total of less than 20 clusters (currently 12 clusters are planned). As no reference values of the Intra-Cluster Correlation (ICC) for AESI, meningitis or malaria are currently available in the literature, simulations have been performed in order to estimate over dispersion in the Poisson regression model. Based on these estimations, an over dispersion of 2 is assumed for the cluster design comparison estimations.

Based on these assumptions, power estimations are presented for the main objectives in the following sections.

9.5.1. Sample size for co-primary objectives

The study size for the co-primary objectives is done for the exposed clusters in order to give precision of the incidence of the endpoints where the vaccination will take place.

Among children enrolled in the active surveillance, 20,250 children are assumed to be vaccinated (at least partially).

The co-primary objectives will estimate the incidence of AESI, and meningitis. The precision of the estimate is related to the incidence and the period at-risk of these events following any dose, with a censoring of the follow-up time when the study participant receives the next dose. For some of the AESI the incidence could be very rare (around 1/100,000 person-years [PY]) and the period at-risk considered could be from 2 weeks till 6 months for AESI, and 12 months for meningitis.

Table 6 provides an estimation of the 95% CIs based on:

- A sample of 20,250 children (2,250 partially vaccinated, and 18,000 vaccinated),
- Different numbers of detected events (for the less frequent events),
- Different risk periods following dose administration (with censoring to one month for the two first doses),
- A follow-up corresponding to the risk period after dose 4,
- A schedule with 50% of the vaccinated children receiving the 4th dose of RTS,S/AS01$_E$, or with 75% receiving the 4th dose of RTS,S/AS01$_E$ (4 doses).

For example, the 95% CI around the observed incidence of 15.5 per 100,000 PY (1 event detected, in a risk period of 6 weeks following each dose [censored at the administration of the following dose], with 50% of the study participants receiving the 4th dose of RTS,S/AS01$_E$) will be [0.4, 86.1]. Other assumptions are displayed in Table 6 (rounded to 20,250 study participants).

Table 6 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events following dose administration based on 20,250 study participants, different numbers of detected events, different risk periods and two scenarios for the 4th dose uptake of RTS,S/AS01E

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
50% of the children with primary schedule received a 4th dose (in vaccinated clusters)					
1	2 weeks	2552.88	39.2	1.0	218.2
1	6 weeks	6468.75	15.5	0.4	86.1
1	3 months	10406.25	9.6	0.2	53.5
1	6 months	17718.75	5.6	0.1	31.4
1	12 months	32343.75	3.1	0.1	17.2
3	2 weeks	2552.88	117.5	24.2	343.4
3	6 weeks	6468.75	46.4	9.6	135.5
3	3 months	10406.25	28.8	5.9	84.3
3	6 months	17718.75	16.9	3.5	49.5
3	12 months	32343.75	9.3	1.9	27.1
5	2 weeks	2552.88	195.9	63.6	457.1
5	6 weeks	6468.75	77.3	25.1	180.4
5	3 months	10406.25	48.0	15.6	112.1
5	6 months	17718.75	28.2	9.2	65.9
5	12 months	32343.75	15.5	5.0	36.1
75% of the children with primary schedule received a 4th dose (in vaccinated clusters)					
1	2 weeks	2725.96	36.7	0.9	204.4
1	6 weeks	6987.98	14.3	0.4	79.7
1	3 months	11531.25	8.7	0.2	48.3
1	6 months	19968.75	5.0	0.1	27.9
1	12 months	36843.75	2.7	0.1	15.1
3	2 weeks	2725.96	110.1	22.7	321.6
3	6 weeks	6987.98	42.9	8.9	125.5
3	3 months	11531.25	26.0	5.4	76.0
3	6 months	19968.75	15.0	3.1	43.9
3	12 months	36843.75	8.1	1.7	23.8
5	2 weeks	2725.96	183.4	59.6	428.0
5	6 weeks	6987.98	71.6	23.2	167.0
5	3 months	11531.25	43.4	14.1	101.2
5	6 months	19968.75	25.0	8.1	58.4
5	12 months	36843.75	13.6	4.4	31.7

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990]
A sample size of 20,250 study participants was used for this table.
The follow-up per study participant is computed assuming previously mentioned distribution of the administration of RTS,S/AS01E, with one-month of interval between the first three doses, which limits the follow-up of dose 1 and dose 2 when the risk period is higher than 1 month.

In addition, these incidences will be estimated, using the data collected for both active and enhanced hospitalisation surveillances, for all children less than 5 years of age during the study. Table 7 provides an estimation of the 95% CIs for the surveillances for all children less than 5 years of age based on:

- A birth cohort of 11,500 children (corresponding to the assumed birth cohort either of the exposed clusters or the unexposed clusters);
- A follow-up of 2 years (as expected to be in the EPI-MAL-002), and 5.2 years (see Section 9.2.5 for the details of study period approximated to be 62 months);
- Different numbers of detected events (for the less frequent events and chosen to estimate similar incidences with two assumed follow-ups).

For example, the 95% CI around the observed incidence of 21.7 per 100,000 PY (25 events detected) will be [14.1, 32.1] for a follow-up of 2 years ***and respectively the 95% CI around the observed incidence of 23.9 per 100,000 PY (71 events detected) will be [18.7, 30.1]) for a follow-up 5.2 years.*** Other assumptions are displayed in Table 7.

(Amended 15 October 2020)

Table 7 Estimation of the lower (LL) and upper (UL) limits of observed incidences of events among all children less than 5 years of age based on 11,500 birth cohort, and different numbers of detected events

No. of events	Period at risk	Total person-years	Incidence (in 100,000 PY)	LL (in 100,000 PY)	UL (in 100,000 PY)
Events in all children < 5 years during a follow-up of 2 years					
1	2 years	115000	0.9	0.0	4.8
5	2 years	115000	4.3	1.4	10.1
25	2 years	115000	21.7	14.1	32.1
50	2 years	115000	43.5	32.3	57.3
Events in all children < 5 years during a follow-up of 5.2 years					
2	5.2 years	297083	0.7	0.1	2.4
14	5.2 years	297083	4.7	2.6	7.9
71	5.2 years	297083	23.9	18.7	30.1
141	5.2 years	297083	47.5	40.0	56.0

Note: 95% confidence interval limits are computed using the Poisson exact method [Ulm, 1990]

9.5.2. Sample size for meningitis monitoring

The study size for the monitoring of meningitis cases is only for the exposed clusters as the monitoring will use the background incidence estimated from the EPI-MAL-002 study.

The potential risk of meningitis observed in MALARIA-055 will be further monitored using MaxSPRT method [Kulldorff, 2011].

Table 8 below provides the average accrued number of cases needed to reject H_0 (i.e. no increase in the risk of meningitis after introduction of the RTS,S/AS01$_E$ vaccine) for different upper limits T (see Section 9.7.9.2) and for different true RRs when alpha = 0.05.

Table 8 Average length of surveillance* and power for the Poisson-based MaxSPRT [Kulldorff, 2011] for different true relative risks when alpha = 0.05

	Average number of cases to reject H_0					Power (%)				
True RR	**1.5**	**2**	**3**	**5**	**8**	**1.5**	**2**	**3**	**5**	**8**
T = 8	4.80	6.70	6.89	4.29	3.05	24.60%	60.16%	**97.00%**	**100.00%**	**100.00%**
T = 10	6.08	8.29	7.43	4.37	3.10	28.16%	68.78%	**99.06%**	**100.00%**	**100.00%**
T = 12	7.48	9.66	7.67	4.43	3.14	31.60%	75.60%	**99.66%**	**100.00%**	**100.00%**

T is the expected number of meningitis cases under the null hypothesis; RR is the true relative risk
* The average length of surveillance is defined not in terms of set time period, but the time to record a certain number of meningitis cases.

With T = 10 (estimated as the cumulative number of meningitis cases based on EPI-MAL-002 background incidence, EPI-MAL-003 cohort size and period of follow-up of 1 year following dose 3), a true RR = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters. Note that the total follow-up at the end of the study will be longer which increases the power.

(Amended 15 October 2020)

9.5.3. Sample size to estimate the risk associated with the vaccination

9.5.3.1. Before-after design

The RR (for AESI, meningitis and cerebral malaria) by comparing the partially or fully vaccinated children of the EPI-MAL-003 exposed clusters versus the children of the EPI-MAL-002 (same age group and same country [site]) that would be detected with 80% power and two-sided alpha = 5% (without multiplicity adjustment and without adjustment for covariates) is given in Table 9 for different values of the baseline incidences (in PY), and the RR for mortality overall and by gender is given in Table 10.

Table 9 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the before-after design based on a Poisson regression method [PASS, *2012*]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	10827.6	64.2	19.2	3.9
6 weeks	329.8	13.7	6.5	2.4
3 months	91.9	7.8	4.3	2.0
6 months	31.4	4.8	3.1	1.7
12 months	12.8	3.2	2.3	1.5
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	9721.6	61.2	18.6	3.8
6 weeks	302.2	13.1	6.3	2.3
3 months	84.1	7.5	4.2	1.9
6 months	29.0	4.6	3.0	1.7
12 months	12.0	3.1	2.3	1.5

* This incidence corresponds to the assumption considered for meningitis
** This incidence corresponds to the assumptions considered for cerebral malaria

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, *2012*]

Period at-risk	Baseline incidence *1*000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	***2.63***	***3.87***
6 weeks	***1.85***	***2.36***
3 months	***1.62***	***1.97***
6 months	***1.45***	***1.68***
12 months	***1.32***	***1.47***
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	***2.60***	***3.80***
6 weeks	***1.83***	***2.33***
3 months	***1.60***	***1.93***
6 months	***1.43***	***1.66***
12 months	***1.30***	***1.45***

(Amended 15 October 2020)

9.5.3.2. Cluster design

In the same way, the RR (for AESI, meningitis and cerebral malaria) by comparing the partially or fully vaccinated children of the EPI-MAL-003 exposed clusters versus the children from the EPI-MAL-003 unexposed clusters that would be detected with 80% power, an over dispersion (coefficient of 2) and two-sided alpha = 5% (without multiplicity adjustment and without adjustment for covariates) is given in Table 11 for different values of the baseline incidences (in PY), and the RR for mortality overall and by gender is given in Table 12.

Table 11 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	10479.2	63.4	19.1	3.9
6 weeks	325.5	13.7	6.5	2.4
3 months	91.4	7.8	4.4	2.0
6 months	31.4	4.9	3.1	1.7
12 months	12.9	3.3	2.3	1.5
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	9141.4	59.6	18.3	3.8
6 weeks	295.0	13.1	6.3	2.3
3 months	82.5	7.4	4.2	1.9
6 months	28.6	4.6	3.0	1.7
12 months	12.0	3.1	2.3	1.5

* This incidence corresponds to the assumption considered for meningitis
** This incidence corresponds to the assumptions considered for cerebral malaria

Table 12 Detectable relative risk for mortality overall and by gender with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]

Period at-risk	Baseline incidence *1*3000/100000 PY - 80% power	
	Overall	Per gender
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	***2.65***	***3.88***
6 weeks	***1.86***	***2.37***
3 months	***1.63***	***1.98***
6 months	***1.45***	***1.69***
12 months	***1.32***	***1.48***
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	***2.60***	***3.80***
6 weeks	***1.83***	***2.33***
3 months	***1.61***	***1.94***
6 months	***1.44***	***1.66***
12 months	***1.31***	***1.46***

(Amended 15 October 2020)

9.5.4. Sample size for the effect iveness and impact on severe malaria

For the objective to estimate the effectiveness and impact of the RTS,S/AS01$_E$ vaccine on episodes of severe malaria (including *P. falciparum* malaria) diagnosed by RDT and/or microscopy, the following baseline assumptions were used for the sample size calculations:

- Alpha: 5%
- Baseline incidence rate of severe malaria: 0.03 episode per PY for moderate endemicity; 0.05/PY for high endemicity. Over all study sites (the two levels of endemicity are covered by the sites selected), the incidence of 0.03 episode per PY is considered to take the conservative approach. The study EPI-MAL-005 will provide us with the endemicity at the time of the enrolment.
- 22,500 children in the exposed clusters with assumptions around the distribution according the administration of RTS,S/AS01$_E$ as detailed at the beginning of Section 9.5.
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01$_E$.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters.
- An over dispersion (coefficient of 2).

Effectiveness (direct effect) and impact (indirect, total and overall effects) will be measured, meaning that reference and comparison groups will not include the same cohort of children depending on the analyses.

The effect which can be detected with 80% of power using the Poisson regression method [PASS, 2005], considering the study site as a covariate to adjust for the various endemicity (assumed to include a correlation equal to 0.20) has been estimated for the total and direct effects.

9.5.4.1. Effectiveness (direct effect)

The direct effect is based on the following groups:

- Reference group: Unvaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 unvaccinated children from the exposed clusters);
- Comparison group: Vaccinated children from the exposed clusters of the “After” active surveillance (i.e. EPI-MAL-003 vaccinated children from the exposed clusters).

Table 13 presents the direct effect which could be detected with 80% of power, going from 23% to 33% for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

Table 13 Detectable direct effect for severe malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

		Power	80%		
	Severe Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	31%	33%	38%
D3-> D4+1Y (50%)	0.03		22%	24%	27%
D3-> D4+1Y (75%)	0.03		21%	23%	26%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.4.2. Impact using the before-after design

The total effect for the before-after design is based on the following groups:

- Reference group: Unvaccinated children from the "Before" active surveillance (i.e. EPI-MAL-002), same age group and same country (site);
- Comparison group: Vaccinated children from the exposed clusters of the "After" active surveillance (i.e. EPI-MAL-003 exposed clusters).

Of note, sample size for impact of vaccination is estimated for the total effect, but analysis will be done also for indirect and overall effects.

Table 14 presents the total effect which could be detected with 80% of power, going from ***16***% to ***23***% for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

(Amended 15 October 2020)

Table 14 Detectable total effect for severe malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, *2012*]

		Power	80%		
	Severe Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	21%	23%	26%
D3-> D4+1Y (50%)	0.03		16%	18%	21%
D3-> D4+1Y (75%)	0.03		15%	16%	18%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.4.3. Impact using the cluster design

The total effect for the cluster design is based on the following groups:

- Reference group: Unvaccinated children from the unexposed clusters of the "After" active surveillance (i.e. EPI-MAL-003 unexposed clusters);
- Comparison group: Vaccinated children from the exposed clusters of the "After" active surveillance (i.e. EPI-MAL-003 vaccinated children from the exposed clusters).

Table 15 presents the total effect for the cluster design which could be detected with 80% of power, going from 16% to 23% for a correlation equal to 0.20, and depending on the scenario.

Table 15 Detectable total effect for severe malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

		Power	80%		
	Severe Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	21%	23%	26%
D3-> D4+1Y (50%)	0.03		17%	19%	21%
D3-> D4+1Y (75%)	0.03		15%	16%	19%

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.5. Sample size for the effectiveness and impact on cerebral malaria

The following baseline assumptions were used for the sample size calculations in order to estimate the RR of the RTS,S/AS01$_E$ vaccine on cerebral malaria:

- Alpha: 5%;
- Baseline incidence rate of cerebral malaria: 0.005 episode per PY;
- 22,500 children in the exposed clusters;
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01$_E$.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters.
- An over dispersion (coefficient of 2).

As done for severe malaria in Section 9.5.4, direct effect and indirect, total and overall effects will be measured and Poisson regression method [PASS, 2005] was used to estimate the RR which can be detected with 80% of power for the total and the direct effects.

9.5.5.1. Effectiveness (direct effect)

Table 16 presents the direct effect which could be detected with 80% of power, going from 1.88 to 2.66 for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

Table 16 Detectable direct effect in terms of relative risk for cerebral malaria with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

		Power	80%		
			Correlation of covariates		
	Cerebral Malaria		0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	2.40	2.66	3.10
D3-> D4+1Y (50%)	0.005		1.79	1.92	2.12
D3-> D4+1Y (75%)	0.005		1.76	1.88	2.07

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.5.2. Impact using the before-after design

Table 17 presents the total effect which could be detected with 80% of power, going from ***1.51*** to ***1.82*** for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

(Amended 15 October 2020)

Table 17 Detectable total effect in terms of relative risk for cerebral malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, *2012*]

		Power	80%		
	Cerebral Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	1.71	1.82	1.99
D3-> D4+1Y (50%)	0.005		1.51	1.58	1.70
D3-> D4+1Y (75%)	0.005		1.45	1.51	1.60

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.5.3. Impact using the cluster design

Table 18 presents the total effect in terms of RR which could be detected with 80% of power, going from 1.52 to 1.82 for a correlation equal to 0.20, and depending on the scenario.

Table 18 Detectable total effect in terms of relative risk for cerebral malaria in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

		Power	80%		
	Cerebral Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	1.72	1.82	2.00
D3-> D4+1Y (50%)	0.005		1.53	1.60	1.72
D3-> D4+1Y (75%)	0.005		1.45	1.52	1.61

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

9.5.6. Sample size for the effectiveness and impact on mortality rate, overall and per gender

For the objective to estimate the effectiveness and impact of the RTS,S/AS01$_E$ vaccine on mortality rate, overall and per gender, the following baseline assumptions were used for the sample size calculations:

- Alpha: 5%;
- Reference mortality rate: ***1/100PY***

*In real-life setting under 5 years mortality in SSA is estimated to be 5% (World Bank).

- 22,500 children in the exposed clusters for overall estimation and half for gender-specific estimation;
- Follow-up of one year after the administration of the third dose or follow-up from the administration of the third dose to one year following the administration of the fourth dose of RTS,S/AS01$_E$.

Moreover, as part of the cluster design, the following additional assumptions were used:

- 22,500 children in the unexposed clusters for overall estimation and half for gender-specific estimation;
- An over dispersion (coefficient of 2).

As done for severe malaria in Section 9.5.4, direct effect and indirect, total and overall effects will be measured and Poisson regression method. [PASS, 2005] was used to estimate the mortality rate ratio which can be detected with 80% of power for the total and the direct effects.

(Amended 15 October 2020)

9.5.6.1. Effectiveness (direct effect)

Table 19 presents the direct effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going ***1.56*** to ***2.00*** for overall and from ***1.88*** to ***2.66*** per gender, and depending on the scenario.

(Amended 15 October 2020)

Table 19 Detectable direct effect in terms of mortality rate ratio, overall and per gender with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	*0.01*	*1.86*	*2.00*	*2.23*	*2.40*	*2.66*	*3.10*
D3-> D4+1Y (50%)	*0.01*	*1.51*	*1.59*	*1.70*	*1.79*	*1.92*	*2.12*
D3-> D4+1Y (75%)	*0.01*	*1.49*	*1.56*	*1.68*	*1.76*	*1.88*	*2.07*

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

(Amended 15 October 2020)

9.5.6.2. Impact using the before-after design

Table 20 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from ***1.34*** to ***1.53*** for overall and from ***1.51*** to ***1.82*** per gender, and depending on the scenario.

(Amended 15 October 2020)

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, *2012*]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	*0.01*	*1.47*	*1.53*	*1.63*	*1.71*	*1.82*	*1.99*
D3-> D4+1Y (50%)	*0.01*	*1.34*	*1.39*	*1.46*	*1.51*	*1.58*	*1.70*
D3-> D4+1Y (75%)	*0.01*	*1.30*	*1.34*	*1.40*	*1.45*	*1.51*	*1.60*

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

(Amended 15 October 2020)

9.5.6.3. Impact using the cluster design

Table 21 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from ***1.35*** to ***1.54*** for overall and from ***1.52*** to ***1.82*** per gender, and depending on the scenario.

Table 21 Detectable total effect in terms of mortality rate ratio, overall and per gender in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	***0.01***	***1.47***	***1.54***	***1.64***	***1.72***	***1.82***	***2.00***
D3-> D4+1Y (50%)	***0.01***	***1.35***	***1.40***	***1.48***	***1.53***	***1.60***	***1.72***
D3-> D4+1Y (75%)	***0.01***	***1.31***	***1.35***	***1.41***	***1.45***	***1.52***	***1.61***

D3-> D3+1Y: Scenario assessing the effect one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose

D3-> D4+1Y (50%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 50% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01E

D3-> D4+1Y (75%): Scenario assessing the effect one year after the fourth dose of RTS,S/AS01$_E$ vaccine evaluated from third dose; 75% of children with the complete primary schedule (3 doses) receiving the fourth dose of RTS,S/AS01$_E$

(Amended 15 October 2020)

9.6. Data management

A validated defined electronic data collection tool will be used as the method for data collection.

In all cases, study participant initials will not be collected nor transmitted to GSK. Study participant data necessary for analysis and reporting will be entered/ transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designate. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator will be provided with a CD-ROM of the final version of the data generated at his/her investigational site.

9.7. Data analysis

All analyses will be detailed in a Statistical Analysis Plan (SAP).

Descriptive statistics will be computed by cluster status (exposed or unexposed), vaccination status, age group, gender, study site and overall, as well as by type of surveillance.

Moreover, descriptive analysis of safety endpoints will be computed for specific sub-populations such as children with hemoglobinopathy and HIV-positive children.

All comparisons, except for the meningitis cases monitoring (Section 9.7.6.2.2), will be performed separately for each of the designs described in Section 9.5 (i.e. before-after design and cluster design). As a reminder the before-after design will involve the baseline EPI-MAL-002 cohort and the EPI-MAL-003 exposed clusters from the same countries (sites) and same age group. Sensitiv***ity*** analyses will be conducted including ***all*** subjects ***from EPI-MAL-002 study (i.e. subjects*** from both age groups (6-12 weeks, 5-17 months)) using an adjustment on the age. The cluster design will involve the EPI-MAL-003 exposed clusters and the EPI-MAL-003 unexposed clusters.

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9.7.1. Study population

The eligible population is defined in Section 9.2.2.

The enrolled set will include all children enrolled in the study (i.e. either from the exposed or the unexposed clusters), through active and enhanced hospitalisation surveillance, and will include a mix of children vaccinated with RTS,S/AS01$_E$ and unvaccinated children (refer to Sections 9.2.3 and 9.2.4 for inclusion and exclusion criteria). All the information for these study participants will be collected in the eCRF (after receiving signed or witnessed and thumbprinted informed consent).

The Anaylsis set will include all evaluable study participants (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study). A detailed, comprehensive list of reasons for elimination from the Analysis set will be established at the time of data cleaning.

All analyses will be conducted on the Analysis set, unless otherwise detailed. The analyses will be done also on the enrolled set only if there are more than 5% of eliminated study participants; except for the demography where all the tables will be performed for both sets.

A detailed, comprehensive list of reasons for elimination from analyses will be established at the time of data cleaning.

Children from the exposed clusters receiving at least one dose of RTS,S/AS01$_E$ will be defined as the vaccinated study participants and will be identified either through active or enhanced hospitalisation surveillance.

The unvaccinated study participants either from the exposed or the unexposed clusters will include all children not vaccinated with RTS,S/AS01$_E$ and will be identified through active or enhanced hospitalisation surveillance.

In a same way, specific sub-populations such as children with hemoglobinopathy and HIV-positive children will be defined in order to run descriptive analyses for safety endpoints.

9.7.2. Study participant disposition

For the enrolled set and Analysis set, study participant disposition will be summarised, by study sites and overall, by computing for both exposed and unexposed clusters for children from the active surveillance and for children from the enhanced hospitalisation surveillance:

- Number of enrolled children;
- Number (%) of non-eligible children regarding inclusion and exclusion criteria (see Sections 9.2.3 and 9.2.4);
- Number of children in Analysis set;
- Main results:
  - Number of subjects with at least one AESI and number of AESI;
  - Number of subjects with at least one meningitis case and number of meningitis cases;
  - Number of subjects with at least one episode of any malaria and number of malaria cases.

(Amended 15 October 2020)

9.7.3. Demographics and characteristics at study entry

Demographics (age at study entry, gender, site, country) will be summarised for the enrolled set and the Analysis set separately from the exposed and the unexposed clusters, for the vaccinated and unvaccinated children enrolled in the active and enhanced hospitalisation surveillance using descriptive statistics.

Frequency tables will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

The subjects from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-003 unexposed clusters Analysis set will be compared for their demographic characteristics.

In the same way, the subjects from the EPI-MAL-003 exposed clusters Analysis set and the EPI-MAL-002 Analysis set will be compared.

9.7.4. Exposure description

For all study participants from the exposed clusters, the vaccine history will be summarized. As detailed in Section 9.3.3.1, vaccine history will be collected from different sources (i.e. individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system). If any of the sources confirm RTS,S/AS01$_E$ vaccination, it will be assumed that vaccination has taken place. Based on this information, the RTS,S/AS01$_E$ vaccine coverage in the exposed clusters may be estimated.

In addition, the number of RTS,S/AS01$_E$ doses received will be described for the vaccinated children. The age at each dose receipt and the time between doses will also be described using descriptive statistics.

The vaccination status will be described by type of surveillance, study site, and gender.

Exposure to other vaccines (Yes/No) during the study period will be summarised in frequency tables (n, %) for both exposed and unexposed clusters for the RTS,S/AS01$_E$ vaccinated and unvaccinated children.

The exposure to other vaccines will be compared between the baseline cohort (EPI-MAL-002) and the EPI-MAL-003 exposed clusters as well as between the EPI-MAL-003 unexposed clusters and the EPI-MAL-003 exposed clusters.

9.7.5. Analysis for co-primary objectives

9.7.5.1. Analysis population

The population will include the study participants from the active surveillance of the exposed clusters of the EPI-MAL-003 study.

A secondary population will include the study participants from the active and enhanced hospitalisation surveillance of the exposed clusters of the EPI-MAL-003 study, computing incidence for all children < 5 years.

9.7.5.2. Statistical approach

9.7.5.2.1. Incidence rate of AESI

Incidence following immunisation

The incidence rate of each AESI and other AE leading to hospitalisation will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable. The at-risk period will follow any dose, with a censoring of study participants when they receive the following dose. The minimum at-risk period for the analyses is 2 weeks. All AESI expected to occur between 0 day and 13 days following dose administration (see Table 3) will be analysed with an at-risk period of

2 weeks. The at-risk period of 6 weeks will be used for AESI expecting to occur between 14 days and 6 weeks. Finally, at-risk periods of 3 months, and 6 months will be for the AESI expected to occur between 6 weeks and 3 months, and between 3 months and 6 months, respectively.

The person-time for an event of interest (e.g. juvenile chronic arthritis) will be calculated as the time between the reference date (date of first RTS,S/AS01$_E$ vaccination for the vaccinated study participants and virtual vaccination corresponding to the week before first visit for the unvaccinated study participants) and the end of the at-risk period or the earliest of the followings:

- Date of first diagnosis of event of interest (e.g. first episode of juvenile chronic arthritis);
- Date of end of study period;
- Date when child reaches 5 years;
- Date of last contact (lost-to follow-up, defined as two unsuccessful attempts to visit the child at home within the month of the scheduled visit);
- Date of death.

Note that a child may come back into the study after a certain period of lost-to-follow-up. In such case, the person-time will only consider the duration when the child was present on site (e.g. from reference date to migration date, then from immigration date to the end).

Each AESI will be grouped as follows after case ascertainment for both confirmed and non-confirmed cases (see Section 9.2.7.4):

- Nerves and central nervous system: ADEM, encephalitis, Guillain-Barre Syndrome, HHE, generalised convulsive seizure;
- Hepato-, gastrointestinal and renal system: intussusception, hepatic failure or renal insufficiency;
- Skin and mucous membrane, bone and joints system: juvenile chronic arthritis, Stevens-Johnson syndrome/toxic epidermal necrolysis, Henoch-Schonlein purpura, Kawasaki disease;
- Systemic diseases and haematology: diabetes mellitus type I, thrombocytopenia, anaphylaxis.

Meningitis will not be grouped with other AESI and will be considered as a single endpoint (see case definition in Section 9.2.6.4).

Incidence rates of these composite endpoints will be calculated as described for individual AESI in case of multiple cases in a study participant, only the first event will be considered in this analysis.

(Amended 15 October 2020)

Incidence for children < 5 years

In addition, the incidence will be estimated for all children < 5 years. In such case, the numerator will be the number of cases of specified events during the study. The person-time denominators for each rate will be reflective of the entire community population in the age group of interest. Each child will contribute person-time until the relevant age (at study end or at 5 years, whichever occurs first).

9.7.5.2.2. Incidence rate of aetiology-confirmed meningitis

Incidence rate (and 95% CI) of aetiology-confirmed meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for an AE.

Of note, the at-risk period of 12 months will be used for meningitis. This assumption is based on meningitis cases reported in MALARIA-055. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.

9.7.6. Analysis for secondary safety objectives

9.7.6.1. Analysis population

The analyses of secondary endpoints will be conducted and adjusted by the exposure status. The same population as for the co-primary objectives (see Section 9.7.5.1) will be used.

Study participants from the active surveillance of the EPI-MAL-002 study, and study participants from the active and enhanced hospitalisation surveillance of the EPI-MAL-002 study will be used for comparison purposes with the exposed clusters of EPI-MAL-003 study in a before-after design. Subjects from the 5-17 months age group of the EPI-MAL-002 study will be included and a sensitive analysis will be conducted with subjects from both age groups (6-12 weeks, 5-17 months), using an adjustment on the age.

Moreover, study participants from the active and enhanced hospitalisation surveillance of the unexposed clusters of the EPI-MAL-003 study will be used for comparison with the exposed clusters of the EPI-MAL-003 study in a cluster design.

9.7.6.2. Meningitis cases

9.7.6.2.1. Incidence rate of aetiology-confirmed, probable and/or clinically suspected meningitis

The incidence rate (and 95% CI) of probable meningitis, the incidence rate (and 95% CI) of aetiology-confirmed and/or probable meningitis, and the incidence rate (and 95% CI) of aetiology-confirmed, probable and/or clinically suspected meningitis (final classification based on second line laboratory results and after external panel of experts review) will be estimated with the same approach as for aetiology-confirmed meningitis (described in Section 9.7.5.2.2).

9.7.6.2.2. Meningitis cases monitoring

For all suspected meningitis at the site level (based on first line laboratory results), a monthly listing report will be checked by the monitoring and GSK safety teams, and every 6 months (could be adapted based on the findings resulting from EPI-MAL-002) the number of cases of meningitis as well as the cumulative number of cases will be tabulated in the progress report. The description of the cases will be done according to the first line laboratory classification (see Section 9.2.7.4.1).

Among vaccinated subjects from both exposed and unexposed clusters, the maximum likelihood and the log-likelihood ratios will be estimated each month if new cases are detected by means of MaxSPRT method [Kulldorff, 2011] on all suspected meningitis occurring within the at-risk period at the site level. The upper limit T (needed in MaxSPRT method, [Kulldorff, 2011]) will be re-estimated based on the findings resulting at the end of EPI-MAL-002. If the log-likelihood ratio reaches a critical value (see Section 9.7.9.2) during the study, the comparison between vaccinated and unvaccinated study participants (see Section 9.7.6.7) will be done after having received the complete assessment of suspected cases (using the second line laboratory classification). For interim analysis and at the end of the study, if the threshold is not reached, the comparisons between vaccinated and unvaccinated study participants using the before-after design and the cluster design will be done anyway.

If the signal is confirmed, further investigation will be performed with additional focus on the subset of children diagnosed with meningitis (see also Section 9.2.7.4.1).

9.7.6.3. Incidence rate of cerebral malaria

Incidence rate (and 95% CI) of cerebral malaria will be estimated with the same approach as for an AE***SI*** as described in Section 9.7.5.2.

(Amended 15 October 2020)

9.7.6.4. Mortality rate

Mortality rate and 95% CI (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), both overall and by gender, will be estimated with the same approach as for an AE***SI*** as described in Section 9.7.5.2 using the entire follow-up as at-risk period. As also explained in this section, different mortality risk periods might be considered as sensitivity analyses based on the distribution of the TimetoDeath after vaccination.

(Amended 15 October 2020)

9.7.6.5. Cause of hospitalisation *due to AESI, meningitis or malaria* and death in children < 5 years vaccinated with RTS,S/AS01$_E$ and unvaccinated children < 5 years

Descriptive analysis of the causes of hospitalisation (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) will consist in computing the number of cases, person-time and incidence (with 95% CI).

Descriptive analysis of the causes of death (including AESI, other AE classified by MedDRA SOC and PT level, as well as meningitis and malaria) will be done by gender, RTS,S/AS01$_E$ vaccination status, study site and overall.

(Amended 15 October 2020)

9.7.6.6. Other AE leading to hospitalisation

Incidence rate (and 95% CI) of other AE leading to hospitalisation will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

All other AE leading to hospitalisation will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary and presented by System Organ Class (SOC) and Preferred Term (PT).

(Amended 15 October 2020)

9.7.6.7. Comparison of vaccinated and unvaccinated populations

Comparisons will be performed using the before-after design, the cluster design and comparing vaccinated and unvaccinated subjects within the exposed clusters. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons concludes on an observed imbalance in mortality in girls, the following sensitivity analyses might be conducted:

- Additional comparisons by subgroups:

  Characteristics at the first scheduled visit will be compared between boys and girls. This may allow defining subgroups based on which additional comparison may be conducted.

- Analysis according to the last vaccine administered or co-administered vaccines.

- Analyses of the cause of death:

  Depending on the distribution of the causes of death (see Section 9.7.6.5), analyses of the occurrence of death will be conducted including/excluding specific causes of death overall and by gender. At least, sensitivity analyses including and excluding death associated with malaria and, including and excluding deaths associated with accidents and poisonings will be done overall and by gender.

9.7.6.7.1. Before-after comparison

Whether for incidence following immunisation or for incidence for children < 5 years, two comparisons will be performed, in addition to the different analysis populations mentioned in Section 9.7.6.

Further analyses of AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) (see Section 9.7.5.2) will consist of a comparison of its incidence rate before (i.e. unvaccinated EPI-MAL-002

from active surveillance) and after (vaccinated EPIMAL003 from active surveillance) introduction of RTS,S/AS01$_E$ vaccine by means of a Poisson regression model with the study site as an adjusted factor. The effect of the exposure status will be assessed based on the incidence rate ratio and its 95% CI. The incidence rate following immunisation will use the at-risk period as defined in Section 9.7.5.2.1. In addition, those comparisons will be done for each group of AESI.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is equal to the incidence in the before cohort (EPI-MAL-002)
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the before cohort (EPI-MAL-002).

No adjustment on alpha will be performed.

The Poisson regression model will include the number of cases in each cohort as the dependent variable, the exposure status (vaccinated: EPI-MAL-003 [X=1] versus baseline: EPI-MAL-002 [X=0]) as a binary independent variable, the study site as a covariate, and the log-transformed total PY as an offset. Adjustment on study site will reflect the different endemicity and implementation between countries.

The details are given in Section 9.7.9.1.

Exposure determinants and potential risk factors for AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) could also be collected at study entry and evaluated using univariate and multivariable Poisson regression models only for the incidence following immunisation.

Of note, multivariable models will be conducted for a specific AESI, MedDRA SOC and PT of other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) if a signal is detected (i.e. the null hypothesis is rejected) and if a minimum number of cases of AESI, other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) is observed (at least 10 cases in total).

The adjusted covariates are described in Section 9.3.3:

- Demographic parameters such as age at reference date and gender.
- Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drugs exposure, toxic agent exposure.
- Comorbidity factors such as premature birth, history of trauma.

- Health care seeking behaviour and distance to health care facilities.
- Type of heath care facility.
- Neighbourhood of residence (urban/rural area).
- Total number of outpatient visits per centre.

This list may be adapted according to the data generated from EPI-MAL-002.

The categorisation of covariates will be described in the SAP when the final CRF is available.

Covariates occurring in less than 5% of the study participants (percentage will be computed over both cohorts) will not be included in the model.

Some predefined clinical relevant covariates might be forced into the models and will be listed in the SAP with the rationale (e.g. prior knowledge from literature).

Covariates selection will be done using both statistical significance and change-in estimate method. Confounders will be included in the multivariable models if univariate p-value will be less than 20% or if their inclusion in bivariate model along with the exposure variable (i.e. vaccine status) and study site as fixed effect, change the coefficient of the exposure variable by 10% or more.

Co-linearity (i.e. correlation among predictor covariates) will be assessed on the full model including forced-in covariate and the other selected with the variance inflation factor (level of 10% [Hair, 1995]). If it is necessary to drop a variable due to co-linearity, the decision will be made on order of clinical importance.

Then the selected set of covariates will be entered in the final model without transformations.

The analyses described above in the present section will also be conducted for each group of AESI, and for aetiology-confirmed meningitis, probable meningitis, aetiology-confirmed and/or probable meningitis, and aetiology-confirmed, probable and/or clinically suspected meningitis.

The attributable risk in the vaccinated study participants will be derived for AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) as (Risk Ratio-1)/Risk Ratio [Cole, 1971].

Finally, a model with study site considered as random effect will be performed as sensitive analysis for the analysis of AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) (Section 9.7.9.1.2).

(Amended 15 October 2020)

9.7.6.7.2. Cluster design comparison

Analyses of AESI, other AE leading to hospitalisation, meningitis or cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of the exposed and the unexposed clusters from EPI-MAL-003 by means of a random-effect Poisson regression model with the clusters as random effect.

Univariate and multivariable Poisson regression will also be conducted using the same strategy (Section 9.7.6.7.1) for selection of covariates.

(Amended 15 October 2020)

9.7.6.7.3. Exposed clusters comparison

For the exposed clusters only, analyses of AESI, other AE leading to hospitalisation, meningitis and cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of vaccinated study participants from the exposed clusters of EPI-MAL-003 and unvaccinated study partiipants from the exposed clusters of EPI-MAL-003 by means of a Poisson regression model with the study site as an adjusted factor.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

Univariate and multivariable Poisson regression will also be conducted using the same strategy (Section 9.7.6.7.1) for selection of covariates.

(Amended 15 October 2020)

9.7.6.8. Febrile convulsion

The frequency (with 95% CI) of febrile convulsion within 7 and 30 days post vaccination will be reported in all study participants from the exposed clusters.

In addition, the risk of febrile convulsions will be assessed using a SCCS analysis. Only the cases recorded in the vaccinated study participants during the active surveillance will be used. Two risk periods after vaccination will be considered: 0-6 and 7-29 days. Incidence rate with its 95% CI will be computed (see details of the statistical model in Section 9.7.9).

9.7.6.9. Surveillance indicator analysis

The analysis done on AESI will also be conducted on the incidence of foot positional deformations as a birth defect (negative control) and abscess at the injection site (positive control).

The incidence rate of the negative control should not increase after the vaccination, while an increase of the incidence rate of the positive control after vaccination is expected.

9.7.7. Analysis for secondary effectiveness and impact objectives

The analyses of effectiveness and impact will be performed only on children enrolled in the active surveillance for both exposed and unexposed clusters.

9.7.7.1. Analysis population

Two main analyses on effectiveness and impact endpoints will be performed:

- one year after the 3rd dose of RTS,S/AS01$_E$ vaccine evaluated from 3rd dose, and for children who have received the 3 doses before 12 months of age,
- one year after the 4th dose of RTS,S/AS01$_E$ evaluated from 3rd dose, and for children who have received the 3 doses before 12 months of age and the 4th dose of RTS,S/AS01$_E$ before 30 months of age.

Additional analyses will be performed on effectiveness and impact endpoints at:

- two years after the 3rd dose of RTS,S/AS01$_E$ vaccine evaluated from 3rd dose, and for children who did not receive the 4th dose of RTS,S/AS01$_E$,
- two years after the 4th dose of RTS,S/AS01$_E$ for children who received it, evaluated from the 1st dose of vaccine,
- two years after the 4th dose of RTS,S/AS01$_E$ for children who received it, evaluated from the 3rd dose of vaccine.

Comparisons will be performed using the direct effect design, the before-after design and the cluster design. All comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

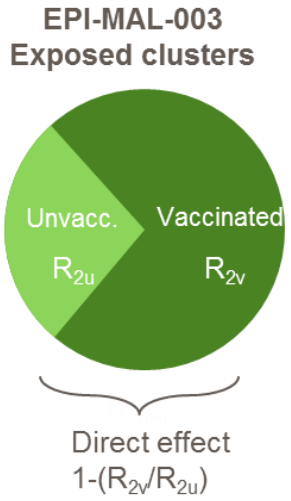
For occurrence of death, the comparisons will be done overall and by gender. If any of the comparisons will conclude on an observed imbalance in mortality in girls, additional comparisons might be performed on subgroups. Those subgroups will be defined based on the observed difference between boys and girls in the characteristics at first visit (see also Section 9.7.6.7). In addition, an analysis according to last vaccine administered and/or co-administered will also be done.

9.7.7.1.1. Effectiveness (direct effect)

For any malaria, severe malaria and cerebral malaria, vaccine effectiveness (direct effect) will be estimated on adjusted models as explained in Figure 3 [Halloran, 1997] below.

In the same way, for occurrence of anaemia and mortality rate, direct effect will be estimated.

Figure 3 Diagram on effectiveness (adapted from Halloran and Longini [Halloran, 1997])



R2v = risk of endpoint after vaccine introduction among vaccinated study participants
R2u = risk of endpoint after vaccine introduction among unvaccinated study participants

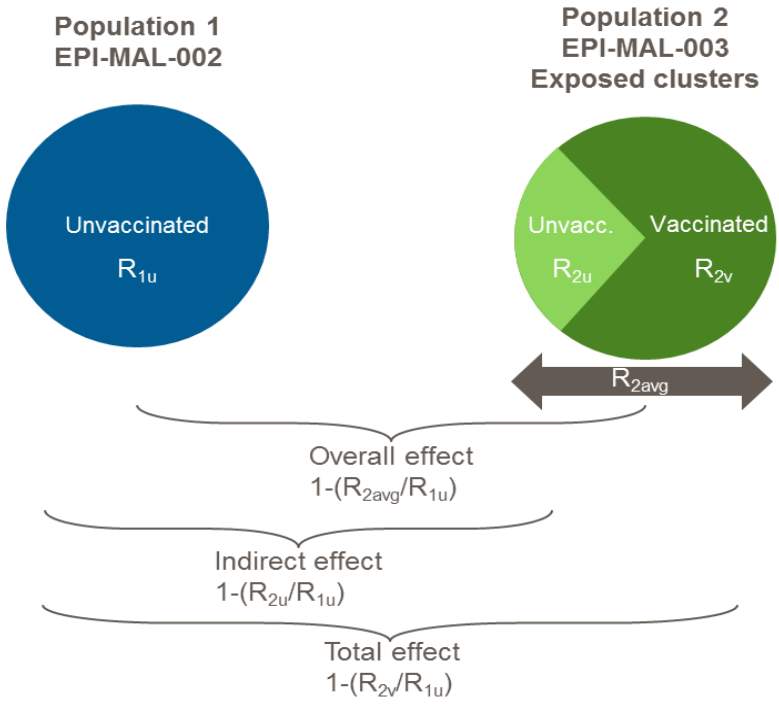
The direct effect will be computed on the exposed clusters of EPI-MAL-003 and is defined as the comparison between unvaccinated study participants and vaccinated study participants (from active surveillance).

9.7.7.1.2. Impact using the before-after design

For any malaria, severe malaria and cerebral malaria, impact of vaccination (indirect, total and overall effects) will be estimated on adjusted models as explained in Figure 4 [Halloran, 1997] below.

In the same way, for occurrence of anaemia and mortality rate, indirect, total and overall effects will be estimated.

Figure 4 Diagram on impact presenting the different vaccine effects for the before-after design (adapted from Halloran and Longini [Halloran, 1997])



R1u = risk of endpoint before vaccine introduction among unvaccinated study participants
R2v = risk of endpoint after vaccine introduction among vaccinated study participants
R2u = risk of endpoint after vaccine introduction among unvaccinated study participants
R2avg = risk of endpoint after vaccine introduction in the overall population (vaccinated and unvaccinated study participants)

The population will depend on the type of effect and is therefore detailed according to these different types:

- Indirect effect for before-after design:

  The indirect effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 (‘before’) and unvaccinated study participants from EPI-MAL-003 (exposed clusters of ‘after’) (from active surveillance).

- Total effect for before-after design:

  The total effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 (‘before’) and vaccinated study participants from EPI-MAL-003 (exposed clusters of ‘after’) (from active surveillance).

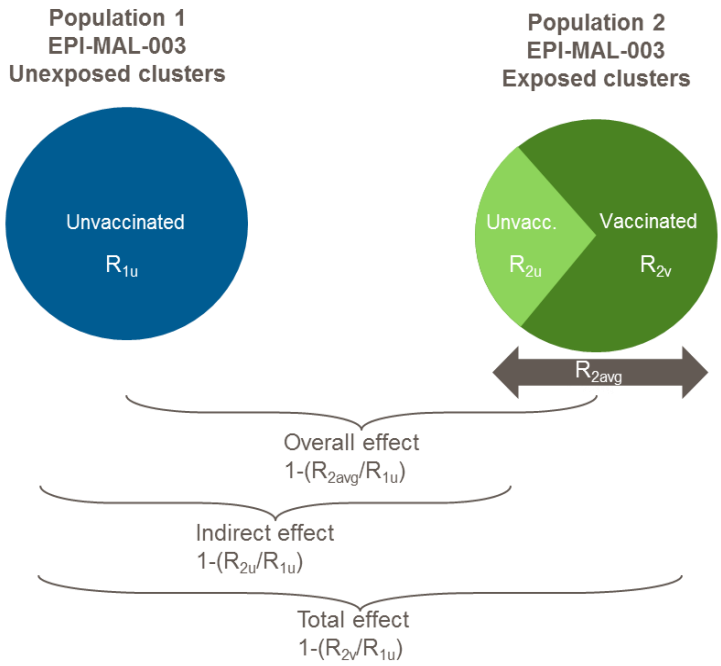
- Overall effect for before-after design:

  The overall effect is defined as the comparison between unvaccinated study participants from EPI-MAL-002 (‘before’) and vaccinated and unvaccinated study participants from EPI-MAL-003 (exposed clusters of ‘after’) (from active surveillance).

9.7.7.1.3. Impact using the cluster design

For the same endpoints, impact of vaccination will be estimated as part of the cluster design on adjusted models as explained in Figure 5 [Halloran, 1997] below.

Figure 5 Diagram on impact presenting the different vaccine effects for the cluster design (adapted from Halloran and Longini [Halloran, 1997])



R1u = risk of endpoint in the unexposed clusters
R2v = risk of endpoint in the exposed clusters among vaccinated study participants
R2u = risk of endpoint in the exposed clusters among unvaccinated study participants
R2avg = risk of endpoint after vaccine introduction in the overall population (vaccinated and unvaccinated study participants)

The types of effect for the cluster design are detailed below:

- Indirect effect for the cluster design:

  The indirect effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

- Total effect for the cluster design:

  The total effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

- Overall effect for the cluster design:

  The overall effect is defined as the comparison between unvaccinated study participants from the EPI-MAL-003 unexposed clusters and vaccinated and unvaccinated study participants from the EPI-MAL-003 exposed clusters (from active surveillance).

9.7.7.2. Comparison of incidence rate of effectiveness or impact endpoints

Incidence rates for each event will be calculated by dividing the number of cases by person-time as defined in Table 22.

For analyses using detailed information from the eCRF, children whose parents do not consent for them to take part in the active surveillance group will not be included in the denominator.

As part of the before-after design, these incidence rates will be compared by means of Poisson regression models (the dependent variable will be the number of events), using the exposure status as a binary independent variable in the model and the study site as a covariate. The details are given in Section 9.7.9.1.

Univariate and multivariable Poisson regression models will be conducted. Those adjusted covariates are described in Section 9.3.3:

- Demographic parameters such as age at reference date and gender.
- Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drug exposure, toxic agent exposure.
- Use of malaria control measures such as bednets, indoor residual spraying, seasonal malaria chemoprevention.
- Comorbidity factors such as premature birth, history of trauma.
- Health care seeking behaviour and distance to health care facilities.
- Type of heath care facility.
- Neighbourhood of residence (urban/rural area).
- Total number of outpatient visits per centre.
- Seasonal MTI (i.e. parasite prevalence) estimated in study EPI-MAL-005 on the vaccine ineligible group (see Annex 2 for definition).
- Other centre level covariates estimated in study EPI-MAL-005 per year: malaria control intervention use, bednet use and health care seeking behaviour.

The same strategy as described in Section 9.7.6.7.1 will be used for covariates selection to be included in the multivariable model.

As done for safety endpoints, for cluster-design comparison random-effect Poisson regression model will be used.

Table 22 Incidence rate and prevalence calculations for effectiveness and impact objectives (children enrolled in active surveillance)

Endpoints	Numerator	Denominator
Any malaria	# cases of any malaria Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Any *P. falciparum* malaria	# cases of any malaria due to *P. falciparum* Source: Outpatient visits and hospitalisations at all health care facilities	Person-years contribution of enrolled children
Severe malaria	# cases of severe malaria Source: Hospitalisations	Person-years contribution of enrolled children
Severe *P. falciparum* malaria	# cases of severe malaria due to *P. falciparum* Source: Hospitalisations	Person-years contribution of enrolled children
Cerebral malaria	# cases of cerebral malaria Source: Hospitalisations	Person-years contribution of enrolled children
Anaemia in hospitalised children	# cases of anaemia Source: Hospitalisations	Number of enrolled children
Death – all cause	# deaths (due to any cause) Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS (or equivalent surveillance system) register	Person-years contribution of enrolled children
Malaria attributed deaths	# cases of deaths with malaria listed as a contributing cause Source: Scheduled home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS (or equivalent surveillance system) register	Person-years contribution of enrolled children
Hospitalisation due to AESI, meningitis, malaria	# of children hospitalised for AESI,… during study period Source: Hospitalisations	Person-years contribution of enrolled children
Malaria attributed hospitalisation	# of children hospitalised during study period where malaria is listed as the primary diagnosis Source: Hospitalisations	Person-years contribution of enrolled children

Note: For cerebral malaria, incidence following immunisation will be derived (see Section 9.7.5.2.1)

9.7.7.3. Comparison of time to event of effectiveness or impact endpoints

The first occurrence of each effectiveness and impact endpoint event will be coded as a binary variable (Yes/No).

For each effectiveness and impact outcome:

- The time between reference date and date of event will be analysed using Kaplan-Meier method and Cox regression models.
- The reference date will be adapted according to the analysis population (e.g. the date of third RTS,S/AS01$_E$ vaccination for the vaccinated cohort, and the equivalent date for the unvaccinated cohort).

- The date of event will be the date of first occurrence of the event or date of death for death endpoint.
- The date of censoring will be the date of end of study period, date when the child reaches 5 years, date of death (for endpoints other than death), date of last contact, or migration date, whichever comes first.

Kaplan-Meier curves presenting the cumulative probability of an event will be displayed and compared between groups for risk factors of interest using the Log-rank test (univariate analyses).

Univariate Cox regression models will also be performed in order to obtain unadjusted hazards ratios of the risk factors of interest. In addition, a multivariable Cox regression model will be performed in order to estimate the relative contribution of each risk factor adjusting for the simultaneous effects of the other covariates. Those adjusted covariates are described in Section 9.3.3:

- Demographic parameters such as age at reference date and gender.
- Medical history and other risk factors such as chronic disease or diagnosed congenital disease, known HIV infection, malaria, malnutrition, drug exposure, toxic agent exposure.
- Use of malaria control measures such as bednets, indoor residual spraying, seasonal malaria chemoprevention.
- Comorbidity factors such as premature birth, history of trauma.
- Health care seeking behaviour and distance to health care facilities.
- Type of heath care facility.
- Neighbourhood of residence (urban/rural area).
- Total number of outpatient visits per centre.
- Seasonal MTI (i.e. parasite prevalence) estimated in study EPI-MAL-005 on the vaccine ineligible group (see Annex 2 for definition).
- Other centre level covariates estimated in study EPI-MAL-005 per year: malaria control intervention use, bednet use and health care seeking behaviour.

For covariates selection to be included in the multivariable Cox model, the same strategy as described in Section 9.7.6.7.1 for Poisson Regression will be used.

Results from the multivariable time survival analyses (Cox model) will include mean and median (if estimable) time (with 95% CI) and hazards ratios (with 95% CI). The survival curves predicted by the model will be displayed.

9.7.7.3.1. Effectiveness

The models will include exposure status and the study site as covariate. Hazard ratio will be derived with its Wald's 95% CI. The model will include the exposure status as:

- Vaccinated study participants versus unvaccinated study participants both from the EPI-MAL-003 exposed clusters.

9.7.7.3.2. Impact using the before-after design

For the before-after design, the models will include different exposure status and the study site as covariate. Hazard ratio will be derived with its Wald's 95% CI. Further models will include the exposure status as:

- Unvaccinated study participants from EPI-MAL-002 versus unvaccinated study participants from the EPI-MAL-003 exposed clusters;
- Unvaccinated study participants from EPI-MAL-002 versus vaccinated study participants from the EPI-MAL-003 exposed clusters;
- Unvaccinated study participants from EPI-MAL-002 versus unvaccinated and vaccinated study participants from the EPI-MAL-003 exposed clusters.

9.7.7.3.3. Impact using the cluster design

For the cluster design, models will include the exposure status as:

- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus unvaccinated study participants from the EPIMAL-003 exposed clusters;
- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus vaccinated study participants from the EPIMAL-003 exposed clusters;
- Unvaccinated study participants from the EPI-MAL-003 unexposed clusters versus unvaccinated and vaccinated study participants from the EPI-MAL-003 exposed clusters.

Univariate and multivariable Cox models will also be performed using same strategy for covariates selection.

In the design, as the different events from a same cluster are treated as independent observations in the Cox model, robust variance estimates adjusted for the correlation within clusters will be obtained using the robust estimation method derived as an extension of the information sandwich estimator [Lin, 1989; Zeger, 1986].

9.7.8. Statistical considerations

All the statistical calculations will be done in SAS 9.2 or higher.

Unless specified otherwise, all the statistical tests will be two-sided at alpha level of 0.05.

9.7.8.1. Handling of missing data

A worst case allocation will be done for suspected events (i.e. suspected AESI, suspected malaria) for which confirmation of the outcome is not available. In such case a sensitivity analysis will be done considering these unresolved events as confirmed.

For the determinants included in multivariable models, a complete cases analysis will be performed as primary analysis (i.e. missing data will not be substituted).

As sensitivity analysis, a precise diagnosis of missing pattern will be done to describe the kind of missing data (i.e. missing at random, missing completely at random and missing not at random). Considering the diagnosis an appropriate method of imputation will be conducted and will only concern the covariates forced in the models. The strategy will be the following:

- For continuous covariates, a multiple imputation [Rubin, 1987] method will be applied to handle missing value if missing at random mechanism is confirmed. Indeed, as noted by Sterne et al [Sterne, 2009], multiple imputations may give misleading results in case data are missing not at random;
- For categorical covariates, missing indicator method will be done (i.e. a specific category of missing value will be created).

Of note, if the "complete cases" analysis contains 90% of the study participants, no imputation will be done. In the case that for a single covariate more than 50% of values are missing, the covariate will not be included in the model.

The method of imputation will be detailed in the SAP.

9.7.8.2. Descriptive statistics

Frequency tables including number of cases and percentages will be generated for categorical variables.

Mean, standard error, median and range will be provided for continuous variables.

9.7.9. Statistical models

9.7.9.1. Poisson regression model

9.7.9.1.1. Fixed effect model

Poisson regression will be conducted using the SAS GENMOD procedure. The dependent variable is the number of events (Y). The main model (Model 1) will include the exposure status (vaccinated [$X=1$] versus unvaccinated [$X=0$]) as a binary independent variable, the study site [Z] as a fixed effect, and the log-transformed total person-time (PY) of each vaccinated and unvaccinated cohort as an offset.

Main model: $\ln(Y) = \beta_0 + \beta_1 X + \beta_2 Z + \ln(PY)$

The coefficients β_1 and β_2 are the coefficients associated to exposure effect and study sites, respectively. The risk ratio (vaccinated/unvaccinated) will be derived as the exponential of the coefficient associated with the exposure status and its 95% Wald CI.

The SAS code is:

```
PROC GENMOD data=<filename> ;
 CLASS X Z;
 MODEL Y= X Z / OFFSET=Ln_PY DIST=poisson LINK=log ;
RUN;
```

For each model, the following assumptions will be checked in order to interpret the results obtained from the Poisson regression: the outcome variable follows a Poisson distribution and does not have an excessive number of zeros. The deviance will measure the adequacy of the model. If the scaled deviance is closed to one, the regression model is adequate. Otherwise, the validity of the model is questionable. In particular, value greater than 1 indicates over dispersion.

In case of over dispersion, corrective measures will include the introduction of a dispersion parameter with respect to the Poisson model. This will be done by adding the option DSCALE and examining the fit statistics. If over dispersion is still a problem, another alternative approach such as a negative binomial distribution model will be considered.

This last method will be detailed in the further SAP. Of note, the same procedure PROC GENMOD will be adapted by specifying option DIST=negbin in the model statement:

```
PROC GENMOD data=<filename> ;
 CLASS X Z;
 MODEL Y= X Z / OFFSET=Ln_PY DIST=negbin LINK=log ;
RUN;
```

9.7.9.1.2. Mixed regression

Sensitivity analysis of the before-after design will use Mixed-Poisson model including study site as random-effect. For the cluster design, Mixed-Poisson model will also be used including clusters as random-effect. Those models will be conducted using the SAS GLIMMIX procedure.

The method will also be detailed in the SAP.

9.7.9.2. Maximised sequential probability ratio tests (MaxSPRT)

The Sequential Probability Ratio Test (SPRT) is a method adapted to safety surveillance first proposed by Spiegelhalter et al [Spiegelhalter, 2003].

One strength of SPRT is the fact that repeated measurement error adjustments are taken into account in the SPRT process. The Type I and Type II error levels also apply to the entire process (not to each specific month), hence multiplicity testing is handled.

However, SPRT is sensitive to the choice of RR required in the alternative hypothesis.

MaxSPRT, based on a composite alternative hypothesis, works well across a range of RRs [Kulldorff, 2011].

MaxSPRT will be based on:

- Null hypothesis (H0): there is no increase in the risk of meningitis after introduction of the vaccine.
- Alternative hypothesis (H1): there is a RR-fold increase of the risk of meningitis after introduction of the vaccine where RR>1.

Let C_t be the random variable representing the number of meningitis cases within D days after vaccination given in the period [0, t] (Month t, TBC) and let c_t be the corresponding number of meningitis.

Under the null hypothesis, C_t follows a Poisson distribution with mean μ_t.

For the Poisson model, the MaxSPRT likelihood ratio test statistic is

$$LR_t = e^{\mu t - Ct} (c_t / \mu_t)^{Ct}$$

when $c_t \geq \mu_t$ and LRt = 1 otherwise

The log-likelihood ratio is

$$LLR_t = (\mu_t - c_t) + c_t \ln(c_t / \mu_t)$$

when $c_t \geq \mu_t$ and LLRt = 0 otherwise

Upper limit

The MaxSPRT method uses a critical value for the different MaxSPRT based log-likelihood ratios. This critical value is defined by the alpha level and by an upper limit which is the expected number of accrued events under the null hypothesis.

Kulldorff et al [Kulldorff, 2011] provide tables based on exact calculations with critical values for different upper limits.

The null hypothesis is then rejected when the MaxSPRT based log-likelihood ratio reaches the critical value. The MaxSPRT analysis will be done based on all suspected meningitis at the site level. If the null hypothesis is rejected at one moment, the comparison between vaccinated and unvaccinated study participants will be done (see Section 9.7.6.7), after having received the complete assessment of the meningitis cases (second line laboratory classification). Of note, for interim analysis and at the end of the study, if the threshold is not reached, the comparisons between vaccinated and unvaccinated study participants using the before-after design and the cluster design will be done anyway (see Section 9.7.6.2.2).

9.7.9.3. Cox proportional hazards model

The Cox model will be computed using the SAS PHREG procedure. The dependent variable is the time between the reference date and the event. The reference date will be adapted according to the analysis population (e.g. the date of third RTS,S/AS01$_E$ vaccination for the vaccinated cohort, and the equivalent date for the unvaccinated cohort). The unvaccinated study participants could be obtained from EPI-MAL-002 or from EPI-MAL-003, either in the exposed or the unexposed clusters.

Time to event for a study participant with no event will be censored at the earliest of the following time-points:

- End of study period
- Lost-to-follow-up

- Death (for endpoint other than death).

For the before-after design, the first model will include the exposure status (vaccinated study participants versus unvaccinated study participants both from EPI-MAL-003) as a binary independent variable and the study site as a class covariate (see Section 9.7.7 for further models). The adjusted hazard ratio will be derived as the exponential of the coefficient associated with the exposure status and its 95% Wald CI.

A survival curve will be estimated for the vaccinated and unvaccinated study participants (using the Option Plots (overlay)=survival in the SAS PHREG procedure).

For the cluster design, as described in section 9.7.7.3.3, The COVS(AGGREGATE) will specified in SAS PHREG procedure to compute the robust sandwich covariance matrix estimate.

The choice of the best fitted model will be based on the consistency of the effects of the covariates observed in the different multivariable models and the Akaike's Information Criterion (AIC) and the Schwarz Bayesian Criterion (SBC).

9.7.9.4. Self-controlled case-series

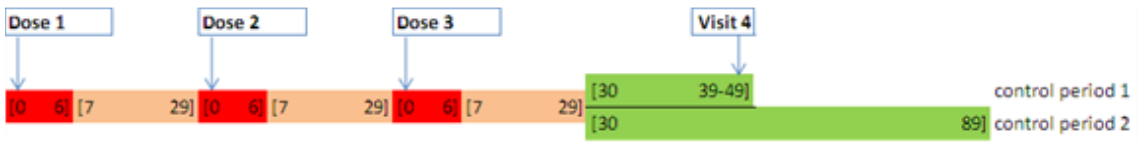
9.7.9.4.1. Background

The SCCS was developed to investigate associations between vaccination and acute potential AE [Farrington, 1995]. The SCCS is based only on cases, and provides consistent estimates of the relative incidence rate. The effect estimate is calculated as the ratio of the incidence rate of events during a given post-exposure period (risk period), to the incidence rate of events during the absence of the exposure (control period).

9.7.9.4.2. Risk and control periods

Two periods at-risk will be defined: Day 0 to Day 6, and Day 7 to Day 29, with Day 0 defined as the day of vaccination. These two periods will be compared to two different control periods: a 2-week period (between Day 30 and day of the visit 4 [Day 39-49]) and a two-month control period (between Day 30 and Day 89) after vaccination.
Two different control periods are utilised as the probability to report an event decreases after the day of Visit 4 (recall bias). The first risk period will be primarily used to analyse the risk of febrile convulsions.

Figure 6 Conceptual representation of the risk periods and two control periods



If there is more than one month between 2 doses, control periods will be considered after dose 1 and dose 2 with the same timeframe as the dose 3.

For the study participants who received several doses, risk and control periods will be defined after each dose. The risk period after Dose 1 (Dose 2) will be censored at the time of the second (third) dose vaccination in case of a second (third) dose vaccination less than 30 days after the first (second) dose vaccination. The control period after the first (respectively second) dose will be censored at the time of the second (respectively third) dose vaccination.

The post-vaccination period will be censored at the date of death or date of last contact (lost to follow-up) or date when the child reaches 5 years.

It cannot be ruled out that the probability to be vaccinated could be impacted by the occurrence of the event. However, this assumption will be assessed because the SCCS analyses will be done in a cohort setting, vaccination rate for second / third dose will be computed for the children who experience febrile convulsions after first / second dose and compared with the vaccination rate in children who don't experience febrile convulsion. In case this comparison suggests lower probability for vaccination after occurrence of febrile convulsion, the SCCS method for curtailed post-event exposure [Farrington, 2009] will be used.

9.7.9.4.3. Statistical calculations

The statistical calculation will be done in SAS 9.2 or higher using the specific SAS macro developed by Whitaker et al [Whitaker, 2006] and available online from http://statistics.open.ac.uk/sccs.

9.7.9.4.4. Mathematical model

Due to the relatively short duration of the period of observation (3 months) compared to a possible age effect, no age effect will be included in the model.

Each individual ***i*** is observed within a time interval (a_i, b_i). This interval is the observation period for the individual ***i***. The observation period for individual ***i*** is then partitioned into k=0,1 periods. Risk period, $k = 1$, corresponds to an increased risk relative to control period which is coded $k = 0$.

Conditioning on the exposure history over the entire observation period, it is assumed that events of interest for individual ***i*** arise as a non-homogeneous Poisson process with rate λ_{ik}. If n_{ik} is the number of events arising for individual ***i*** and risk period ***k***, then

$$n_{ik} \approx \text{Poisson}\left(\lambda_{ik} e_{ik}\right)$$

Conditioning on the total number of events

$$n_i = \varphi_i + \beta_k$$

arising in (a_i, b_i), the log-likelihood contribution of individual ***i*** is

$$l_i = \sum_k n_k \log\left(\frac{\lambda_{ik} e_{ik}}{\sum_s \lambda_{is} e_{is}}\right)$$

With a log-linear model for the Poisson rate of the form

$$\log(\lambda_{ik}) = \varphi_i + \beta_k$$

Where φ_i is an individual effect, and β_k is the exposure effect associated with risk period. The parameter β_k is the log relative incidence.

The log-likelihood estimate of β_k is

$$l(\beta) = \sum_i n_{ik} \log\left(\frac{\exp(\beta_k) e_{ik}}{\sum_r \exp(\beta s) e_{ir}}\right)$$

The analysis will compare the incidence rate in the 0-6 day risk period and in the 7-29 day risk period with the overall incidence rate in the two control periods: a 2-week period (between Day 30 and day of the visit 4 [Day 39-49]) and a two-month control period after (between Day 30 and Day 89) vaccination.

Point estimates of the relative incidence rate and its 95% CI will be derived.

9.7.10. Conduct of analysis

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

9.7.11. Sequence of analyses

Descriptive progress reports (including listings and statistical tables for description of AESI, other AE leading to hospitalisation, meningitis and malaria, including severe malaria and cerebral malaria) will be produced every 6 months after study start.

9.7.12. Statistical considerations for interim analyses

An interim analysis will be performed one year after the last study participant received the last dose of RTS,S/AS01$_E$ vaccine primary schedule (i.e. 3rd dose). This interim analysis will be done with clean data* on safety endpoints, and effectiveness and impact endpoints (considering one year after the third dose of RTS,S/AS01$_E$ vaccine evaluated from third dose, and for children who have received the 3 doses before 12 months of age, see Section 9.7.7.1).

Of note, further details will be provided in the SAP.

* Some data may change after the interim analysis as access to the eCRF will still be granted to sites and investigators throughout the follow-up period, until study conclusion.

Final analysis will be carried out on clean data collected up to study conclusion.

Moreover, if a safety signal is detected before that timepoint, the GSK safety physician in collaboration with the study site principal investigator and RAFT could request that the external panel of experts conduct a causality assessment. The external panel of experts may ask for ad-hoc interim analyses to conduct this assessment.

9.7.13. Statistical analyses during special circumstances

Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.

(Amended 15 October 2020)

9.8. Quality control

To comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) or other applicable guidelines, administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership and publications must be met.

9.8.1. Monitoring by GSK Biologicals site monitors or delegates

Monitoring visits by a GSK Site Monitor or delegate are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP or other applicable guidelines and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), verifying that the site staff and facilities continue to be adequate to conduct the study).

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of study participants are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV GSK understands verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor will freeze the screen, after she/he estimates that data are authentic, accurate and complete.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

9.8.2. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

9.8.3. Audits

To ensure compliance with GCP or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

9.9. Limitations of the research methods

Following the SAGE/MPAC recommendations, this protocol takes into account a follow-up of enrolled children to the age of 5 years, with events collected for each study participant in the active surveillance over 44 months. This post-implementation safety study will enrol children in the age range 5-17 months at first dose.

Some uncertainties remain regarding recommendations for use of RTS,S/AS01$_E$ in SSA and what will be the vaccine uptake at the start of the vaccine programme implementation, for both the primary series and for the 4th dose of RTS,S/AS01$_E$. Contents of the protocol might be adapted depending on NRA approval and MoH guidelines in each of the participating countries.

To better take into account the potential scenarios and to perform the study most close to routine medical practice, a cohort design that allows the prospective collection of standardised information seems to be the most suitable approach. Collecting data at a large population level (population size estimated at 45,000 study participants – 22,500 in exposed and 22,500 in unexposed clusters) is challenging from an operational perspective in SSA countries. Where possible, to base the studies on existing HDSS or equivalent surveillance system offers the opportunity to benefit from existing research and health care structures, in a population that is already part of a demographic and health indicators survey, and thus likely to be willing to participate in additional research related to malaria and the implementation of the RTS,S/AS01$_E$ as a new malaria control intervention. This approach will facilitate the early collection of data on both the safety and effects on malaria of the RTS,S/AS01$_E$ vaccine. Pre-malaria vaccine implementation of the surveillance efforts will allow the collection of data in a well-characterised population and better understanding of fluctuations over time in the community of AE (including AESI and meningitis) and malaria disease.

This study will target enrolling at least 20,250 vaccinated children for evaluation of the safety of RTS,S/AS01$_E$ (in total, 22,500 children are estimated to be enrolled in active surveillance in the exposed clusters, assuming that 80% of study participants in the exposed clusters will receive at least three doses of RTS,S/AS01$_E$, 10% will receive one or two doses and 10% will not have any dose even though they are assigned to the exposed clusters cohort).

GSK acknowledges that this sample may be limited for detection of very rare diseases for evaluation of safety of RTS,S/AS01$_E$. To address safety research with very rare outcomes, most epidemiological studies are based on existing disease-specific registries or large healthcare databases such as insurance claim databases, which do not exist in SSA at the time being. Thus, the limitation in the ability to detect increases in rare events is partly related to the fact that the vaccine will be implemented only in SSA. The enhanced hospitalisation surveillance should help to identify additional cases of AESI, other AE leading to hospitalisation, meningitis, and any severe malaria occurring in children living in the study area but not enrolled in the active surveillance.

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified. Training of physicians and field staff will start during the pre-implementation study (EPI-MAL-002). For the study sites of EPI-MAL-003 where the EPI-MAL-002 was not conducted, training will be provided before start of EPI-MAL-003. All efforts will be made to ensure an optimal standardised way of collecting data across the different sites. Progress reports every 6 months will help in monitoring the participation rate, the vaccination coverage and the trends in event detection. In the participating sites where the RTS,S/AS01$_E$ vaccine will be implemented at the beginning of the pilot implementation programme (exposed clusters), the vaccine coverage is not expected to be low. If the vaccine coverage is very high, actions will be taken to ensure that the target of 2,250 unvaccinated children (in the exposed clusters) is reached.

Detecting the occurrence of AESI and meningitis cases following immunisation with RTS,S/AS01$_E$ after its introduction in vaccination programmes are the primary objectives of this study. AESI and meningitis cases require specific diagnostic methods and such data may not be routinely collected in the study settings, potentially leading to under-reporting. Therefore, specific training and monitoring of the field teams (community health workers, health care facilities staff, physicians and hospital staff) will be provided. The reinforcement of the pharmacovigilance practices and clinical and laboratory data collection most close to routine medical practice is a key component of both studies, and of both the exposed and unexposed clusters in the EPI-MAL-003 study. All procedures will be performed in line with the current national guideline recommendations in each of the participating countries. On one hand, improvement in surveillance over time may increase sensitivity in detecting those events during EPI-MAL-003 better than in the early phase of EPI-MAL-002 and this potential bias to the before-after comparison will be taken into account when analysing data collected over time. Surveillance quality indicators will be utilised to help detect trends in changes in surveillance capacity. On the other hand, the sensitivity in detecting these events during EPI-MAL-003 might be different between the exposed and the unexposed clusters, for example due to different health care structures, different accesses to care, or different routine case ascertainment procedures. To balance for characteristics which themselves could influence the frequency of the outcome measures, clusters will be stratified by the capacity of hospitals and health facilities within the clusters, by malaria transmission (measured during the baseline period as community parasite prevalence) and by geographic location. Surveillance quality indicators will also be used to help detect differences between the clusters.

Longitudinal detection of events such as meningitis might also be difficult to interpret because of the changing meningitis disease epidemiology. The study will take place in some countries of the “meningitis belt”, which is affected yearly by bacterial meningitis epidemics (mostly meningococcal meningitis). This zone comprises 22 countries from Senegal in the West to Ethiopia in the East. During 1993-2012, nearly one million suspected meningitis cases were reported; 80% of epidemics were caused by *Neisseria meningitidis* serogroup A. Despite successful introduction of a meningococcal A conjugate vaccine in the African meningitis belt since 2010 [Novak, 2012], meningococcal meningitis outbreaks may occur in some study sites during the EPI-MAL-002 and EPI-MAL-003 study periods, due to other *Neisseria meningitidis* serogroups, or if the study site is in a region/country which has not yet introduced the

vaccine. Therefore, the interpretation of differences in meningitis incidence rates should take into account the epidemiological context of each site. As for AESI, all efforts will be made to standardize meningitis diagnosis and reach an optimal proportion of laboratory confirmed cases to establish the aetiology. The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts (blinded to RTS,S vaccination status as much as possible). Additional epidemiological investigations (such as case-control or SCCS designs) might be necessary to establish causality if meningitis cases are reported more frequently in EPI-MAL-003 than in EPI-MAL-002 or in EPI-MAL-003 exposed clusters than in EPI-MAL-003 unexposed clusters. In addition, other evidence such as data generated by the meningitis surveillance in place in those countries, or the monitoring of meningitis in the older non-vaccine eligible children will be taken into account for the analysis of the events.

Because surveillance will be conducted in study areas covering mainly rural areas, children who are severely ill might die before being transported to hospital. In EPI-MAL-002 and EPI-MAL-003, in the event of death, the cause of death will be systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire* for children who died at home or medical judgment/medical records for children who died at a primary health care facility or hospital. However, ascertaining the cause of death remains a concern considering the limitation of the verbal autopsy methods in the field, this is why all-cause mortality is an important endpoint to consider in this study.

*If a site is not part of the INDEPTH, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

All efforts will be made to standardize data collection during EPI-MAL-002 and EPI-MAL-003, both in exposed and unexposed clusters. However, due to the long duration of both studies, changes in diagnostic procedures, implementation of malaria control measures such as seasonal malaria chemoprevention [WHO, 2012(a)], and changes in treatment measures will have to be considered during the analyses of the safety and effectiveness/impact data. Potential confounders will be collected at individual level during EPI-MAL-002 and EPI-MAL-003 and at community level during EPI-MAL-005. Some study participants might also leave the study area during the study period but this is regularly documented through demographic census (scheduled at least once a year during the study periods).

In addition to the 22,500 children in the unexposed clusters, this study will target enrolling at least 2,250 unvaccinated children in the exposed clusters for evaluation of effectiveness and impact of RTS,S/AS01$_E$. The uncertainty about recruitment of a sufficiently large unvaccinated group in the exposed clusters will be clarified when vaccine recommendations by the respective MoH will be known. Estimates for direct effect based on the population size were computed using the most conservative assumptions. The vaccine uptake in the exposed clusters may be very high and the number of unvaccinated children in EPI-MAL-003 may be too low to reliably estimate the direct vaccine effect. In this instance, the unvaccinated comparison group may have

to be derived from EPI-MAL-002 (estimations of the overall and total vaccine effects in the before-after design) or from the EPI-MAL-003 unexposed clusters (estimations of the overall and total vaccine effects in the cluster design). The addition of an unvaccinated cohort in EPI-MAL-003 (either from the exposed or the unexposed clusters) should address most concerns with regards to biases potentially introduced in the 'before' (EPI-MAL-002) and 'after' (EPI-MAL-003 exposed clusters) impact approach. It should provide an estimate of effectiveness (direct effect); together with data gathered during EPI-MAL-002 or in EPI-MAL-003 unexposed clusters, the indirect, total and overall effects may be estimated through two different approaches (Section 9.7.7). Potential differences between vaccinated and unvaccinated groups cannot be excluded, for example, unvaccinated children may have different background risk of malaria or health care seeking behaviours. To be able to compare the groups, parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine, regardless of whether they subsequently decide to vaccinate their child with RTS,S/AS01$_E$ or not. In addition, the same follow-up will be conducted (same study period, same timing for the inclusion visit and same number of home visits) and the same data collection will be prospectively implemented. However, the objective is to be able to collect data to estimate both the direct effect and the vaccine impact (indirect, total and overall effects). Considering the low proportion of vaccinated study participants in the population at the beginning of the vaccination programme implementation where EPI-MAL-003 will be performed, there is some likelihood that an indirect effect (also named herd effect) will not be estimable in this study.

To embed the various measures of vaccine effect within the post-implementation safety study EPI-MAL-003 has several advantages: (1) Effectiveness/impact data will be obtained at early stages because those countries will be the early adopters of the vaccine, (2) there will be benefit from the comprehensive infrastructure initially put in place for the safety component and from the large vaccinated population. This will also allow vaccine effects to be estimated at Year one and Year two after the last dose, thus avoiding having to develop new infrastructures in different locations. In addition, ethical concerns are minimal as withholding or delaying vaccination is avoided.

The co-primary objectives will provide estimates of the incidence of AESI and of aetiology-confirmed meningitis. The secondary objectives will provide estimates of the incidence of other meningitis case definitions, assess the potential association between RTS,S/AS01$_E$ vaccination and the occurrence of the different endpoints, and estimate the vaccine effectiveness and impact of vaccination with RTS,S/AS01$_E$ on the incidence of any malaria (including *P. falciparum* malaria), severe malaria (including *P. falciparum* malaria) and cerebral malaria.

In the framework of the secondary objectives, the comparisons will be done considering the before-after design (comparing occurrence of events in subjects from EPI-MAL-002 with subjects from the exposed clusters of EPI-MAL-003), and considering the cluster design (comparing occurrence of events in subjects from the unexposed clusters of EPI-MAL-003 with subjects from the exposed clusters of EPI-MAL-003). Both comparisons will be done using the same type I error, without adjustment of multiplicity to take a conservative approach [CPMP, 2002].

Integrating the Phase IV in the MVIP and adding a concurrent unvaccinated cohort (unexposed clusters) to EPI-MAL-003 have some impact on study designs but also allow strengthening the post-approval plan of RTS,S/AS01$_E$. The latter now considers two comparisons (before-after and cluster design comparisons) allowing adjustment for both temporal and geographical variability in terms of malaria transmission, disease incidence, access to care, use of other malaria control measures,…. On one hand, temporal bias might occur due to seasonality and year to year variations, or due to variation in control measures,… On the other hand, geographical bias might occur due to differences in health care infrastructure/facilities between sites, due to the epidemiology of several diseases, especially of infectious disease, or due to variation in controls measures,… Therefore, the two comparisons are considered complementary and should provide more robust results.

The before-after design enables a more powerful continuous monitoring of meningitis through MaxSPRT analysis as well as a more powerful comparison at the time of the interim analysis. Indeed, the enrolment of the unvaccinated comparator arm (before) is complete at the moment the EPI-MAL-003 study starts. It will therefore provide precise estimates of the different incidences.

It is important to note that a fixed number of clusters are included in the cluster design comparison (currently 6 exposed clusters and 6 unexposed clusters of around 4,000 subjects each are planned) which does not allow for robust intra-cluster adjustment. As concluded in [Hemming, 2011], designing a cluster trial with a fixed number of clusters might mean that the study will not be feasible, irrespective of how many individuals are included within each cluster. Also, cluster trials with fewer than five clusters per arm are, in general, inadvisable, since parametric tests may be unreliable with such small numbers [Medical Research Council, 2002]. In addition, the clusters that are/will be allocated to the Phase IV studies have not been randomized to allow before-after comparison (EPI-MAL-002 sites that will provide baseline incidences of the endpoints of interest will be clusters implementing RTS,S/AS01$_E$ vaccine). Moreover unexposed EPI-MAL-003 clusters will be conveniently selected by the MoH based on the following characteristics: malaria transmission, geographic location, access to care and population size. These characteristics will be captured through the yearly cross-sectional survey in the EPI-MAL-005 study to adjust the comparison. In order to minimize the impact of those major limitations on the interpretability of the study results, GSK Biologicals has put measures in place to maximize cluster comparability and to assess consistency of the results using different study designs. However, if the intra-cluster correlation coefficient is high (intra-cluster correlation coefficient > k / n where k is the number of clusters, and n is the average number of subjects per cluster [Hemming, 2011]), then the results should be interpreted with caution.

Finally, since the Phase IV is fully integrated in the malaria vaccine pilot implementation programme, contamination between exposed and unexposed clusters (also called cross-contamination) is a potential risk that should be considered. It is possible that children living in unexposed clusters will seek for vaccination in neighbouring exposed clusters. Such “contamination” may tend to under-estimate vaccine impact. As per WHO-led evaluation protocol of the pilot implementation programme, the level of contamination will be reduced by selecting clusters which are as geographically large as possible,

making it more difficult for people to seek vaccinations outside their own cluster. Moreover, as detailed in Section 9.3.3.1, in the framework of EPI-MAL-003, vaccine history will be collected at individual level from different sources (i.e. individual vaccination cards, vaccination registers and vaccination HDSS or equivalent surveillance system) in order to fully describe vaccine coverage in both exposed and unexposed clusters.

A SAP will complement the protocol to detail the way the data will be handled for each analysis. Contents of the protocol might be adapted based on NRA approval and MoH guidelines at country level. The interpretation of the results will take into account the limitations described above.

(Amended 15 October 2020)

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the ICH Guideline for GCP, Guidelines for Good Pharmacoepidemiology Practices (GPP) [ISPE, 2015], other applicable guidelines, all applicable study participant privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study prior to a site initiating the study in any country, according to local requirements, or will document that neither a favourable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- IRB/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Study participants' parent(s)/LAR(s) informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK Biologicals will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed and thumbprinted informed consent must be obtained from each study participant's parent(s)/LAR(s) or the impartial witness, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model ICF which will embody the applicable ICH GCP or other applicable guidelines, and GSK Biologicals required elements. While it is strongly recommended that this model ICF be followed as closely as possible, the

informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Safety definitions

11.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

11.1.2. Definition of a serious adverse event

A SAE is any adverse event that:

a. Results in death.

b. Is life-threatening.

   NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participants was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

   NB: In general, hospitalisation signifies that the study participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

   Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the adverse event should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE.

d. Results in disability/incapacity,

   NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

For the details of what qualifies for reporting to GSK for this study please refer to Section 11.3.

11.2. Detecting and recording adverse events

11.2.1. Time period for detecting and recording adverse events

All relevant AEs will be collected and recorded from the time the parent(s)/LAR(s) of the study participant consent for their child/ward to participate in the study until study conclusion (i.e. study end or the child reaches 5 years of age, whichever occurs first).

11.3. Recording of adverse events via eCRF

Any AE, which is serious (refer to Section 11.1.2) and which, in the opinion of the investigator, is suspected to be related to the protocol required blood draw for any suspected AESI or meningitis case, will be recorded in the Expedited Adverse Event screen in the eCRF, which will subsequently be uploaded into GSK's safety database for potential expedited reporting to health authorities.

For some other specific events (see list below), which are captured in various screens in the eCRF (e.g. meningitis screen, malaria screen), minimal data also need to be recorded for the event in the Expedited Adverse Event screen of the eCRF:

- Any case of suspected AESI in a child who received at least one dose of RTS,S/AS01$_E$;
- Any case of suspected meningitis in a child who received at least one dose of RTS,S/AS01$_E$;

- Any case of severe malaria, including cerebral malaria, in a child who received at least one dose of RTS,S/AS01$_{E;}$
- Any case with a fatal outcome in a child who received at least one dose of RTS,S/AS01$_{E;}$
- Any other AE (i.e. other than those listed above) which is identified during a hospitalization in a child who received at least one dose of RTS,S/AS01$_E$ AND which, in the opinion of the investigator, is related to RTS,S/AS01$_E$;

In addition to the minimal data recorded in the Expedited Adverse Event report screen of the eCRF for these events, data from other screens in the eCRF will also be uploaded into GSK's safety database for providing more complete information on the case for potential expedited reporting to health authorities.

NOTE: These events all need to be entered in the EXPEDITED ADVERSE EVENT report screen of the eCRF within 24 hours of the investigator becoming aware of the event.

11.3.1. Evaluation of adverse events

11.3.1.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all AEs recorded in the Expedited Adverse Event screen of the eCRF.

The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such a SAE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

11.3.1.2. Assessment of causality

The investigator will provide an assessment of causality for all AEs recorded in the Expedited Adverse Event screen of the eCRF.

The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, other concomitant therapy and other risk factors will be considered and investigated. The investigator will also consult the Product Information (Summary of Product Characteristics) to determine his/her assessment.

There may be situations when an AE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the AE to GSK Biologicals. The investigator may change his/ her opinion of causality in light of follow-up information and update the information previously recorded in the eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Note: for all AEs recorded in the Expedited Adverse Event screen of the eCRF, apart from those events considered as related to the study procedure involving a blood draw for suspected cases AESI or meningitis, the investigator will be asked to provide an assessment of causality between the event and RTS,S/AS01$_E$.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the event may have been caused by the RTS,S/AS01$_E$ vaccine?

YES	:	There is a reasonable possibility that the RTS,S/AS01$_E$ vaccine contributed to the event.
NO	:	There is no reasonable possibility that the RTS,S/AS01$_E$ vaccine contributed to the event. There are other, more likely causes and administration of the RTS,S/AS01$_E$ vaccine is not suspected to have contributed to the event.

Possible contributing factors include:

- Medical history
- Medication(s)
- Protocol required blood draw for a suspected AESI or meningitis case
- Other procedure not required by the protocol
- Erroneous administration
- Other cause (specify).

11.3.1.3. Assessment of outcomes

The investigator will provide an outcome for all AEs recorded in the Expedited Adverse Event screen of the eCRF using the following options:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae.
- Fatal.

11.4. Reporting of adverse events not via eCRF

The following events need to be reported but not within the framework of the study.

- Any AE which, in the opinion of the investigator, is suspected to be related to a GSK licensed product other than RTS,S/AS01$_E$ must be reported, within 24 hours of awareness, directly to GSK Safety for entry in GSK's safety database, and potential expedited reporting to ***relevant National H***ealth authorities. See Sponsor Information Sheet for contact details for reporting these types of events (Annex 4).
- Any AE which, in the opinion of the investigator, is suspected to be related to a non-GSK licensed product should be reported, to the relevant National Health authority following national reporting procedures for adverse drug reactions.
- ***Any AE which, in the opinion of the investigator is suspected to be related to RTS,S/AS01$_E$ and which is not collected per study protocol, must be reported to relevant National Health authorities following the local pharmacovigilance legislation.***

(Amended 15 October 2020)

11.4.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must complete, then date and sign a paper Expedited Adverse Event Report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department using the following contact details (again within 24 hours of awareness).

Back-up Study Contact for Reporting AEs
24/24 hour and 7/7 day availability:
Email: PPD
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD or PPD

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is back working again, the investigator (or designee) must complete the Expedited Adverse Event report in the eCRF. The final valid information for regulatory reporting will be the information reported through the electronic reporting system.

11.4.2. Updating of adverse event information after removal of write access to the study participant's eCRF

If additional AE information is received after removal of the write access to the study participant's eCRF, new or updated information should be recorded on the appropriate paper report (see Section 11.4.1), with all changes signed and dated by the investigator. The updated report should be faxed to GSK Biologicals Clinical Safety and Pharmacovigilance department using the contact details provided in Section 11.4.1.

11.4.3. Regulatory reporting requirements for adverse events

GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under epidemiological investigation. Prompt notification of AEs by the investigator to the Study Contact for Reporting AEs is essential so that legal obligations and ethical responsibilities towards the safety of other study participants are met.

11.5. Follow-up of adverse events

- For AESIs, meningitis or cerebral malaria, children, will be followed up after hospital discharge up to study conclusion in order to evaluate any sequelae. This will be done by a check-up at the hospital 1 month, 6 months and 1 year after hospital discharge (see Section 9.2.7.5).
- For all events, including AESIs, meningitis and cerebral malaria, the investigator will follow-up the study participant until the event has resolved, subsided, stabilised, disappeared, or until is otherwise explained, or the study participant is lost to follow-up. Follow-up to characterize an SAE is described in Sections 9.1.1 and 9.2.7.

GSK Biologicals may request that the investigator performs or arranges for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE. The investigator is obliged to assist. If a study participant dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

To comply with Guidelines for GPP or other applicable guidelines administrative obligations relating to data collection, archiving data, audits, confidentiality and publications must be fulfilled.

Study information from this protocol will be posted on public registers (e.g. GSK Clinical Study Register, clinicaltrials.gov, Pan African Clinical Trials Registry) and the European Union Post-Authorisation Studies (EU PAS) register before the start of the study, as applicable.

Progress reports will be written and submitted every six months. An interim analysis will be performed one year after the last study participant received the last dose of RTS,S/AS01$_E$ vaccine primary schedule (i.e. 3rd dose). This interim analysis will be done with clean data* on safety endpoints, and effectiveness and impact endpoints.

* Some data may change after the interim analysis as access to the eCRF will still be granted to sites and investigators throughout the follow-up period, until study conclusion.

A final report will be written and submitted.

For the three studies (EPI-MAL-002, EPI-MAL-003, EPI-MAL-005) a Safety Post Approval Program Partnership Committee has been created and will ensure preparation and review of manuscripts resulting from the studies. This Committee is composed of local principal investigators with GSK representation. This Committee acts as the main governance body for the studies. (Charter is available upon request.)

A manuscript will be submitted to a peer reviewed journal for publication within the policy defined timelines. In addition, study information will be posted to the GSK Clinical Study Register.

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(Amended 15 October 2020)

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	List of stand-alone documents
2.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Glossary of terms
3.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Trademarks
4.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Sponsor Information
5.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Case definitions for protocol-defined AESI and surveillance indicators
6.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Study specific guidance document
7.	115056 (EPI-MALARIA-003 VS AME)	***15 October 2020***	Amendment to the protocol
8.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Protocol Amendment ***2*** sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Protocol Amendmen***t 2*** investigator agreement
10.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	ENCePP Checklist for study protocols

Annex 2 Glossary of terms

Active surveillance:	Screening for AESI and other diseases during study follow-up visits at the community level.
Adverse event of special interest (AESI):	A predefined list of adverse events that are potentially associated with RTS,S/AS01$_E$, that have historically been associated with vaccines other than RTS,S/AS01$_E$, or may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines.
Adverse event:	Any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Cohort event monitoring:	A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time [The Uppsala Monitoring Centre, 2011].
Cohort study:	A form of epidemiological study where study participants in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
DTP/HepB/Hib	This refers to Diphtheria, Tetanus, and Pertussis (DTP), or DTP-Hepatitis B (DTP-HepB tetravalent) or DTP-HepB-Haemophilus influenza type b (Hib) (DTP-HepB-Hib pentavalent) vaccines.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enhanced hospitalisation surveillance:	Case detection during hospitalisation through monitoring of medical records and registries.
Epidemiology study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all study participants at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Exposed clusters	Study sites where the RTS,S/AS01$_E$ vaccine will be implemented at the beginning of the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Hospitalisation:	Study participants requiring overnight stay in a health care facility.
Interventional human subject research:	Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.
National EPI:	Routine vaccination programmes, administered by the national EPI system in place, usually given at 6, 10 and 14 weeks of age (e.g. DTP/HepB/Hib vaccines. NOTE: in some countries the EPI schedule may differ by a few weeks).
Pharmacovigilance:	Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs) [WHO, 2012(b)].
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.

Serious adverse event:	A serious adverse event (SAE) is any untoward medical occurrence that: a. results in death; b. is life-threatening; c. requires hospitalisation or prolongation of existing hospitalisation; d. results in disability/incapacity; Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.
Site monitor:	An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.
Study participant number:	A unique number identifying a study participant, assigned to each study participant consenting to participate in the study.
Study participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Unexposed clusters	Study sites where the RTS,S/AS01$_E$ vaccine will not be implemented in the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.
Vaccine ineligible	Vaccine ineligible is defined as those study participants that on the basis of age would be ineligible for RTS,S/AS01$_E$ vaccination, regardless of vaccine availability at the time of assessment. The age will depend on the label for RTS,S/AS01$_E$ vaccination in the country.

Annex 3 Trademarks

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the abstract), the names of the vaccines will be written without the superscript symbol ™ or ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Mosquirix™	*Plasmodium falciparum* and hepatitis B vaccine (recombinant, adjuvanted)
Rotarix®	Live attenuated human rotavirus vaccine
Pediarix®	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus combined vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
RotaTeq® (Merck & CO., Inc.)	Live, oral, pentavalent rotavirus vaccine

Annex 4 Sponsor Information

1. **Sponsor:**

GlaxoSmithKline Biologicals

Rue de l'Institut 89, 1330 Rixensart, Belgium

2. **Sponsor Medical Expert for the Study:**

Refer to the local study contact information document.

3. **Sponsor Study Monitor:**

Refer to the local study contact information document.

4. **Study Contact for Reporting of a Serious Adverse Event (SAE):**

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 11 Management and reporting of adverse events /adverse reactions.

Annex 5 Case definitions for protocol-defined AESI and Surveillance Indicators

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Nerves and Central Nervous System		
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)	**LEVEL 1** • Diffuse or multifocal demyelination revealed on histopathological sampling **OR** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus **AND** • On MRI: diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences **AND** • Monophasic character of the illness (absence of relapse within a minimum of 3 months of symptomatic nadir) **LEVEL 2** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry)	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus **AND** • On MRI: Diffuse or multi- focal involvement of the white matter on T2, weighted diffusion and/or FLAIR sequences **AND** • Follow up insufficient to confirm a monophasic nature of the illness (absence of relapse within a minimum of three months after the clinical nadir). **LEVEL 3** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Alterations in deep tendon reflexes (hyper or hypo reflexia, asymmetry). • Cerebellar impairment such as ataxia, dysmetria, cerebellar nystagmus. **Exclusion criteria for all levels of diagnostic certitude** • Authentication of an acute infection or of a differential diagnosis is compatible with the clinical picture • Relapse of the illness at any moment after a minimum period of three months of clinical improvement after the nadir of clinical symptoms. • MRI images or histopathology in the clinical diagnosis is compatible with the case definition with the diagnosis of ADEM. **In Summary** ADEM can be confirmed if: • The clinical diagnosis is compatible with the case definition. • All differentials diagnoses have been excluded • The CSF exam supports the diagnosis of ADEM. NB: Plan for diagnostic confirmation by a neurologist (and MRI if possible). Generally the illness completely resolves in a few months. The diagnosis must be confirmed by a clinical examination performed 3 months after the nadir of the clinical symptoms.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
ENCEPHALITIS	**LEVEL 1** • Demonstration of acute inflammation of the central nervous system parenchyma (+/- the meninges) on histopathology **LEVEL 2** • Signs of encephalopathy (depressed level of consciousness, somnolence , acute personality change for more than 24 hours) **AND** *One or more of the following signs:* • Absent or diminished reflexes to external stimuli (such as a loud noise or painful stimuli) • Absent or markedly diminished eye contact • Inadequate or absent response to an external stimuli • Seizures with loss of consciousness **OR** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, more often focal) • Sensory abnormalities • Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) • Cerebellar dysfunction, such as ataxia, dysmetria, cerebellar nystagmus **AND** *Two or more of the following signs:* • Fever (≥ 37.5°C) • CSF: Pleocytosis – >15 leukocytes/ mm^3 in a child 2 months of age or younger – >5 leukocytes/ mm^3 in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis. **LEVEL 3** • Signs of encephalopathy (depressed level of consciousness, somnolence, acute personality change for more than 24 hours) **AND** *One or more of the following signs:*	Sejvar JJ, Kohl KS, Bilynsky R, et al; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5771-92.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Absent or diminished response to external stimuli (such as a loud noise, painful stimuli) • Absent or markedly diminished eye contact • Inconsistent or absent response to an external stimuli • Seizures with associated loss of consciousness **OR** Focal or multifocal impairment of the central nervous system *with ≥ 1 of the following signs:* • Focal cortical impairment (particularly but not exclusively: aphasia, alexia, agraphia, cortical blindness) • Cranial nerve abnormality/abnormalities • Visual field defect/defects • Presence of primitive reflexes (Babinski's sign, an inexhaustible glabellar reflex, snout/sucking reflex) • Motor weakness (diffuse or focal, most often focal) • Sensory abnormalities • Altered deep tendon reflexes (hypo or hyperreflexia, asymmetry) • Cerebellar impairment, such as ataxia, dysmetria, cerebellar nystagmus **AND** *One of the following signs:* • Fever (≥ 37.5°C) • CSF: Pleocytosis – >15 leukocytes/ mm^3 in a child 2 months of age or younger – >5 leukocytes/ mm^3 in a child 2 months of age or older • EEG signs compatible with an encephalitis • Cerebral imagery compatible with an encephalitis **Evaluation Criteria** • Exclude the presence of all diseases (cancer, toxic-metabolic encephalopathy, vascular problems, trauma, meningitis etc.) **In Summary** The diagnosis of encephalitis is confirmed if: • The clinical diagnosis is compatible with the case definition. **AND** • The CSF analysis is compatible with an encephalitis picture. **AND** • The differential diagnoses (especially meningitis) have been excluded.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
GUILLAIN-BARRÉ SYNDROME	**LEVEL 1** • Bilateral weakness (symmetric) with flaccid extremities (usually of all 4 limbs) **AND** • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities **AND** • Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase **AND** • Electromyography: Electrophysiological signs the clinical diagnosis is compatible with the case definition with GBS **AND** • Albuminocytologic dissociation: hyperproteinorachia (elevation of CSF protein) and normal CSF white cell count [< 50 cells/µl] **AND** • Absence of plausible differential diagnosis (to explain the motor weakness) **LEVEL 2** • Bilateral AND flaccid weakness of the extremities **AND** • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities **AND** • Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau **AND** • CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value) **OR** • If CSF not collected or results not available, electrophysiologic studies consistent with GBS **AND** • Absence of identified alternative diagnosis for weakness **LEVEL 3** • Bilateral AND flaccid weakness of the extremities **AND** • Decreased or absent deep tendon reflexes in the impaired (paralyzed) extremities	Sejvar JJ, Kohl KS, Gidudu J, et al. The Brighton Collaboration Guillain-Barré Syndrome Working Group. Guillain-Barré Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine. 2011; 29(3): 599–612.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND • Monophasic nature of the illness AND the interval between the beginning of the signs and the nadir of weakness is between 12 hours and 28 days AND the appearance of a subsequent clinical plateau phase **AND** • Absence of plausible differential diagnosis (to explain the motor weakness) **In Summary** The diagnosis of Guillain-Barre Syndrome can be confirmed if: • The clinical diagnosis is compatible with the case definition • The poliovirus is not isolated from the stool • The CSF examination is compatible with GBS: Hyperproteinorachia (elevation of CSF protein), absence of pleocytosis. • There is diagnostic confirmation by a neurologist.	
GENERALIZED CONVULSIVE SEIZURE	**LEVEL 1** • Witnessed sudden loss of consciousness **AND** • Generalized tonic, clonic, tonic-clonic or atonic motor manifestations **LEVEL 2** • Reported sudden loss of consciousness **AND** • Generalized tonic, clonic, tonic-clonic or atonic motor manifestations **LEVEL 3** • Reported sudden loss of consciousness **AND** • Other generalized motor manifestations **In Summary** The diagnosis of generalized seizure can be confirmed if: • The clinical diagnosis is compatible with the case definition. • The history of present illness evokes seizure activity • The etiological work up is negative: (i.e. acute intoxication, trauma, severe malaria etc. have all been excluded). **(Amended 15 October 2020)**	Bonhoeffer J, Menkes J, Gold MS, et al; The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22:557-562.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
HYPOTONIC HYPORESPONSIVE EPISODE (HHE)	**LEVEL 1** • Hypotonia (muscular weakness) **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **LEVEL 2** • Indeterminate muscle tone **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **OR** • Hypotonia (muscular weakness) **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Indeterminate skin color **LEVEL 3** • Normal muscle tone **AND** • Reduction or absence of response to sensory or verbal stimuli **AND** • Pallor or cyanosis **OR** • Hypotonia (muscular weakness) **AND** • Indeterminate response to sensory or verbal stimuli **AND** • Palor or cyanosis.	Bonhoeffer J, et al. Brighton Collaboration HHE Working Group. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004; 22(5-6): 563–568.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Hepato-Gastrointestinal and Renal System		
HEPATIC FAILURE	**Major criteria** • Total serum bilirubin ≥1.5 times the upper limit of normal (ULN) **OR** • Elevation of the serum transaminases (ALT, AST ≥ 3 times the upper limit of normal (ULN)) **AND** • Coagulopathy unresponsive to vitamin K (prothrombin time (PT) ≥ 15 seconds or INR ≥1.5). **In Summary** The diagnosis of hepatic insufficiency can be confirmed if: • The diagnosis can be considered if the major criteria are present and confirmed on at least two blood draws. • The etiologies of the most frequent causes of jaundice and alterations of liver function tests and, the non-hepatic encephalopathies are excluded: viral hepatitis, malaria, sickle cell anemia, exposure to toxins and medicines. NB: In case of fortuitous discovery of a perturbation in the hepatic panel without clinical manifestations, it is recommended to do a follow up hepatic panel.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012;30(33): 5038–5058.
INTUSSUSCEPTION	**I) Definition of criteria** DIAGNOSTIC CRITERIA • Surgical criteria – Demonstration of intussusception during exploratory surgery • Imaging criteria – Demonstration of intussusception via non-barium or aircontrast enema; – Demonstration via ultrasound of an intra-abdominal mass with specific characteristics – target (or doughnut) sign on transverse images and pseudokidney or sandwich sign on longitudinal images – the reduction of these signs by hydrostatic enema is also confirmed by ultrasound. **Major criteria** • Symptoms and signs of intestinal obstruction: – History of vomiting bile **AND** – Clinical examination shows acute abdominal distention and abnormal or absent bowel sounds **OR** – Radiological examination (plain abdominal X-ray) shows air-fluid levels and loops of distended small bowel.	Bines JE, Kohl K, Forster J, et al and the Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:569–574.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	• Signs of intussusception, ≥ 1 following signs: – Abdominal mass – Rectal mass – Rectal prolapse – Plain abdominal X-ray shows a soft tissue mass – Abdominal ultrasound shows a soft tissue mass – Abdominal CT shows a soft tissue mass • Evidence of vascular compromise or venous congestion: – Anal bleeding **OR** – Currant jelly stools" **OR** – Blood detected during rectal examination **Minor criteria** • Predisposing factors: aged < 1 year, male • Abdominal pain • Lethargy • Pallor • Hypovolemic shock • Plain abdominal X-ray showing an abnormal and unspecific distribution of air in the intestines. **II) Diagnostic certainty levels** **LEVEL 1** • Surgical criteria: The demonstration of invagination of the intestine at surgery; **AND/OR** • Radiologic criteria: The demonstration of invagination of the intestine by either air or liquid contrast enema; **OR** The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on postreduction ultrasound; **AND/OR** • Autopsy criteria: The demonstration of invagination of the intestine. **LEVEL 2** • Clinical criteria: Two major criteria or One major criterion and three minor criteria. **LEVEL 3** • Clinical criteria: Four or more minor criteria.	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
RENAL INSUFFICIENCY	**Major criteria** Creatinine ≥ 1.5 times the upper limit of normal (ULN) or 1.5 times the patient's initial value. **Minor criteria** Urine production <0.5ml/kg/hour **In Summary** Renal insufficiency can be confirmed if: • The major criteria is present and confirmed (at least two blood draws) • The etiological diagnosis has been carried out.	Gershman M., et al, Brighton Collaboration Viscerotropic Disease Working Group. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038–5058.
Skin and Mucous Membranes & Bones and Joints		
HENOCH SCHÖNLEIN PURPURA	**I) Definition of criteria** **MAJOR CRITERIA** • Purpura (mandatory criterion) Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia • Abdominal pain Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding • Histopathology Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit • Arthritis or arthralgias Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. • Renal involvement Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick. **MINOR CRITERIA** • Other diagnoses unlikely (exclude meningitis) **II) Diagnostic certainty levels** **LEVEL 1** • Purpura or petechiae (mandatory) with lower limb predominance	

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND ≥ 1 following criteria • Abdominal pain • Histopathology • Arthritis or arthralgias • Renal involvement **AND** • Absence of thrombocytopenia **LEVEL 2** • Purpura or petechiae (mandatory) with lower limb predominance **AND** • Absence of thrombocytopenia.	
JUVENILE CHRONIC ARTHRITIS	Juvenile Chronic Arthritis is defined by an evolution of symptoms of at least three months. The clinical examination often reveals a child with growth retardation. The different clinical forms are the following: **1. Pauciarticular form (the most common form between 1 and 3 years of age).** Clinically this presents with: • Involvement of four or less joints • Symmetric involvement of the small joints • Tenosynovitis of the flexor tendons and erosive nodules (frequent) • Rheumatoid factor seronegativity These signs can be associated with: • A positive anti-nuclear antibody (among 40 to 75% of children) • Uveitis **2. Polyarticular form** • Affects 5 or more joints • Rheumatoid factor IgM can be positive or negative • Hips, cervical spine, hands and feet are the joints the most often affected, followed by the knees, wrists and ankles. • Among the patients seronegative for the rheumatoid factor, an association of fever, hepatosplenomegaly and symmetrical arthritis has been described. **3. Systemic form** • Accompanied by a fever up to 39.5°C during at least two weeks • A typical rash on the trunk and thighs can be seen • Frequent involvement of the wrists, knees, ankles as well as the temporomandibular joint, and the hands. • The illness typically lasts between 2 and 5 years before complete resolution	Medical websites resources: e.g. http://www.arthritis.co.za/jra.htm; http://emedicine.medscape.com/article/1007276-overview; http://www.med.univ-rennes1.fr/etud/pediatrie/arthrite_cique.hthronm

<table>
<tr><th>Body system/ AESI</th><th>Diagnosis/Level of Diagnostic Certainty</th><th>References</th></tr>
<tr><td></td><td>In Summary
The diagnosis of Juvenile Chronic Arthritis (JCA) can be confirmed if:
• The clinical diagnosis responds to the case definition
• The biological panel shows signs of chronic inflammation
• The most frequent differential diagnoses are excluded
• If necessary, the diagnosis should be confirmed by a specialist. The symptoms must last at least 3 months before concluding JCA. A confirmation of the diagnosis requires a follow up visit 3 months after the beginning of the illness.</td><td></td></tr>
<tr><td>STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)</td><td>Symptoms start by a feeling of malaise, fever, headache, cough and conjunctivitis. Then the macular eruption appears, rapidly transforming into confluent bullae over one to three days. Nails and eyebrows can be lost due to epidermal involvement.
The diagnosis of Stevens-Johnson syndrome becomes evident with the appearance of cutaneous lesions, the rapid and expansive progression of symptoms, which include two mucosal sites.
<table>
<tr><th>Diagnosis</th><th>Lesion morphology</th><th>Body surface area detachment</th></tr>
<tr><td>SJS</td><td>Maculae, bullae, atypical target lesions</td><td>≤10%</td></tr>
<tr><td>SJS-TEN overlap</td><td>Maculae, bullae, atypical target lesions</td><td>10-30%</td></tr>
<tr><td>TEN with spots</td><td>Maculae, bullae, atypical target lesions</td><td>≥30%</td></tr>
</table>
In Summary
The diagnosis of STEVENS-JOHNSON SYNDROME (SJS) can be confirmed if:
• The clinical diagnosis responds to the case definition
• The etiological research indicates exposure to a triggering element (medication, immunization, toxin, febrile state, virus)
• In case of doubt, consultation of a specialist is necessary.</td><td>Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129:92-6.</td></tr>
<tr><td>KAWASAKI DISEASE</td><td>I) DEFINITION OF CRITERIA
Major criteria
• Fever ≥ 5 days
• Clinical criteria:
Signs of mucocutaneous inflammation:
– Polymorphic exanthem
– Non-exudative bilateral conjunctivitis</td><td>Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on</td></tr>
</table>

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	– Involvement of the lips and oral cavity: erythema, cracked lips, "strawberry red" tongue, diffuse inflammation of the oral and pharyngeal mucosa – Involvement of the hands and feet: erythema of the palms and/or soles, oedema of the hands and/or the feet. Hand and/or foot periungual peeling skin (week 2-3 of disease course) – Usually unilateral neck lymphadenopathy (≥ 1.5 cm) **Minor criteria** • Erythrocyte sedimentation rate ≥ 40 mm/h or CRP ≥ 3 mg/dL • Echocardiogram showing coronary artery or heart involvement **II) Diagnostic certainty levels** **LEVEL 1** • Fever ≥ 5 days **AND** • ≥ 4 clinical criteria: **AND** • Other diagnoses unlikely after clinical examination and laboratory tests **LEVEL 2** • Fever ≥ 5 days **AND** • < 4 clinical criteria: **AND** • Erythrocyte sedimentation rate ≥ 40 mm/h OR CRP ≥ 3 mg/dL **AND** • Other diagnoses unlikely after clinical examination and laboratory tests **LEVEL 3** • Fever ≥ 5 days **AND** • < 4 clinical criteria: **AND** • Normal erythrocyte sedimentation rate OR normal CRP **AND** • Coronary artery or heart involvement **AND** • Other diagnoses unlikely after clinical examination and laboratory tests.	Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
Cardiovascular system and blood disorders		
ANAPHYLAXIS	**For all levels of diagnostic certainty** • Sudden onset AND • Rapid progression of signs and symptoms AND • Involving multiple (≥ 2) organ systems, as follows: **LEVEL 1** • ≥1 major dermatological criterion **AND** • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion **LEVEL 2** • ≥1 major cardiovascular AND ≥1 major respiratory criterion **OR** • ≥1 major cardiovascular OR respiratory criterion **AND** • ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) **OR** • ≥1 major dermatologic AND ≥1 minor cardiovascular AND/OR minor respiratory criterion **LEVEL 3** • ≥1 minor cardiovascular OR respiratory criterion **AND** • ≥1 minor criterion from each of ≥2 different systems/categories **In Summary** The diagnosis can be confirmed if: • The clinical diagnosis is compatible with the case definition (at least 2 major signs/criteria) • Symptom onset occurred after a short period of time (a few minutes to hours) after exposure to a food item, an insect sting, a vaccination, or contact with a product allergen (such as peanuts) • If the child reports a known allergy, one major sign/criteria following exposure to a known allergen is sufficient for a diagnosis of anaphylaxis.	Rüggeberg JU, Gold MS, Bayas JM et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-5684.
DIABETES MELLITUS TYPE 1	• Serum fasting glucose ≥ 7mmol/L (> 126 mg/dL) **OR** • Postprandial serum glucose ≥11.1mmol/L (≥ 200 mg/dL) 2 hours after ingesting 1.75 g/kg (max.75g) of glucose (oral glucose tolerance test) **OR** • A1C Hemoglobin ≥ 6.5% AND Hyperglycemia	WHO Definition and Diagnosis of diabetes mellitus and intermediate hyperglycaemia, 2006 and http://www.nlm.nih.gov/medlineplus/encyclopedia.html

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND • No other cause of hyperglycemia **In Summary** The diagnosis of type 1 diabetes mellitus can be confirmed when a confirmed hyperglycemia responds to the case definition.	
THROMBOCYTOPENIA	**LEVEL 1** • Platelet concentration < to 150 x 10^6/mL **AND** – Confirmation par blood smear **OR** – Clinical signs of spontaneous bleeding (i.e. non traumatic)* **LEVEL 2** • Platelet concentration < to 150 x 10^6/mL. **Spontaneous bleeding (i.e. non traumatic), includes purpura (i.e. petechiae, purpura sensu stricto, ecchymoses) exudative hemmorhage, hematomas, hematemesis, occult bleeding par rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding, conjunctival bleeding, intracranial bleeding.* **In Summary** The diagnosis of thrombocytopenia can be confirmed if: • It corresponds to the level 1 of diagnostic certainty case definition • An etiological investigation was carried out.	Wise RP, Bonhoeffer J, Beeler J, et al. Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5717–5724.
Surveillance indicators		
INJECTION SITE ABSCESS **Abscess of infectious aetiology**	**LEVEL 1** • Spontaneous or surgical drainage of the mass contents **AND** • Microbiologic confirmation (Gram stain, culture or other exam) of the presence of bacteria with or without altered polynuclear neutrophils in the aspirated/drained fluid. **LEVEL 2** In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. • Spontaneous or surgical drainage of the purulent fluid from the mass contents **OR** • Mass collection diagnosed by an imaging technique or the mass is fluctuant.	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31): 5821–5838.

Body system/ AESI	Diagnosis/Level of Diagnostic Certainty	References
	AND • Signs of localized inflammation including at least one of the following aspects: erythema, pain on light palpation, and warmth to the touch at the injection site. **AND** • Resolution of symptoms after antibiotic therapy	
INJECTION SITE ABSCESS **Sterile abscess**	**LEVEL 1** • Spontaneous or surgical drainage of the mass contents **AND** • Drainage liquid obtained before the beginning of antibiotic therapy and no infectious pathogen found on examination (Gram stain, culture or other examination) **LEVEL 2** In situations where microbiologic confirmation (Gram stain, culture or other examination) was not performed, or was performed after the start of antibiotic therapy, or was not ordered at all. • Non purulent fluid is spontaneous or surgically drained from the mass **OR** • A collection of material, such as fluid, is diagnosed by imagery or, there is fluctuance on palpation. **AND** • Absence of signs of local inflammation: erythema, pain on light palpation, warmth to the touch at the injection site **OR** • No improvement following a course of an antibiotic treatment. **In Summary** An injection site abscess is confirmed by a clinical diagnosis responding to the case definition.	Kohl K, et al. The Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Abscess at injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31): 5821–5838.
FOOT POSITIONAL DEFORMATIONS	Metatarsus adductus characterised by medial deviation (adduction) of the forefoot while the hindfoot remains in a normal position, thus forming a "C" shape, or concavity of the medial aspect of the foot **OR** Positional calcaneovalgus feet characterised by hyperdorsiflexion of the foot with the abduction of the forefoot, which often results in the forefoot resting on the anterior surface of the lower leg **OR** Clubfoot characterised by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward.	

Annex 6 Study specific guidance document

Screening tool for assessing serious delays in developmental milestones and/or physical disabilities in children from 3 months to 36 months of age

If the caregiver responds negatively to 2 or more questions, the child should be referred to a medical consultation for further investigations according to routine medical practice. All questions are to be responded by YES or NO.

A. Screening questions for caregiver of children aged 3-4 months

A1	Does your baby smile to familiar people?
A2	Has your baby begin to make sounds?
A3	Does your baby follow moving people or objects with eyes?
A4	Does your baby hold his head unsupported?
A5	Does your baby bring his hands to his mouth?

B. Screening questions for caregiver of children aged 5-9 months

B1	Does your baby grasp objects with both hands?
B2	Can your baby sit with support?
B3	Does your baby respond to sounds by making sounds?
B4	Does your baby know familiar faces and know if someone is a stranger?

C. Screening questions for caregiver of children aged 10-15 months

C1	Does your baby sit without support?
C2	Does your baby crawl on hands and knees?
C3	Does your baby take steps holding on to furniture, walls, etc?
C4	Does your baby try to imitate words and sounds and respond to simple requests?
C5	Does your baby show fear in some situations?

D. Screening questions for caregiver of children aged 16-21 months

D1	Does your child point to things?
D2	Does your child say several single words?
D3	Does your child walk without any help?
D4	Does your child use 4-10 different words?

E. Screening questions for caregiver of children aged 22-28 months

E1	Does your child copy others, especially adults and older children?
E2	Does your child say short sentences?
E3	Does your child follow simple instructions?
E4	Does your child run?
E5	Does your child scribble or draw?
E6	Does your child enjoy simple stories or songs?

F. Screening questions for caregiver of children aged 29-36 months

F1	Does your child walk, run, climb, and kick a ball easily?
F2	Does your child talk using 2 to 3 short sentences?
F3	Can your child say his name or age?
F4	Does your child understand what “two” means?
F5	Does your child feed himself?

Annex 7 Amendment to the protocol

GlaxoSmithKline Biologicals **Vaccine Value & Health Science (VVHS)** Protocol Amendment 1	
eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Amendment number:	Amendment 1
Amendment date:	24 April 2019
Co-ordinating author:	PPD, Lead Scientific Writer (GSK Biologicals)

Rationale/background for changes:

Considering the RTS,S/AS01$_E$ vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site.

- Protocol Amendment 1 has been put in place because the EPI-MAL-002 study will no longer be conducted in Malawi meaning that the EPI-MAL-003 sample size of the before/after comparison has been updated.
- The reference to EPI-MAL-002 study conduct in Malawi was removed and clarifications provided in other sections.

Amended text has been included in bold italics and deleted text in ~~strikethrough~~ in the following sections:

1 **Section 1** – EU PAS Register No included

2 **Section 1 - Countries of study:** Sites in sub-Saharan Africa (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system ~~census ad of vaccine registries.~~

Sites in sub-Saharan Africa (SSA) countries have been ~~or will be~~ selected ----------

In order to align with the MVIP, the study sites for the GlaxoSmithKline (GSK) Phase IV studies have been~~, or will be,~~ selected from the 3 countries where the RTS,S/AS01E vaccine will be implemented. Sites from ***Ghana and Kenya*** ~~these 3 countries~~ that were part of study EPI-MAL-002 should become study sites in study EPI-MAL-003 which will be exposed clusters.

3 **Section 1 - Authors**: PPD , **Clinical and** Epidemiology Scientist ~~(Keyrus Biopharma for~~ GSK Biological, PPD ***, Statistician (4Clinics for GSK Biologicals),*** PPD ***, Epidemiology Lead – Malaria (GSK Biologicals),*** PPD ***, Project Delivery Lead (GSK Biologicals***), PPD ***, Clinical Laboratory Sciences Study Manager (Busisness & Decision for GSK Biologicals),*** PPD ***, Senior Study Delivery Lead (GSK Biologicals),*** PPD , ***Clinical Operations Head for Africa*** ~~Senior Local Delivery Lead~~ (GSK Biologicals), PPD ***, Local Delivery Lead (GSK Biologicals***), PPD ~~To be confirmed,~~ Local Medical Leads ***(GSK Biologicals).***

4 **Section 1-Countries of study:** Sites in sub-Saharan Africa (SSA) countries have been selected for EPI-MAL-003 based on the existence of a health and demographic surveillance system (HDSS) from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) or equivalent surveillance system ~~census ad of vaccine registries.~~

5 **Responsible Parties**: PPD (DVM, MSc, PhD; Senior Epidemiology Lead - Malaria) and PPD (~~PhD~~***MD***; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact persons for this study.

6 **Section 2 Opinion Holder**: © 2017-2019 GSK group of companies or its licensor.

7 **Section 4 Abstract- Rationale and background:** RTS,S/AS01$_E$ ~~will be~~ ***is*** the first vaccine to be implemented for the prevention of malaria and it ***is*** ~~will be~~ the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

In order to align with the MVIP, the study sites for the GSK Phase IV studies have been~~, or will be,~~ selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented. Sites from ***Ghana and Kenya*** ~~these 3 countries~~ that were part of study EPI-MAL-002 ***are exposed clusters in EPI-MAL-003*** ~~should become study sites in EPI-MAL-003 which will be exposed clusters~~. The first vaccine introduction is foreseen in ~~2018~~ ***2019***.

8 **Section 4 Abstract- Population, including the setting and study population:**

~~Some sites have already been identified to conduct the~~ ***All*** EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005 studies ***sites have been identified***.~~from the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system census and of vaccine registries.~~

Following the SAGE/MPAC recommendations of pilot implementations of RTS,S/AS01$_E$ in 3-5 distinct settings in SSA restricted to moderate-to-high transmission of malaria, sites in SSA countries with moderate-to-high transmission of malaria have ~~started enrolment~~ ***enrolled*** for EPI-MAL-002

In order to align with the MVIP, the study sites for the GSK Phase IV studies have been~~, or will be,~~ selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented. Sites from ***Ghana and Kenya*** that were part of study EPI-MAL-002 ***are exposed clusters in EPI-MAL-003*** ~~should become study sites in EPI-MAL-003 which will be exposed clusters~~.

~~In case one or more of the sites conducting EPI-MAL-002 cannot participate in EPI-MAL-003, a replacement strategy has been elaborated. It could consist of extending the recruitment period (depending on vaccine implementation strategy).~~

9 **Section 4 Abstract- Data sources:**

- Total number of children < 5 years of age ***(according to year and gender)*** recorded at the beginning of the study, at least once a year during the study duration and at the end of the study;
- Other demographic data (cause and date of deaths, migrations), ***if available***;
- Information related to vaccination***, if available***.

10 Section 5 Amendments and Updates:

Amendment 1 Final:24 April 2019.

The rationale for protocol amendment 1, is provided in Annex 7. ~~None~~.

11 **Section 6 Milestones:** This programme ***initially planned*** ~~**will**~~ ***to*** make the RTS,S/AS01$_E$ vaccine available in selected areas, starting in 2018

Start of data collection	~~Q2 2018~~* ***Q1 2019***
End of data collection	~~Q1 2024~~***Q3 2024***~~*~~
Study progress reports	1 progress report every 6 months
Interim epoch analysis	~~Q4 2021~~ ***Q3 2022***~~**~~ and ad-hoc (if triggered by a safety signal)
Registration in the EU PAS register	To be determined
Statistical analysis completed	~~Q3 2024~~ ***Q3 2025***
Final report of study results	~~Q4 2024~~ ***Q4 2025***

~~* Tentative; dependent on implementation of vaccine use by Ministry of Health~~

~~*~~Tentative date; depending on recruitment timelines ***and implementation of vaccination by the Ministries of Health***

~~***~~ Tentative date, depending on recruitment timelines and implementation ***of vaccination by the Ministries of Health***

12 **Section 7.1 Background:** RTS,S/AS01$_E$ ~~will be~~ ***is*** the first vaccine to be implemented for the prevention of malaria and it ~~will be~~ ***is*** the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

If the RTS,S/AS01$_E$ vaccine is implemented at the expected target of ***2019*** ~~2018~~, EPI-MAL-002 and EPI-MAL-003 may partly be run concomitantly in the same study sites.

Sites selection has been~~/ will be~~ done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO

13 **Section 7.4 Summary of the study rationale**: The first vaccine introduction is foreseen in ***2019*** ~~2018~~, if approved and recommended by local health authorities.

As much as possible, sites have been selected for EPI-MAL-002 and EPI-MAL-005 based on the existence of Health and Demographic Surveillance System (HDSS) or equivalent surveillance system ~~census and vaccine registries~~.

14 **Section 9.1 Study design: Catch-up group:** Children ***identified at 1st RTS,S/AS01E dose administration (schedule will depend on pilot implementation programme and national regulation)*** who ***either received all DTP/HepB/Hib doses before study start or*** received at least one dose of DTP/HepB/Hib ***and are*** older than the age corresponding to the 3rd DTP/HepB/Hib dose ***at study start***~~.identified at 1st RTS,S/AS01E dose administration (schedule will depend on pilot implementation programme and national regulation).~~ Th***is*** ~~at~~ group will include only RTS,S/AS01E vaccinated children ~~(~~from exposed clusters~~)~~. Indeed, the objective of this catch-up is to include all the children who will receive the RTS,S/AS01E vaccine and who could not be recruited at ***the*** time of DTP/HepB/Hib administration ***because the study had not yet started.***

All ~~enrolled~~ children ***enrolled in the active surveillance*** will be followed-up through home visits (Figure 1, see also Section 9.2.7.1). Children receiving at least one dose of RTS,S/AS01E will be defined as the vaccinated study participants. For these children, the home visits will be conducted at predefined timepoints after administration of the RTS,S/AS01E vaccine, up to 2 years after the last dose. For children ***not vaccinated with RTS,S/AS01E*** ~~in the exposed clusters whose parents/LARs elect not to have them vaccinated with RTS,S/AS01E (unvaccinated children) and children in the unexposed clusters~~, visits will be scheduled at equal points in time. ***Note that, in practice, it is possible to find RTS,S/AS01E vaccinated children in an unexposed cluster (e.g., parents/LARs from an unexposed cluster can decide to have their child vaccinated in another cluster where the vaccine is available) or RTS,S/AS01E unvaccinated children in an exposed*** cluster (e.g. parents/LARs from an exposed cluster can decide not to have their child vaccinated).

Figure 1 footnote: The catch-up group of the active surveillance will include a group of ***children identified at 1st RTS,S/AS01E dose administration (schedule will depend on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start.*** This group includes RTS,S/AS01E vaccinated children from exposed clusters.

~~children who received at least one dose of DTP/HepB/Hib, whose age corresponds to the age after 3rd DTP/HepB/Hib dose and identified at the 1st dose of RTS,S/AS01E vaccine.~~

15 **Section 9.1.1 Rationale for the study design**: In addition, as the vaccine will be implemented using a cluster design (sites in Kenya and Ghana ~~Malawi~~ where the EPI-MAL-002 ~~was~~ ***is*** running should become part of the intervention areas, and new sites ~~will be~~ ***have been*** selected to be part of the comparison areas of the EPI-MAL-003), a concurrent unvaccinated cohort may be added as a comparator.

Selected study sites are expected to have a HDSS or equivalent surveillance system in place. If a site does not have ***a HDSS*** ~~an equivalent surveillance system~~ in place, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

16 **Section 9.2.1 Study population**: Note: If a site is not part of the INDEPTH network ~~or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for demographic census might be implemented to ensure consistency across study sites.

For this reason, other sites in SSA settings with moderate-to-high transmission of malaria, pertaining to a region where the RTS,S/AS01$_E$ vaccine is planned to be implemented according to MVIP, were~~/will be~~ added to the already defined study sites for EPI-MAL-002 as described below.

In order to align with the MVIP, the study sites for the GSK's baseline, Phase IV and ancillary studies (i.e. EPI-MAL-002, EPI-MAL-003 and EPI-MAL-005, respectively) have been~~, or will be,~~ selected as follows:

- Sites have been~~, or will be,~~ selected from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented ***in the framework of the MVIP***. ~~The only exception is for~~ Burkina Faso sites ***that started EPI-MAL-002 have early terminated the study activities on 06 June 2018 (with the exception of the follow-up check-ups at the hospital for children diagnosed with meningitis, cerebral malaria or with an AESI). Burkina Faso sites will not be included in EPI-MAL-003 because the MVIP will not take place in the country***~~as they have already started EPI-MAL-002. They will continue participating in EPI-MAL-002 until study end; however they will not be included in EPI-MAL-003 because the MVIP will not take place in the country.~~ Their data will therefore not be included neither in the before/after comparison analyses of the EPI-MAL-002 and EPI-MAL-003 studies**,** nor in any other indicators planned to be generated by EPI-MAL-002 data to inform analyses of the EPI-MAL-003 study (e.g. background incidence of meningitis for study sample size and the exposure to other vaccines). ***Considering the RTS,S/AS01$_E$ vaccine implementation date in Malawi that was initially planned in October 2018, the baseline data that might have been collected in Malawi in the EPI-MAL-002 study would have been too limited to be relevant for the before/after comparisons in this country. Therefore, GSK, in agreement with the WHO, decided to focus the conduct of the EPI-MAL-002 study in Ghana and Kenya, not initiating the study in Malawi, and partially compensating the expected sample size from Malawi sites by using the high recruitment foreseen in the Kombewa (Kenya) and Kintampo (Ghana) sites and extending recruitment in the Navrongo site.***
- As per WHO guidance, study sites from Ghana and Kenya ~~and Malawi~~ included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters. ~~Two new sites located in Malawi are planned to be included in EPI-MAL-002.~~

Exposed and unexposed clusters will be comparable in terms of malaria transmission, health facilities level, geographical region and population size.

  - As per WHO guidance, study sites from Ghana and Kenya ~~Malawi~~ included in EPI-MAL-002 should become study sites in EPI-MAL-003 which will be exposed clusters.
  - Selection of the ~~unexposed~~ ***remaining*** study sites/clusters that will be included in the EPI-MAL-003 study is ***completed*** ~~ongoing~~ and is fully embedded in the MVIP.

- In summary: currently, a total of ***3***~~5~~ sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa] ~~2 in Burkina Faso [Sapone, Nouna]~~) are enrolling study

participants in the EPI-MAL-002 study. ~~Two sites in Malawi have fulfilled the criteria of the study feasibility assessment and are planned to initiate the EPI-MAL-002 study in Q1-Q2 2018~~. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 ***sites*** should become exposed study sites/clusters in EPI-MAL-003. Selection of the ***remaining*** ~~unexposed~~ study sites/clusters that will be included in the EPI-MAL-003 study is ***completed*** ~~ongoing~~ and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.

- ~~A replacement strategy has also been elaborated in case one or more of the sites conducting EPI-MAL-002 cannot participate in EPIMAL003. It could consist of extending the recruitment period (depending on vaccine implementation strategy).~~

17 **Section 9.2.2 Eligible population:** In addition, parents/ LARs will be invited to enrol their child into the active surveillance when children ***are presenting for 1st administration of RTS,S/AS01$_E$ vaccine and who either received all DTP/HepB/Hib doses before study start or*** ~~who~~ received at least one dose of DTP/HepB/Hib ***and are,*** ~~,~~ older than the age corresponding to the 3rd DTP/HepB/Hib dose at ***study start,*** ~~, are presenting for 1st administration of RTS,S/AS01$_E$ vaccine~~ (catch-up group).

For enhanced hospitalisation surveillance, parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are under the age of 5 years and who can be linked to the HDSS or equivalent surveillance system ~~census~~, will be approached to enrol their child into this study

18 **Section 9.2.3 Inclusion criteria:** For enrolment in the active surveillance – Catch-up group: children must be aged < 18 months, received at least one dose of DTP/HepB/Hib vaccine, whose age corresponds to the age after the 3rd dose of DTP/HepB/Hib vaccine, ~~(~~***~~= identified at 1st RTS,S/AS01$_E$ dose administration~~ who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start)*** and identified at 1st RTS,S/AS01$_E$ dose administration (This group will include children from exposed clusters only)

19 **Section 9.2.6.9 Death:** * If a site is not part of the INDEPTH network~~, or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

20 **Section 9.2.7.1.1 Enrolment and follow-up:** Parents/ LARs will be invited to enrol their child into the active surveillance when children are presenting for administration of DTP/HepB/Hib vaccine (V0) (any visit for DTP/HepB/Hib vaccine) ***or 1st RTS,S/AS01$_E$ dose during the catch-up group enrolment period (Section 9.2.3).***

21 **Section 9.2.7.1.2 Surveillance of AESI, other AE leading to hospitalisation or death, meningitis and malaria during follow-up**: If a site is not part of the INDEPTH network, ~~or does not have an equivalent surveillance system in place,~~ the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites

An alert system by mobile phone will be developed in the early stages of EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate suspected AESI, meningitis or ~~severe~~ ***cerebral*** malaria episodes to study staff in near real time.

22 **Section 9.2.7.1.4. Outline of study procedures Table 4 footnote 1:**

Completion of Enrolment visit procedures should be achieved within a maximum of 10 days after the administration of DTP/HepB/Hib vaccine for the DTP group or at Visit 1 for the catch-up group.

Table 4 footnote 6: If a site is not part of the INDEPTH network, ~~or does not have an equivalent surveillance system in place,~~ the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites

23 **Section 9.2.7.3.2. Laboratory assays:** ~~GSK~~***The Principal Investigator or designee of each study site/cluster*** will ensure ***monitoring of the availability of*** ~~that all~~ consumables and reagents ***for*** ~~are available to perform first line~~ routine ***practice*** testing ~~for~~ ***of*** ~~all diseases under investigation~~ ***study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents*** ~~according to good medical practice and routine practice~~.

24 **Section 9.2.7.4.1. Meningitis cases:** If needed, ***in case of stock out***, GSK will ***assess the need of*** supplement***ing*** reagents and consumables ~~to ensure that all diagnostic procedures can be conducted according to protocol~~.

Job Aids for medical staff and training on standardised diagnosis are put in place ***as*** in EPI-MAL-002 to improve the sensitivity and specificity of the case diagnosis for all meningitis.

25 **Final meningitis case ascertainment**: The experts will be blinded with regards to ***RTS,S*** vaccine exposure ***as much as possible***.

They will also be provided with all the data available in the eCRF (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records).

26 **Section 9.2.7.4.2 AESI:** The experts will be blinded with regards to ***RTS,S*** vaccine exposure ***as much as possible***. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.1).

27 **Section 9.2.7.4.3. Other AE leading to hospitalisation or death**: They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records) and classify the cases.

28 **Section 9.2.7.4.4. Malaria**: They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination ***(excluding RTS,S)*** and any other relevant information identified in patient medical records) and classify the cases according to the case definitions (see Section 9.2.6.6.)

29 **Section 9.2.7.7. Capacity building: Laboratory support:** ***GSK will support the first line laboratory testing. First, an external laboratory, CLS, is contracted to assess laboratory quality system and as needed, will provide technical assistance in quality systems as well as laboratory training and support/coaching. Second, the principal investigator or designee of each study site/cluster is requested to ensure monitoring of the availability of consumables and reagents for routine practice testing of study endpoints and inform GSK in case of recurrent/long-term stock outs. When recurrent/long-term stock outs are reported, GSK will assess the need of providing consumables and reagents such as*** ~~GSK will ensure that all first line laboratory diagnostic procedures can be conducted according to routine practice by complementing reagents and consumables where needed. Specifically, if necessary,~~ lumbar puncture kits ~~and~~ or malaria RDT ~~will be provided to the sites to facilitate adherence to the routine procedures required~~ for diagnosis of meningitis and malaria, ***respectively***. ~~In addition, an external laboratory, CLS, is contracted to provide Quality Assessment & Control and training for laboratory technicians.~~

Use of time sensitive event device: In addition to data systems traditionally utilised in post approval safety studies, an alert system using mobile phones has been developed ***as*** in EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate time-sensitive events to study staff. The alert system will be implemented in order to closely monitor AESI, meningitis cases, and ~~severe~~ ***cerebral*** malaria and to ensure that all the procedures and tests specified in the protocol are done for a proper diagnosis of the diseases while maintaining the safety of the patients.

In addition, GSK will also be made aware of AESI, meningitis cases, and ~~severe malaria cases including~~ cerebral malaria cases (GSK will not receive any patient's personally identifiable information via that system).

30 **Section 9.3.3.2. Recorded in EPI-MAL-005:** Bednet use, seasonal malaria chemoprevention and other malaria control measures will also be collected at the ~~HDSS or equivalent surveillance system~~ ***study site*** population and individual level***s*** (which will be summarized at centre level).

31 **Section 9.4.1. HDSS** ***(or equivalent surveillance system)*** **databases ~~(or equivalent surveillance systems):~~** ~~Each HDSS or equivalent surveillance system~~ site maintains a demographic database which is updated on a regular basis to include births, deaths, immigrations and emigrations. Data regarding vaccinations ***may*** ~~is~~ also included in the study site database.

If a site is not part of the INDEPTH network ~~or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for demographic census and for verbal autopsy might be implemented to ensure consistency across study sites.

32 **Section 9.4.2. Active surveillance and enhanced hospitalisation surveillance:** The surveillance system will also be implemented in the study area at each health care level ~~within the HDSS or equivalent surveillance system catchment area~~.

33 **Section 9.5.3.1. Before-after design:**

Table 9 Detectable relative risk for AESI, meningitis and cerebral malaria with 80% power for the before-after design based on a Poisson regression method [PASS, ~~2005~~2012]

Period at-risk	Baseline incidence (PY) - 80% power			
	10/100000	50/100000 *	100/100000	500/100000 **
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	*10827.6*~~4665.0~~	*64.2*~~44.0~~	*19.2*~~14.7~~	*3.9*~~3.4~~
6 weeks	*329.8*~~198.2~~	*13.7*~~10.8~~	*6.5*~~5.4~~	*2.4*~~2.2~~
3 months	*91.9*~~61.1~~	*7.8*~~6.4~~	*4.3*~~3.8~~	*2.0*~~1.8~~
6 months	*31.4*~~22.7~~	*4.8*~~4.1~~	*3.1*~~2.8~~	*1.7*~~1.6~~
12 months	*12.8*~~10.1~~	*3.2*~~2.9~~	*2.3*~~2.1~~	*1.5*~~1.4~~
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E				
2 weeks	*9721.6*~~4453.2~~	*61.2*~~43.1~~	*18.6*~~14.4~~	*3.8*~~3.4~~
6 weeks	*302.2*~~189.0~~	*13.1*~~10.6~~	*6.3*~~5.4~~	*2.3*~~2.1~~
3 months	*84.1*~~56.8~~	*7.5*~~6.2~~	*4.2*~~3.7~~	*1.9*~~1.8~~
6 months	*29.0*~~21.6~~	*4.6*~~4.0~~	*3.0*~~2.7~~	*1.7*~~1.6~~
12 months	*12.0*~~9.7~~	*3.1*~~2.8~~	*2.3*~~2.1~~	*1.5*~~1.4~~

* This incidence corresponds to the assumption considered for meningitis

** This incidence corresponds to the assumptions considered for cerebral malaria

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, ~~2005~~2012]

Period at-risk	Baseline incidence 3000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	*1.77*~~1.66~~	*2.2*~~2.04~~
6 weeks	*1.4*~~1.38~~	*1.7*~~1.57~~
3 months	*1.3*~~1.28~~	*1.5*~~1.42~~
6 months	*1.2*~~1.21~~	*1.4*~~1.31~~
12 months	*1,17*~~1.15~~	*1.25*~~1.22~~
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	*1.8*~~1.66~~	*2.2*~~2.03~~
6 weeks	*1.4*~~1.37~~	*1.6*~~1.56~~
3 months	*1.3*~~1.28~~	*1.5*~~1.41~~
6 months	*1.2*~~1.21~~	*1.3*~~1.30~~
12 months	*1.17*~~1.15~~	*1.24*~~1.21~~

34 Section 9.5.4.2. Impact using the before-after design:

Table 14 Detectable total effect for severe malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, ~~2005~~2012]

		Power	80%		
	Severe Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.03	Effects	***21%***~~18%~~	***23%***~~20%~~	***26%***~~23%~~
D3-> D4+1Y (50%)	0.03		***16%***~~14%~~	***18%***~~16%~~	***21%***~~18%~~
D3-> D4+1Y (75%)	0.03		***15%***~~13%~~	***16%***~~14%~~	***18%***~~16%~~

35 Section 9.5.5.2. Impact using the before-after design:

Table 17 Detectable total effect in terms of relative risk for cerebral malaria in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, ~~2005~~ 2012]

		Power	80%		
	Cerebral Malaria		Correlation of covariates		
			0.00	0.20	0.40
D3-> D3+1Y	0.005	Effects	***1,71***~~1.62~~	***1,82***~~1.72~~	***1,99***~~1.86~~
D3-> D4+1Y (50%)	0.005		***1,51***~~1.43~~	***1,58***~~1.49~~	***1,70***~~1.58~~
D3-> D4+1Y (75%)	0.005		***1,45***~~1.38~~	***1,51***~~1.44~~	***1,60***~~1.52~~

36 Section 9.5.6.2. Impact using the before-after design:

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, ~~2005~~2012]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	0.03	***1.25***~~1.22~~	***1.28***~~1.25~~	***1.33***~~1.29~~	***1.37***~~1.33~~	***1.42***~~1.37~~	***1.50***~~1.44~~
D3-> D4+1Y (50%)	0.03	***1.19***~~1.16~~	***1.21***~~1.18~~	***1.25***~~1.21~~	***1.27***~~1.23~~	***1.31***~~1.26~~	***1.36***~~1.31~~
D3-> D4+1Y (75%)	0.03	***1.16***~~1.14~~	***1.19***~~1.16~~	***1.22***~~1.19~~	***1.24***~~1.21~~	***1.27***~~1.23~~	***1.32***~~1.28~~

37 **Sections 9.7.1., 9.7.2 and 9.7.3** "Total cohort" replaced by "enrolled set", "According-to-protocol (ATP) cohort" replaced by "Analysis set" and "cohort" replaced by "set" where applcable.

38 Section 9.7.6.2.2. Meningitis cases monitoring: ~~In the exposed clusters~~, *Among vaccinated subjects from both exposed and unexposed clusters*, the maximum likelihood and the log-likelihood ratios will be estimated each month *if new cases are detected* by means of MaxSPRT method [Kulldorf, 2011] on all suspected meningitis *occurring within the at-risk period* at the site level.

39 **Section 9.9. Limitations of the research methods:** ~~Candidate countries with moderate/high transmission of malaria and where the pilot implementation is likely to take place have already been identified for participation to EPI-MAL-003. Other settings in SSA with moderate-to-high transmission of malaria, from the 3 countries where the RTS,S/AS01$_E$ vaccine will be implemented (see Section 9.2.1), might be added to the already defined study sites, and/or recruitment in the sites already defined might be increased to reach the target number of study participants, ensuring alignment with countries identified by WHO for the staged pilot implementation.~~

For the study sites of EPI-MAL-003 ~~which are unexposed clusters and~~ where the EPI-MAL-002 was not conducted, training will be provided before start of EPI-MAL-003.

The case ascertainment process to classify meningitis cases will be based on additional laboratory testing (mainly based on molecular detection methods such as PCR) and the review of individual data by external experts (blinded to ***RTS,S*** vaccination status ***as much as possible***).

*If a site is not part of the INDEPTH~~, or does not have an equivalent surveillance system in place~~, the INDEPTH procedures for verbal autopsy might be implemented to ensure consistency across study sites.

40 **Section 13 References:** ***PASS 2012: Poisson Regression Power Analysis (Signorini D). 'Sample size for Poisson regression', Biometrika. 1991;78(2): 446-450.***

41 **Annex 1 List of stand-alone documents:**

No.	Document Reference No	Date	Title
7.	***115056 (EPI-MALARIA-003 VS AME)***	***24 April 2019***	***Amendment to the protocol***
8.	115056 (EPI-MAL-003 VS AME)	***24 April 2019***	Protocol ***Amendment 1*** sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	***24 April 2019***	***Protocol Amendment 1*** investigator agreement
10.	115056 (EPI-MAL-003 VS AME)	***24 April 2019***	ENCePP Checklist for study protocols

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Amendment number:	2
Amendment date:	15 October 2020
Co-ordinating author:	PPD, Lead Scientific Writer (GSK)

Rationale/background for changes:

- GSK decided to focus the co-primary study objectives to events classified as identified risk (febrile convulsion) or potential risk (meningitis, cerebral malaria) as per *Mosquirix* RMP. As a consequence, the study objective 'other AEs leading to hospitalisation' is now considered as a secondary objective.
- As the term "Other AEs leading to hospitalisation or death" intended to refer to all the hospitalisations due to other AEs (including the fatal ones) and does not include fatalities that did not occur in the hospital, "or death" has been removed in order to avoid any confusion.
- The EHS eligibility criteria has been revised to include only subjects who are at least 6 weeks and < 5 years of age to allow collection of medical events for a targeted population (avoiding the collection of events related to perinatal period, except foot positional deformation as birth defect).
- The MVIP is considering implementing the malaria vaccine in unexposed clusters as from 2023. This decision will directly impact the temporal (before/after) and concurrent (exposed versus unexposed clusters) comparisons. Based on this, GSK decided to stop the EHS recruitment as from 01 January 2023 in sites that were not involved in the EPI-MAL-002 study and study conclusion will be conducted in a timely manner for already enrolled subjects in those sites (EHS will stop in all sites in Malawi, Siaya and Nyando sites in Kenya and unexposed sites in Ghana).
- Measures that may be applicable during special circumstances (e.g., COVID-19 pandemic) in order to protect participant's welfare and safety, and as far as possible ensure the potential benefit to the participant and promote data integrity have been outlined.
- The mobile phone alert system that was planned to be implemented will no longer be implemented and wording about it in the protocol has been deleted.
- There was an inaccuracy in the baseline incidence of mortality used in the sample size computations for the risk and for the effectiveness and impact on mortality overall and per gender. The baseline incidence has been corrected to 1,000/100,000 person-years according to World Bank estimates.

Amended text has been included in bold italics and deleted text in ~~strikethrough~~ in the following sections:

1. **Section 1 - Research question and objectives:** Co-primary objectives: To estimate the incidence of adverse events of special interest (AESI)~~, and of other adverse events (AE) leading to hospitalisation or death,~~ in children vaccinated with RTS,S/AS01$_E$.

2. **Section 1** – **Authors**: PPD Epidemiology Lead – Malaria (GSK Biologicals), PPD , ***Epidemiology Lead - Malaria*** ~~Clinical and Epidemiology Scientist~~ (GSK Biologicals), PPD , ***Oversight Data Manager***, PPD , PPD ***/ (ICON for GSK Biologicals),*** ~~Mobile Phone Alert System: Parexel (represented by~~ PPD ~~, Senior Project Manager)~~

3. **Section 2** – **OPINION HOLDER**: © 2017~~-2019~~ GSK group of companies or its licensor.

4. **Section 3 - RESPONSIBLE PARTIES**: PPD ~~(DVM, MSc, PhD; Senior Epidemiology Lead - Malaria) and~~ PPD ***(PhD; Epidemiology Lead – Malaria) /*** PPD (MD; Epidemiology Lead – Malaria) are the GSK Biologicals designated contact person~~s~~ for this study.

5. **Section 4 – ABSTRACT**: **Rationale and background:** The first vaccine introduction ***started in April*** ~~is foreseen in~~ 2019 ***in Malawi and Ghana***.

   other adverse events (AE) leading to hospitalisation ~~or death~~,

   The three studies ~~will be~~ ***are*** conducted in similar if not identical settings and with the same methodology for identification and characterisation of the events of interest

6. **Section 4 – Research question and objectives**: **Co-primary objectives:** To estimate the incidence of AESI , ~~and of other AE leading to hospitalisation or death~~, in children vaccinated with RTS,S/AS01E.

   Secondary Objectives – Safety:

- To estimate the incidence of other AEs leading to hospitalisation.
- To describe risk factors for AESI, ~~other AE leading to hospitalisation or death~~, meningitis, and malaria.
- To describe the causes of hospitalisation (including AESI, ~~other AE,~~ meningitis and malaria).
- To assess the potential association between vaccination and AESI, ~~and other AE leading to hospitalisation or death~~ by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.
- ***To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.***

Effectiveness and impact: the incidence of ~~all-cause hospitalisations and~~ hospitalisations attributed to malaria (including *P. falciparum*).

7. **Section 4 – ABSTRACT: Study design:** The diseases under surveillance for safety include AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and severe malaria including cerebral malaria.

   Unexposed clusters: Study sites where the RTS,S/AS01$_E$ vaccine will not be implemented ***at the beginning of*** ~~in~~ the pilot implementation programme by Ministries of Health using an expanded schedule of their routine EPI.

8. **Section 4 – ABSTRACT: Variables**: **Co-primary endpoints:**

- ~~Occurrence of other AE leading to hospitalisation or death~~

Secondary endpoints:

Safety endpoints

- Occurrence of hospitalisation (including those attributed to an AESI, ~~other AE~~, meningitis or malaria), or death.
- ***Occurrence of other AE leading to hospitalisation***

9. **Section 4-ABSTRACT: Data sources**

- Data relevant to the diagnosis of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and malaria (including cerebral malaria)
- Baseline incidence rates of AESI, other AE leading to hospitalisation or ~~death~~…….

10. **Section 4 - ABSTRACT: Study size**

- With the before-after design, and depending on the follow-up, the total effect for severe malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, ranges from ~~14~~ 16% to ~~20~~ 23%, and the direct effect, from 23% to 33%.
- With the before-after design, and depending on the follow-up, the total effect for cerebral malaria which could be detected with 80% of power for a correlation coefficient of covariate equal to 0.2, expressed as RR ranges from ***1.51*** ~~1.44~~ to ***1.82*** ~~1.87~~, and the direct effect, from -***1.55*** ~~1.88~~ to ***1.88*** ~~2.66.~~

11. **Section 4 – ABSTRACT: Data analysis**

    Analysis of co-primary objectives: The incidence rate of each AESI, ~~and other AE leading to hospitalisation or death~~ will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time. A 95% CI will be computed using an exact method for a Poisson variable.

12. **Section 5 – AMENDMENTS AND UPDATES:**

Amendment 2 Final: 15 October 2020

The rationales for protocol amendment 1 & ***protocol amendment 2, ~~is~~ are*** provided in Annex 7.

13. **Section 6 – MILESTONES:** This programme initially planned to make the RTS,S/AS01$_E$ vaccine available in selected areas, starting in 2018 [WHO, 2017], ***but the RTS,S/AS01$_E$ vaccine was implemented in selected areas/clusters of 3 SSA countries in 2019***.

    ~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of 20,250 RTS,S/AS01E recipients. Similarly,~~

Milestone	Planned date
End of data collection	~~Q3~~ ***Q1*** ~~2024~~***2025****
Study progress reports	1 progress report every 6 months
Interim epoch analysis	~~Q3~~ ***Q2*** ~~2022~~***2023****~~*~~ and ad-hoc (if triggered by a safety signal)
Registration in the EU PAS register	***EUPAS28541*** ~~To be determined~~
NCT Number	***NCT03855995***
Statistical analysis completed	~~Q3~~ ***Q4*** 2025*
Final report of study results	~~Q4~~ ***Q1*** ~~2025~~***2026****

*Tentative date; depending on recruitment timelines and implementation of vaccination by the Ministries of Health
~~**Tentative date, depending on recruitment timelines and implementation of vaccination by the Ministries of Health~~

14. **Section 7.1 –Background:** GSK Biologicals has developed a pre-erythrocytic *Plasmodium (P.) falciparum* malaria vaccine, RTS,S/AS01$_E$, for routine immunisation of children living in malaria-endemic countries of SSA. RTS,S/AS01$_E$ is the first vaccine to be implemented for the prevention of malaria and it ***is*** the first AS01-adjuvanted vaccine to be implemented in the paediatric population.

    The pre-implementation (i.e. before vaccine implementation) surveillance study EPI MAL 002, will measure the baseline incidence of protocol-defined adverse events of special interest (AESI), other adverse events (AE) leading to hospitalisation ~~or death~~, meningitis and malaria morbidity and mortality

    ~~If~~ The RTS,S/AS01E vaccine ***was*** ~~is~~ implemented in selected areas/clusters of 3 SSA countries (Ghana, Kenya and Malawi) in 2019**.** ~~at the expected target of,~~ As the vaccine becomes available in the study sites that are exposed clusters, EPI-MAL-003 will be initiated. EPI-MAL-002 and EPI-MAL-003 ~~may~~ ***are*** partly ~~be~~ run concomitantly in the same study sites.

    The three studies ~~will be~~ ***are*** conducted in similar if not identical settings. Sites selection has been done in collaboration with the Malaria Vaccine Implementation Programme (MVIP) coordinated by WHO [WHO, 2017] (refer also to Section 9.2.1), in order to ensure synergy between the latter and those three studies.

~~In~~ ***From*** each pilot country, about 256,000 children ~~will be~~ ***are expected to be*** included into the pilot implementation programme (about 128,000 children in the RTS,S/AS01$_E$ clusters [exposed clusters] and about 128,000 in the comparison arm [unexposed clusters]).

Table 2 footnote: C3C group: 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. ***Note that it is only for the 5-17 months age category.***

- Low fatality rate overall in study MALARIA-055 compared to what could be expected: 1 to 2% in each group, while in real-life setting mortality under 5 ***years old*** in SSA is estimated to be ~~3% (WHO) to~~ 5% (World bank);

15. **Section 7.3 – Efficacy results of the clinical development of RET,S/AS01$_E$:**

    In three trial sites (Korogwe, Tanzania; Nanoro, Burkina Faso and Kombewa, Kenya) of the MALARIA-055 study, children were followed for 3 additional years to further document the long-term incidence of severe malaria in RTS,S/AS01$_E$ and control groups (study MALARIA-076). Secondary objectives included evaluation of the incidence of clinical malaria, parasite prevalence, and serious adverse events of special interest.

    The incidence of severe malaria was very low in each of the three study sites and was consistent with the epidemiology of the disease in high transmission areas – showing a decreased incidence of severe malaria with increasing age during childhood. There was no indication of rebound of severe malaria during the three additional years of follow-up in children who received either 3, or 4 doses of RTS,S/AS01$_E$.

    In Nanoro (Burkina Faso), the site with highly seasonal malaria transmission, an increased susceptibility to uncomplicated malaria was observed. This increase did however not outweighing the initial benefit offered by the RTS,S/AS01$_E$ vaccine, and most importantly did not appear to result in an increase of severe malaria cases.

    In all three sites vaccine efficacy estimates against clinical malaria and the impact in terms of clinical cases averted remained positive over the six- to seven-year period, starting from the first vaccine dose in study MALARIA-055 until the end of follow-up in study MALARIA -076

    Overall vaccine efficacy over the 7-year follow-up period was:

    - against clinical malaria: 4 doses: 24% (95% CI: 16, 31); 3 doses: 19% (95% CI: 11, 27)

    - against severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32) [Tinto, 2019].

16. **Section 7.4 – Summary of study rationale:** The first vaccine introduction ***occurred*** in 2019 ***after*** approv***al*** ~~ed~~ and recommend***ation*** ~~ed~~ by local health authorities. ***The RTS,S/AS01$_E$ vaccine was implemented in selected areas/clusters of 3 SSA countries and plan to expand the RTS,S/AS01$_E$ vaccination programme to the unexposed areas/clusters from 2023 is under discussion***.~~is foreseen ,~~

or which may hypothetically be associated with RTS,S/AS01$_E$ due to the fact that this vaccine has components which are new compared to current widely used vaccines), other AE leading to hospitalisation ~~or death~~, and meningitis (potential risk) among a minimum of 20,250 vaccinated study participants from exposed clusters.

The pre-implementation study EPI-MAL-002 (i.e. before vaccine implementation), of approximately 30,000 children in several sites in SSA countries (with at least 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented), will measure the baseline incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and malaria morbidity and mortality.

EPI-MAL-003 ~~will be~~ ***is*** conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005

17. **Section 8.1** – **Co-primary objectives:** To estimate the incidence of AESI, ~~and of other AE leading to hospitalisation or death,~~ in children vaccinated with RTS,S/AS01E.

18. **Section 8.2.1** - **Safety**: ***To estimate the incidence of other AE leading to hospitalisation***

- To describe risk factors for AESI, other AE leading to hospitalization ~~or death~~, meningitis, and malaria.

  To assess the potential association between vaccination and AESI, ~~and other AE leading to hospitalisation or death~~ by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$

  To assess the potential association between vaccination and other AE leading to hospitalisation by comparing the incidence of these events in children vaccinated with RTS,S/AS01$_E$ with the incidence of these events in children not vaccinated with RTS,S/AS01$_E$.

19. **Section 9.1 – Study design:** The design will include active surveillance ***(corresponds to a prospective cohort monitoring)*** and enhanced hospitalisation surveillance (Figire 1) in both exposed and unexposed clusters (see Annex 2 for definitions).

    Catch-up group: Children identified at 1st RTS,S/AS01$_E$ dose administration (schedule ~~will~~ depend***s*** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start.

    <u>Enhanced hospitalisation surveillance</u>: All children ***who are at least 6 weeks and*** <5 years ***of age*** ~~under the age of~~, within the study areas in both exposed and unexposed clusters, not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not eligible for active surveillance ***at the time of hospitalisation***, are eligible for enrolment in enhanced hospitalisation surveillance ~~throughout the whole study period~~ (Figure 1, see also Section 9.2.7.2). A home visit will be conducted at

study conclusion. For the purpose of this study, hospitalisation is defined as spending at least one night at a health care facility.

Since the MoHs of the countries participating in the MVIP according to the SAGE/MAPC recommendation plan to expand the RTS,S/AS01$_E$ vaccine implementation to the unexposed clusters from 2023, clusters that were initially unexposed will become exposed with regards to RTS,S/AS01$_E$ vaccination. This change in vaccine implementation directly impacts the current study plan. Therefore, the enrolment of subjects in the enhanced hospitalisation surveillance will be stopped in clusters that were not involved in the EPI-MAL-002 study (i.e. all clusters in Malawi; unexposed clusters in Ghana and 1 exposed and 2 unexposed clusters in Kenya) as from 01 January 2023. Subjects already enrolled in EHS will continue to be followed until study conclusion., in order to capture information on their subsequent hospitalisations. Study conclusion will be conducted in a timely manner from 01 January 2023.

As initially planned, the enrolment of subjects in EHS will be pursued until the end of study in clusters involved in the EPI-MAL-002 study because this will provide relevant information for the before/after comparison.

Figure 1 footnote:

The catch-up group of the active surveillance will include a group of children identified at 1st RTS,S/AS01$_E$ dose administration (schedule ~~will~~ depend***s*** on pilot implementation programme and national regulation) who either received all DTP/HepB/Hib doses before study start or received at least one dose of DTP/HepB/Hib and are older than the age corresponding to the 3rd DTP/HepB/Hib dose at study start***.*** This group includes RTS,S/AS01$_E$ vaccinated children from exposed clusters.

For active surveillance, ***c***ontinuous monitoring of hospitalisations will be done throughout the whole study period. ***For EHS, the continuous monitoring of hospitalisations will be done throughout the whole study period for clusters involved in EPI-MAL-002 study. For the other clusters not involved in EPI-MAL-002 study, enrolment into EHS will be stopped and study conclusion will be conducted in a timely manner from 01 January 2023.***

The diseases under surveillance for safety include AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and severe malaria including cerebral malaria.

20. **Section 9.1.1 - Rational for study design:** Study EPI-MAL-003 ~~will be~~ ***is*** conducted in similar if not identical settings as EPI-MAL-002 and EPI-MAL-005 studies. The pre implementation study EPI MAL 002 (i.e. before vaccine implementation) measures the baseline incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and malaria morbidity and mortality. The mortality rate, overall and by gender, will also be estimated.

    Active surveillance: If a SAE ***(AESI or meningitis or severe malaria including cerebral malaria*** is detected in the child, he or she will be followed for an additional 12 months to further characterise the event.

    Enhanced hospitalisation surveillance

    other AE leading to hospitalisation ~~or death~~

    ~~Throughout the whole study period,~~ All hospitalised children ***who are at least 6 weeks and*** <5 years ***of age*** ~~under the age of~~ within the study areas who are not already enrolled in the active surveillance (because parents/ LARs declined enrolment in active surveillance or because recruitment had been completed) or not

eligible for active surveillance, are eligible for enrolment in enhanced hospitalisation surveillance, to allow for data collection regarding that hospital visit and any subsequent ~~hospital visits~~ ***hospitalisations*** until study conclusion.

21. **Section 9.2.1- Study population:** The cohort is considered dynamic, as ***infants*** ~~newborns~~ and immigrants are included in the cohort and the birth or in-migration date is recorded. Similarly, deaths and outmigrations- are recorded.

- In summary: currently, a total of 3 sites (2 in Ghana [Kintampo, Navrongo] and 1 in Kenya [Kombewa]) ~~are~~ ***have*** ~~enrolling~~ ***enrolled*** study participants in the EPI-MAL-002 study. With the exception of the Burkina Faso sites and according to WHO guidance, all EPI-MAL-002 sites ~~should~~ ***have*** become exposed study sites/clusters in EPI-MAL-003. Selection of the remaining study sites/clusters that will be included in the EPI-MAL-003 study is completed and is fully embedded in the MVIP. Study feasibility in all sites/clusters is assessed through a comprehensive scientific and operational study site assessment.

  Taking into account a global birth cohort of 23,000 children ***at the time of EPI-MAL-002 study preparation***, and the refusal rate of parents for their children to join the study, an expected number of at least 45,000 children, including 22,500 children in the exposed clusters (with minimum of 20,250 children vaccinated with RTS,S/AS01$_E$ and a minimum of 2,250 unvaccinated children) and 22,500 children in the unexposed clusters will be part of the active surveillance of the study. The vaccine coverage in the exposed clusters and enrolment will be monitored through the progress reports. ~~In the participating sites, the vaccine coverage is not expected to be low. However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure that the target of minimum 20,250 RTS,S/AS01$_E$ recipients is reached. Similarly,~~

22. **Section 9.2.2 – Eligible population: For enhanced hospitalisation surveillance**, parent(s)/LAR(s) of all hospitalised children (from both exposed and unexposed clusters), who are ***at least 6 weeks and*** <5 years ***of age*** ~~under the age of~~ and who can be linked to the HDSS or equivalent surveillance system, will be approached to enrol their child into this study:

- If a child, who is first identified during hospitalization by study staff, fulfills the eligibility criteria for enrolment in active surveillance (within the recruitment period), enrolment in active surveillance will be proposed. If the parents/LARs decline enrolment in active surveillance ***and if the child fulfills the eligibility criteria for enrolment in enhanced hospitalisation surveillance***, enrolment in enhanced hospitalisation surveillance will be proposed.

23. **Section 9.2.3 – Inclusion criteria:** For enrolment in the enhanced hospitalisation surveillance: children must be aged ***at least 6 weeks and*** <5 years ***at the time of hospitalisation*** ~~and hospitalised~~ at any time during the study. (This group will include children from exposed and unexposed clusters.)

24. **Section 9.2.5 – Study period:** Taking into account a global birth cohort of 23,000 children ***at the time of EPI-MAL-002 study preparation*** (11,500 children in the exposed clusters, and 11,500 children in the…….

~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of minimum 20,250 RTS,S/AS01$_E$ recipients. Similarly,~~

(Children reporting a SAE ***due to study procedure might*** ~~will~~ have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months).

25. **Section 9.2.6 – Case definitions**

Hepato-Gastrointestinal and Renal System				
Intussusception	Average rate 1 case per 3,300; yearly variations 1:2,500 to 1:5,000 (<1 yr old, Panama) [Sáez-Llorens, 2004]; <5/100,000 PY (<9 wks), 62/100,000 PY (26-29 wks), 26/100,000 PY (52 wks) (US) [Tate, 2008]; 8.1/100,000 PY (<1 yr Australia) [Justice, 2005]	Overall estimate of risk of IS ~~during the 7 days after vaccination with *Rotarix* 6.8 (95% CI: 2.4, 19.0) and with *RotaTeq* 9.9 (95% CI: 3.7, 26.4) after dose 1.~~ ***within 7 days is estimated at 5.4 (95% CI: 3.9-7.4) after 1st dose Rotarix and 5.5 (95% CI:3.3-9.3) after 1st dose RotaTeq.*** Small increase after dose 2 for both vaccines [Carlin, 2013; Rosillon, 2015]	1 to 7 days after 1st and 2nd doses of *Rotarix* and *RotaTeq* vaccines	BC

26. **Section 9.2.6.3:** ***Collection of hospitalisations for an AE other than AESI or meningitis or any malaria or severe malaria (including cerebral malaria) will be stopped as of 01 January 2023 in subjects previously enrolled in EHS, in sites not involved in EPI-MAL-002 study. Hospitalisations for an AE other than an AESI, meningitis, any malaria or severe malaria (including cerebral malaria) will continue to be collected as part of continuous monitoring for subjects enrolled in AS in all sites or EHS in sites involved in EPI-MAL-002 study.***

27. **Section 9.2.6.9:** Deaths, including malaria attributed deaths with an uncertain diagnosis ~~and outcome~~ after review by the GSK safety physician, will be reviewed by the expert panel to confirm the primary/secondary cause of death (see Section 9.2.7.4.3).

28. **Section 9.2.7.1.1 – *Enrolment and follow-up:*** Surveillance of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and malaria will be performed as described below.

29. **Section 9.**2.7.1.2 - Surveillance of AESI, ~~other AE leading to hospitalisation or death,~~ meningitis and malaria during follow-up.

    The surveillance of AESI, ~~other AE leading to hospitalisation or death~~, meningitis and measures of malaria burden will be done at different levels in line with the surveillance strategy implemented for the EPI-MAL-002 study.

- **Reporting by primary health care facilities and hospitals**

  SAE ***due to study procedure might*** have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months.

  ~~An alert system by mobile phone will be developed in the early stages of EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate suspected AESI, meningitis or cerebral malaria episodes to study staff in near real time. The study staff, as designated by the principal investigator, will~~

~~provide necessary guidance for appropriate case management. Mobile phone reporting logs will be cross-checked with hospital discharge logs and primary health care facility registries for process improvement.~~

To maximise the possibility of capturing an AESI, ~~other AE leading to hospitalisation or death,~~ meningitis, or malaria, an active search will be performed by the study staff through hospital rounds and by regular (at least 3 times a week) review of patient records at primary health care facilities.

The eCRFs for the reporting of AESI, ~~other AE leading to hospitalisation or death,~~ meningitis, or malaria will allow timely reporting of the first signs and symptoms detected by the community health workers and health care staff and completion of diagnostic information, as more results from examination in hospitals with specialised care become available. Clinicians in charge of the patients may seek consultation with RAFT study physicians for case confirmation. Data entry is described in Section 9.6.

The maximum intensity (mild, moderate, severe) of each AESI, ~~other AE leading to hospitalisation or death,~~ and meningitis recorded in the eCRFs will be assigned to categories.

30. ***Section 9.2.7.1.3: Surveillance of other AE leading to hospitalisation during follow-up***

    The surveillance of other AE leading to hospitalisatin will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2.

31. ***Section 9.2.7.1.4: Surveillance for death***

    The surveillance of death will be done and reported in the eCRF as described for surveillance of AESI, meningitis and measures of malaria burden in Section 9.2.7.1.2

32. **Section 9.2.7.1.6 - Table 4: List of study procedures for participants in active surveillance**

Visit days	1W (5-10 D) after 1st RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 2nd RTS,S dose or equal point in time for unvacc.	1W (5-10 D) after 3rd RTS,S dose or equal point in time for unvacc.	6W (40-50 D) after 3rd RTS,S dose or equal point in time for unvacc.	6 M (±2 W) after 3rd RTS,S dose or equal point in time for unvacc.	1 W (5-10 D) after 4th dose of RTS,S or equal point in time for unvacc.	6 W (40-50 D) after 4th dose of RTS,S or equal point in time for unvacc.	12 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.	24 M (±2 W) after 4th dose of RTS,S or equal point in time for unvacc.	Study end or child reaches 5 years of age, whichever occurs first *(±2 W)*
Record any detected signs and symptoms including AESI, other AE, leading to hospitalisation ~~or death~~, meningitis, malaria, abscess at injection site, foot positional deformations	●	●	●	●	●	●	●	●	●	

33. **Section 9.2.7.2.13.** Record cases of suspected AESI, other AE leading to hospitalisation ~~or death~~, meningitis cases, malaria episodes diagnosed by RDT and/or microscopy, abscess at injection site and foot positional deformations

34. **Section 9.2.7.2.15 – Study conclusion**

    Note: For subjects enrolled in EHS, data collection of other AE leading to hospitalisation will be stopped as from 1st January 2023 in sites not participating in EPI-MAL-002. For those subjects, a study conclusion visit will be conducted in a timely manner from 01 January 2023. For subjects diagnosed with an AESI, meningitis or cerebral malaria, check-up visits will be performed as planned, at 1 month, 6 months and 1 year after hospital discharge.

35. **Section 9.2.7.2.16 – Outline of study procedures: Table 5 List of study procedure to be conducted in the event of hospitalization**

Type of contact	Hospitalisation visit	Study conclusion visit* (Study end or child reaches 5 years, whichever occurs first) *(±2 W)*
Record any cases of death and cause of death	●	●

**** For subjects enrolled in EHS in sites not participating in EPI-MAL-002, a study conclusion visit will be conducted in a timely manner from 01 January 2023.***

36. **Section 9.2.7.4.3.** ~~Other AE leading to hospitalisation or~~ Death

    ~~Other AE leading to hospitalisation or~~ Death with an uncertain diagnosis ~~and outcome~~ after review by the GSK safety physician will be reviewed by the external panel of experts. These cases will be flagged in the eCRF during the manual cleaning

by the GSK safety physician, for external expert review. Two selected experts will independently review ***and confirm the possible cause of death*** ~~the cases~~. They will be provided with all available medical information (e.g. medical and family history, physical examination, clinical presentation/picture, laboratory results, concomitant medication/vaccination (excluding RTS,S) and any other relevant information identified in patient medical records) and classify the cases ***according to the cause of death***.

37. **Section *9.2.7.4.4 Other AE leading to hospitalization***

    Other AE leading to hospitalisation or with an uncertain diagnosis and outcome after review by the GSK safety physician will be reviewed by the external panel of experts as described in Section 9.2.7.4.3.

38. Section 9.2.7.5. Management of AESI, other AE leading to hospitalisation ~~or death~~, meningitis cases, malaria, abscess at injection site and foot positional deformations

39. Section 9.2.7.7 Capacity building

- ~~Use of time sensitive event device~~

  ~~In addition to data systems traditionally utilised in post approval safety studies, an alert system using mobile phones has been developed *as* in EPI-MAL-002. Health care staff and first line clinicians will use this system to communicate time-sensitive events to study staff. The alert system will be implemented in order to closely monitor AESI, meningitis cases, and cerebral malaria and to ensure that all the procedures and tests specified in the protocol are done for a proper diagnosis of the diseases while maintaining the safety of the patients. Mobile phone reporting logs will be cross-checked with hospital discharge logs and primary health care facility registries for process improvement.~~

  ~~In addition, GSK will also be made aware of AESI, meningitis cases, and cerebral malaria cases (GSK will not receive any patient's personally identifiable information via that system). The system should act as an alert system between the health care facilities and the principal investigator, but is not intended to replace the reporting through eCRF (as defined in Section 11).~~

40. ***Section 9.2.8 Study procedures during special circumstances***

    During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Active safety follow-up through home visits may be replaced by a telephone call or other means of virtual contact. It is acknowledged that the systematic measurement of body temperature may not be performed.***
- ***For children diagnosed with AESI, meningitis or cerebral malaria, the check-up at the hospital at 1 month, 6 months and 1 year after hospital discharge may be replaced by a telephone call or other means of virtual contact .***

- ***The study conclusion home visit maybe replaced by a telephone call or other means of virtual contact.***
- ***A retrospective data collection of medical events based on medical records may be implemented at any of the health care facilities.***

  Note: Certain restrictions might make it impossible for parents/LARs to provide written consent for changes in study procedures during special circumstances. Parents/LARs of subjects already enrolled will provide consent verbally.

41. **Section 9.3.1 - Co-primary endpoints:**

- ~~Occurrence of other AE leading to hospitalisation or death (see Sections 9.2.6.3 and 9.2.6.9 for definitions).~~

42. **Section 9.3.2.1 - Safety endpoints:**

- Occurrence of hospitalisation (including those attributed to an AESI, other AE, meningitis or malaria) or death.
- ***Occurrence of other AE leading to hospitalisation (see section 9.2.6.3 and section 9.2.6.9 for definitions)***.

43. **Section 9.4.2 – Active surveillance and enhanced hospitalisation surveillance**

e. AESI, other AE leading to hospitalisation ~~or death,~~ meningitis, or malaria will be recorded in the eCRF. Data entry is described in Section 9.6

The investigator will assess the maximum intensity (mild, moderate, severe) that occurred over the duration of the event for all AESI, other AE leading to hospitalisation ~~or death,~~ or meningitis reported during the study. The assessment will be based on the investigator's clinical judgement.

44. **Section 9.4.3 – Baseline study EPI_MAL-002**

The study EPI-MAL-002 is designed to estimate baseline incidence rates of AESI, other AE leading to hospitalisations ~~or death~~, any malaria and severe malaria including cerebral malaria, meningitis, and all-cause and malaria-specific mortality prior to introduction of RTS,S/AS01$_{E.}$

45. **Section 9.5.1 – Sample size for co-primary objectives:** For example, the 95% CI around the observed incidence of 21.7 ~~(23.9)~~ per 100,000 PY (25 events detected) will be [14.1, 32.1] ~~([18.7, 30.1])~~ for a follow-up of 2 years ~~(respectively 5.2 years)~~ ***and respectively the 95% CI around the observed incidence of 23.9 per 100,000 PY (71 events detected) will be [18.7, 30.1]) for a follow-up 5.2 years.***

46. **Section 9.5.2 - Sample size for meningitis monitoring:** With T = 10 (estimated as the cumulative number of meningitis cases based on EPI-MAL-002 background incidence, EPI-MAL-003 cohort size and period of follow-up of 1 year following dose 3), a true RR = 3 can be detected with power exceeding 90% after observing 8 cases of meningitis in EPI-MAL-003 exposed clusters ~~in a follow-up time corresponding to an observed RR equal to 3.~~

47. **Section 9.5.3.1 – Before -after design**

Table 10 Detectable relative risk for mortality overall and by gender with 80% power for the before-after design based on a Poisson regression method [PASS, 2012]

Period at-risk	Baseline incidence *1*~~3~~000/100000 PY - 80% power	
	Overall	By gender
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	~~1.77~~***2.63***	***3.87***~~2.2~~
6 weeks	***1.85***~~1.4~~	***2.36***~~1.7~~
3 months	***1.62***~~1.3~~	***1.97***~~1.5~~
6 months	***1.45***~~1.2~~	***1.68***~~1.4~~
12 months	***1.32***~~1,17~~	***1.47***~~1.25~~
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	***2.60***~~1.8~~	***3.80***~~2.2~~
6 weeks	***1.83***~~1.4~~	***2.33***~~1.6~~
3 months	***1.60***~~1.3~~	***1.93***~~1.5~~
6 months	***1.43***~~1.2~~	***1.66***~~1.3~~
12 months	***1.30***~~1.17~~	***1.45***~~1.24~~

48. **Section 9.5.3.2 – Cluster design**

Table 12 Detectable relative risk for mortality overall and by gender with 80% power for the cluster design based on a Poisson regression (over dispersion equal to 2) method [PASS, 2005]

Period at-risk	Baseline incidence *1*~~3~~000/100000 PY - 80% power	
	Overall	Per gender
50% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	~~1.77~~***2.65***	~~2.23~~***3.88***
6 weeks	~~1.44~~***1.86***	~~1.66~~***2.37***
3 months	~~1.33~~***1.63***	~~1.49~~***1.98***
6 months	~~1.24~~***1.45***	~~1.36~~***1.69***
12 months	~~1.18~~***1.32***	~~1.26~~***1.48***
75% of the children with primary schedule received a 4th dose of RTS,S/AS01E		
2 weeks	~~1.76~~***2.60***	~~2.20~~***3.80***
6 weeks	~~1.43~~***1.83***	~~1.65~~***2.33***
3 months	~~1.32~~***1.61***	~~1.48~~***1.94***
6 months	~~1.24~~***1.44***	~~1.35~~***1.66***
12 months	~~1.17~~***1.31***	~~1.25~~***1.46***

49. **Section 9.5.4.2 – Impact using the before-after design**

Table 14 presents the total effect which could be detected with 80% of power, going from ***16***% ~~14~~ to ***23***%~~20~~ for a correlation coefficient of covariate equal to 0.20, and depending on the scenario.

50. **Section 9.5.5.2 – Impact using the before-after design**

Table 17 presents the total effect which could be detected with 80% of power, going from ***1.51***~~1.44~~ to ***1.82*** ~~1.72~~ for a correlation coefficient of covariate equal to 0.20 expressed as a RR, and depending on the scenario.

51. **Section 9.5.6 - Sample size for the effectiveness and impact on mortality rate, overall and per gender**

- Reference mortality rate: ***1/100PY*** ~~3%~~*

  *In real-life setting under 5 years mortality in SSA is estimated to be ~~3% (WHO) to~~ 5% (World Bank). ~~3% is considered to take the conservative approach.~~

52. **Section 9.5.6.1 – Effectiveness (direct effect)**

Table 19 presents the direct effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going ***1.56***~~1.30~~ to ***2.00***~~1.50~~ for overall and from ***1.88***~~1.44~~ to ***2.66***~~1.76~~ per gender, and depending on the scenario.

Table 19 Detectable direct effect in terms of mortality rate ratio, overall and per gender with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	***0.01***~~0.03~~	***1.86***~~1.43~~	***2.00***~~1.50~~	***2.23***~~1.59~~	***2.40***~~1.66~~	***2.66***~~1.76~~	***3.10***~~1.93~~
D3-> D4+1Y (50%)	***0.01***~~0.03~~	***1.51***~~1.27~~	***1.59***~~1.31~~	***1.70***~~1.36~~	***1.79***~~1.40~~	***1.92***~~1.46~~	***2.12***~~1.55~~
D3-> D4+1Y (75%)	***0.01***~~0.03~~	***1.49***~~1.26~~	***1.56***~~1.30~~	***1.68***~~1.35~~	***1.76***~~1.39~~	***1.88***~~1.44~~	***2.07***~~1.53~~

53. **Section 9.5.6.2 – Impact using before-after design**

Table 20 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from ***1.34***~~1.16~~ to ***1.53***~~1.25~~ for overall and from ***1.51***~~1.23~~ to ***1.82***~~1.37~~ per gender, and depending on the scenario.

Table 20 Detectable total effect in terms of mortality rate ratio, overall and per gender in the before-after design with 80% power based on a Poisson regression method, according to different correlations of covariates [PASS, 2012]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	***0.01***~~0.03~~	***1.47***~~1.25~~	***1.53***~~1.28~~	***1.63***~~1.33~~	***1.71***~~1.37~~	***1.82***~~1.42~~	***1.99***~~1.50~~
D3-> D4+1Y (50%)	***0.01***~~0.03~~	***1.34***1.19	***1.39***~~1.21~~	***1.46***~~1.25~~	***1.51***~~1.27~~	***1.58***~~1.31~~	***1.70***~~1.36~~
D3-> D4+1Y (75%)	***0.01***~~0.03~~	***1.30***~~1.16~~	***1.34***~~1.19~~	***1.40***~~1.22~~	***1.45***~~1.24~~	***1.51***~~1.27~~	***1.60***~~1.32~~

54. **Section 9.5.6.3 – Impact using the cluster design**

Table 21 presents the total effect expressed as mortality rate ratio which could be detected with 80% of power, for a correlation coefficient of covariate equal to 0.20, going from 1.***35***~~1.19~~ to 1.***54***~~1.29~~ for overall and from 1.***52***~~1.28~~ to 1.***82***~~1.42~~ per gender, and depending on the scenario.

Table 21 Detectable total effect in terms of mortality rate ratio, overall and per gender in the cluster design with 80% power based on a Poisson regression method (over dispersion equal to 2), according to different correlations of covariates [PASS, 2005]

		Correlation of covariates					
		Overall			Per gender		
	Mortality	0.00	0.20	0.40	0.00	0.20	0.40
D3-> D3+1Y	***0.01***~~0.03~~	***1.47***~~1.25~~	***1.54***~~1.29~~	***1.64***~~1.34~~	***1.72***~~1.37~~	***1.82***~~1.42~~	***2.00***~~1.50~~
D3-> D4+1Y (50%)	***0.01***~~0.03~~	***1.35***~~1.19~~	***1.40***~~1.22~~	***1.48***~~1.26~~	***1.53***~~1.28~~	***1.60***~~1.32~~	***1.72***~~1.38~~
D3-> D4+1Y (75%)	***0.01***~~0.03~~	***1.31***~~1.17~~	***1.35***~~1.19~~	***1.41***~~1.22~~	***1.45***~~1.24~~	***1.52***~~1.28~~	***1.61***~~1.32~~

55. **Section 9.7 – Data analysis:** Sensitiv***ity*** analyses will be conducted including ***all*** subjects ***from EPI-MAL-002 study (i.e. subjects*** from both age groups (6-12 weeks, 5-17 months)) using an adjustment on the age.

56. **Section 9.7.2 – Study participant disposition**

    ~~Number of subjects with at least one AE leading to hospitalisation or death and number of AE leading to hospitalisation or death;~~

57. **Section 9.7.5.2.1 – Incidence rate of AESI ~~and other AE leading to hospitalisation or death~~**

The incidence rate of each AESI and other AE leading to hospitalisation ~~or death~~ will be calculated by dividing the number of study participants reporting at least one event over the follow-up period by the total person-time

~~For other AE leading to hospitalisation or death the at-risk period for the analyses will be defined with the support of the GSK safety physicians and the panel of experts. In addition, the distribution of the Time-to-Onset of events after vaccination will be described, and additional at-risk periods will be considered based on the results as sensitivity analyses.~~

Incidence rates of these composite endpoints will be calculated as described for individual AESI~~/ other AE leading to hospitalisation or death;~~ in case of multiple cases in a study participant, only the first event will be considered in this analysis.

58. **Section 9.7.6.3 – Incidence rate of cerebral malaria:** Incidence rate (and 95% CI) of cerebral malaria will be estimated with the same approach as for an AE***SI*** as described in Section 9.7.5.2.

59. **Section 9.7.6.4 – Mortality rate:** Mortality rate and 95% CI (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), both overall and by gender, will be estimated with the same approach as for an AE***SI*** as described in Section 9.7.5.2 using the entire follow-up as at-risk period.

60. **Section 9.7.6.5 - Cause of hospitalisation *due to AESI, meningitis or malaria* and death in children < 5 years vaccinated with RTS,S/AS01E and unvaccinated children < 5 years**

~~AE and AESI will be grouped as described above in Section 9.7.5.2.1 (Subsection on: Incidence for children < 5 years). In the same way,~~

61. ***Section 9.7.6.6 - Other AE leading to hospitalisation***

Incidence rate (and 95% CI) of other AE leading to hospitalisation will be estimated with the same approach as for an AESI as described in Section 9.7.5.2.

All other AE leading to hospitalisation will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary and presented by System Organ Class (SOC) and Preferred Term (PT).

62. **Section 9.7.6.7.1 – Before-after comparison**

Further analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) (see Section 9.7.5.2) will consist of a comparison of its incidence rate before (i.e. unvaccinated EPI-MAL-002 from active surveillance) and after (vaccinated EPIMAL003 from active surveillance) introduction of RTS,S/AS01$_E$ vaccine by means of a Poisson regression model with the study site as an adjusted factor.

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is equal to the incidence in the before cohort (EPI-MAL-002)
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the before cohort (EPI-MAL-002).

Exposure determinants and potential risk factors for AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) could also be collected at study entry and evaluated using univariate and multivariable Poisson regression models only for the incidence following immunisation.

Of note, multivariable models will be conducted for a specific AESI, MedDRA SOC and PT of other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) if a signal is detected (i.e. the null hypothesis is rejected) and if a minimum number of cases of AESI, other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) is observed (at least 10 cases in total).

The attributable risk in the vaccinated study participants will be derived for AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) as (Risk Ratio-1)/Risk Ratio [Cole, 1971].

Finally, a model with study site considered as random effect will be performed as sensitive analysis for the analysis of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) (Section 9.6.9.1.2).

63. **Section 9.7.6.7.2 – Cluster design comparison**

Analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis or cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of the exposed and the unexposed clusters from EPI-MAL-003 by means of a random-effect Poisson regression model with the clusters as random effect.

64. **Section 9.7.6.7.3 – Exposed clusters comparison**

For the exposed clusters only, analyses of AESI, other AE leading to hospitalisation ~~or death~~, meningitis and cerebral malaria as well as death (overall death and death by gender) will consist of a comparison of vaccinated study participants from the exposed clusters of EPI-MAL-003 and unvaccinated study participants from the exposed clusters of EPI-MAL-003 by means of a Poisson regression model with the study site as an adjusted factor.

These comparisons will use the following null and alternative hypotheses:

- Null hypothesis (H_0): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is equal to the incidence in the unvaccinated cohort (EPI-MAL-003).
- Alternative hypothesis (H_1): the incidence of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, cerebral malaria or death (overall death and death by gender) in the RTS,S/AS01$_E$ vaccinated cohort (EPI-MAL-003) is not equal to the incidence in the unvaccinated cohort (EPI-MAL003).

65. ***Section 9.7.13 – Statistical analyses during special circumstances***

Special circumstances (see section 9.2.8) may have an impact on the proposed analysis plan. Any changes in the analysis plan will be further described in the SAP.

66. **Section 9.9 - Limitations of the research methods**

The enhanced hospitalisation surveillance should help to identify additional cases of AESI, other AE leading to hospitalisation ~~or death~~, meningitis, and any severe malaria occurring in children living in the study area but not enrolled in the active surveillance.

The surveillance is planned such that cases (AESI, other AE leading to hospitalisation ~~or death~~, meningitis, any and severe malaria, including cerebral malaria) are likely to be identified.

~~However, if the vaccine coverage is low, the recruitment strategy will be adapted to ensure the recruitment of at least 20,250 RTS,S/AS01$_E$ recipients.~~ ~~Similarly,~~

Detecting the occurrence of AESI, ~~other AE leading to hospitalisation or death,~~ and meningitis cases following immunisation with RTS,S/AS01$_E$ after its introduction in vaccination programmes are the primary objectives of this study.

~~Introduction of an alert system using mobile phones to ease communications between the health care staff and the study staff will enable the adherence to national~~

~~recommendations for diagnosis during the study. However, meningitis cases based on clinical symptoms only, or suspected cases, can be expected.~~

The co-primary objectives will provide estimates of the incidence of AESI ~~of other AE leading to hospitalisation or death,~~ and of aetiology-confirmed meningitis.

67. **Section 11.4 – Reporting of adverse events not via eCRF**

- Any AE which, in the opinion of the investigator, is suspected to be related to a GSK licensed product other than RTS,S/AS01$_E$ must be reported, within 24 hours of awareness, directly to GSK Safety for entry in GSK's safety database, and potential expedited reporting to ***relevant National H***ealth authorities.
- ***Any AE which, in the opinion of the investigator, is suspected to be related to RTS,S/AS01$_E$ and which is not collected per study protocol, must be reported to relevant National Health authorities following the local pharmacovigilance legislation***.

68. **Section 13 – References**

AMP: Agence de Médecine Préventive. ***http://amp-africa.org*** ~~http://amp-vaccinology.org/.~~ Accessed 06 September 2017.

Tinto H, Otieno W, Gesase S, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis 2019;19: 821–32

United Nations. Sex differentials in childhood mortality, New York, 2011. ***https://www.un.org/en/development/desa/population/publications/pdf/mortality/SexDifferentialsChildhoodMortality.pdf***. Accessed 06 September 2017 ~~http://www.un.org/esa/population/publications/SexDifChildMort/SexDifferentialsChildhoodMortality.pdf~~

69. **Annex 1 - List of stand-alone documents**

No.	Document Reference No	Date	Title
8.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Protocol Amendment ***2*** sponsor signatory approval
9.	115056 (EPI-MAL-003 VS AME)	***15 October 2020***	Protocol Amendment***t 2*** investigator agreement

70. **Annex 5 – Case definitions for protocol-defined AESI and Surveillance Indicators**

GENERALIZED CONVULSIVE SEIZURE	• The etiological work up is negative: (i.e. ~~febrile seizure~~, acute intoxication, trauma, severe malaria etc. have all been excluded).

Annex 8 Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Date of protocol Amendment	Amendment 2 Final: 15 October 2020
Detailed Title	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01$_E$ vaccine in young children in sub-Saharan Africa.
Sponsor signatory	François Roman, Clinical and Epidemiological Project Lead, DDW Vaccines
Signature	_____
Date	_____

Annex 9 Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	115056 (EPI-MALARIA-003 VS AME)
Date of protocol Amendment	Amendment 2 Final: 15 October 2020
Title	A prospective study to evaluate the safety, effectiveness and impact of the RTS,S/AS01$_E$ vaccine in young children in sub-Saharan Africa.
Investigator name	
Signature	
Date	

Annex 10 ENCePP Checklist for study protocols

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	30
1.1.2 End of data collection[5]	☒	☐	☐	30
1.1.3 Study progress report(s)	☒	☐	☐	30
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	30

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	31-43
2.1.2 The objective(s) of the study?	☒	☐	☐	44-46
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	54-59
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	116-118
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

This is primarily a safety surveillance study

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	46-53
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	89-90
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	111-130

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	53-58
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	58-59
4.2.2 Age and gender?	☒	☐	☐	53-58
4.2.3 Country of origin?	☒	☐	☐	53-58
4.2.4 Disease/indication?	☒	☐	☐	53-58
4.2.5 Co-morbidity?	☒	☐	☐	53-58
4.2.6 Seasonality?	☒	☐	☐	53-58
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	58-59, 70-73

Comments:

To address seasonality change and other malaria control interventions, EPI-MAL-005 will run in parallel with EPI-MAL-003 on a yearly basis

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	91-95
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	91-95
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	91-95
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	112-128
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	60-69, 91-92
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	91-92

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	90-91
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	90-91

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	89-91
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	89-91
8.1.3 Covariates?	☒	☐	☐	89-91
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	89-91
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	89-91
8.2.3 Covariates? (e.g. age, **gender**, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	89-91

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	Part of GSK safety procedure
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	Not applicable
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

For standardised case definition for protocol-defined AESI, see Annex 5

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	94-108

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	112-134
10.2 Is the choice of statistical techniques described?	☒	☐	☐	112-134
10.3 Are descriptive analyses included?	☒	☐	☐	112-134

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.4 Are stratified analyses included?	☒	☐	☐	112-134
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	112-134
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	112-134

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	126-127
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	109, 136
11.3 Are methods of quality assurance described?	☒	☐	☐	133-134
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	133-134
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

There is a system for independent review of the cases by a panel of expert physicians (see pages 83-86)

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	135-140
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	135-140
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	53-58
12.3 Does the protocol address other limitations?	☒	☐	☐	135-140

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	140-141
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	134

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	29

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	146-147
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	146-147

Comments:

Note: Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Approval page.