| | |
|---|---|
| GlaxoSmithKline | **Statistical Analysis Plan** |
| **Detailed Title:** | A prospective study to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of the RTS,S/AS01$_E$ candidate vaccine. |
| **eTrack study number and Abbreviated Title:** | 115055 (EPI-MALARIA-002 VS AME) |
| **Scope:** | All data pertaining to the above study. |
| **Date of Statistical Analysis Plan:** | ***Amendment 2 Final***: 14 Mar 2022 |

***APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)***

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The SAP is divided into:

- a core-body part, detailing the analyses to be performed (current document),
- a study specific Mock TFL (tables, figures, and listings) for the final analysis,
- a study specific Mock TFL dedicated to the interim analysis (IA).

Moreover, progress reports will be produced every 6 months and submitted to regulatory authorities (European Medicines Agency [EMA]) to inform the progression of the study. TFLs for the safety progress report are described in a separate document [Progress Report].

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ADEM** | Acute Disseminated Encephalo-Myelitis |
| **AE** | Adverse Event |
| **AESI** | Adverse Event Of Special Interest |
| **AS** | Active Surveillance |
| **ATP** | According-To-Protocol |
| **CI** | Confidence Interval |
| **CRF** | Case Report Form |
| **DTP** | Diphtheria, Tetanus, Pertussis (acellular) vaccine |
| **DTPw/HepB/Hib** | Diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenza* type b pentavalent vaccine |
| **eCRF** | electronic Case Report Form |
| **EHS** | Enhanced Hospitalisation Surveillance |
| **EMA** | European Medicines Agency |
| **GSK** | GlaxoSmithKline |
| **HDSS** | Health and Demographic Surveillance System |
| **HHE** | Hypotonic Hyporesponsive Episode |
| **HIV** | Human Immunodeficiency Virus |
| **IA** | Interim Analysis |
| **ICF** | Informed Consent Form |
| **IR** | Incidence Rate |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| ***P. falciparum*** | *Plasmodium falciparum* |
| ***P. vivax*** | *Plasmodium vivax* |
| **PI** | Principal Investigator |
| **PT** | Preferred Term |
| **PY** | Person-years |
| **RDT** | Rapid Diagnostic Test |
| **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 |
| **SAP** | Statistical Analysis Plan |

| | |
|---|---|
| **SDTM** | Study Data Tabulation Model |
| **SOC** | System Organ Class |
| **SSA** | Sub-Saharan Africa |
| **TFL** | Tables, Figures and Listings |
| **TTO** | Time To Onset |

# 1. DOCUMENT HISTORY

| Date | Description |
|---|---|
| 6 July 2018 | Final<br>Protocol version: Amendment 6 (6 July 2018) |
| 22 February 2019 | Amendment1<br>Protocol version: Amendment 6 (6 July 2018)<br>• Section 5.2: addition of new ELIM-CODE (2501, 2502, 2503, 2504)<br>• Section 6.1: details on the study group label added<br>• Section 6.8: reference to coding added<br>• Section 6.9.3.2: for IR after schedule the following statement was incorrect and so deleted "In case an event occurs after more than one dose, only the first event will be taken into account."<br>• Section 6.9.3.2: after Table 2, addition of details to manage individual follow-up with migration dates and specific cases when ICF is after first reference date.<br>• Section 6.12: addition of a note related to the number of cases needed to display of tables<br>• Section 7.2.14 addition of last contact date derivation<br>• Section 8.2 separated in section 8.2.1 and section 8.2.2: addition of rules for the selection of subjects included in interim analysis.<br>This statement is deleted: "An interim analysis will be performed when the RTS,S/AS01$_E$ vaccine will be implemented in most of the study sites."<br>• Section 10: reference added EPI-MALARIA-002 VS AME (115055) General Study Information Study Specific Coding Term Retrieval And Supply For MedDRA Coding_version 2.0_20190108 |
| 14 Mar 2022 | Amendment2<br>Protocol version: Amendment 7 Final (5 May 2020)<br><br>Rationale: based on experience of Interim Analysis of EPI-MAL-002, the decision to lighten the final analysis was taken to consider only relevant points and to be compliant with GSK recommendations in terms of number of outputs.<br><br>• Section 5.2: adaptation of ELIM-CODE 2501. The elimination code 2501 is applicable for EPI-MAL-002 (5-17 months at 1st DTP) and EPI-MAL-003 (DTP group enrolled at any DTP). In EPI-MAL-003, 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. By changing the ELIM-CODE 2501 in EPI-MAL-002, the two studies are now aligned.<br>• Section 6.1: deletion of UNK group label for HIV status and haemoglobinopathies<br>• Section 6.4: signs and symptoms, and medical history adapted<br>• Section 6.5: tabulation of tables related to concomitant medications and vaccinations deleted<br>• Sections 6.6 and 6.7: sections related to COVID-19 assessment and protocol deviations added<br>• Section 6.9.2.1: adapted to consider only analysis of confirmed cases for AESI<br>• Section 6.9.2.2: description added of the manual grouping of other AEs<br>• Section 6.9.3.2: final analysis will be done only on confirmed cases according to protocol definition<br>• Section 6.9.3.2: keep only computation of incidence following schedules; IR will only be computed on the top 10 AEs following grouping<br>• Section 6.9.3.3: addition of the date of field implementation of protocol amendment 4<br>• Section 6.10.4: deletion of analysis of risk factors for each MedDRA SOC/PT for AESI and other AEs leading to hospitalisation or death<br>• Section 6.10.7: deletion of computation of IR for surveillance indicator analysis; clarification of surveillance indicator analysis only for AS<br>• Section 6.11.2: deletion of incidence rate and prevalence calculations for deaths attributed to an AE, and logistic regression and cox models for analysis of risk factors |

| Date | Description |
|---|---|
| | • Section 6.12: table 5 adapted<br>• Section 7.2.5: added category "No" or "negative" for specific subgroups<br>• Section 7.2.6: deletion of suspected AESI definition<br>• Section 7.2.7: addition of ICD-10 code related to febrile convulsion<br>• Section 7.2.12: final analysis will only include uncomplicated and severe malaria, including cerebral malaria, as per protocol<br>• Section 7.2.12: addition of process link to retrieve the categories of cause of death<br>• Section 7.2.14: addition of date of RTS,S for last contact date computation and clarification of last contact date<br>• Section 7.3: section handling missing data<br>– Deletion of part related to missing covariates as not applicable for EPI-MAL-002as not applicable for EPI-MAL-002<br>– Addition of rules related to management of missed home visits to be consistent with EPI-MAL-003<br>• Section 7.5:<br>– deletion of sections related to multilevel model, logistic regression and Cox model<br>– adaptation of covariates included in models; mainly deletion of variables from EPI-MAL-005<br>– deletion of models on hospitalised subjects only<br>– adaptation of Table 6<br>• Section 9: changes from protocol:<br>Explaining deletion from analysis of:<br>– Risk factors for other AEs leading to hospitalisation or death<br>– EPI-MAL-005 covariates consideration<br>– Handling of missing data<br>***Amendment 2 text has been included in bold italics*** |

# 2. STUDY DESIGN

The design of the study is defined as a disease surveillance study with prospective cohort event monitoring among infants and young children living in a demographic census in sub-Saharan Africa (SSA) countries.

The design includes active surveillance (AS) (home visits and continuous monitoring of outpatient visits and hospitalisations at all health care facilities) and enhanced hospitalisation surveillance (EHS) (continuous monitoring of hospitalisations).

The study targets enrolling 30,000 children in AS, with about 20,000 children enrolled where the RTS,S/AS01$_E$ vaccine will be implemented. Among the 30,000 children, approximately 15,000 children (with about 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 6-12 weeks group (to collect background data in this age group) and approximately 15,000 children (with about 10,000 children in sites where the vaccine will be implemented) will be enrolled in the 5-17 months group (to mimic administration of RTS,S/AS01$_E$ in the 5-17 months age group).

For EPI-MAL-002 and EPI-MAL-003, the study sites were chosen based on existing infrastructure to identify the study population.

The diseases under surveillance for safety include AESI (Adverse Event of Special Interest), other AE (Adverse Event) leading to hospitalisation or death, and meningitis,

and will be monitored among children enrolled in AS and in EHS. To estimate vaccine impact, several measures of malaria burden will be monitored among children in the AS.

AS will last 44 months for each subject (mimicking 24 months of active follow-up after the 4th dose of RTS,S/AS01$_E$ in EPI-MAL-003) except for subjects enrolled from Burkina Faso sites for which participation in the study was early terminated.

# 3. OBJECTIVES

As per protocol.

## 3.1. Co-Primary Objectives

- To estimate the incidence of AESI[1], and of other AE leading to hospitalisation or death, in children, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology confirmed meningitis, in children, prior to implementation of RTS,S/AS01$_E$.

## 3.2. Secondary Objectives

In children living in the study area, prior to implementation of 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 monitor trends over time of meningitis cases identified at site level (first line laboratory).
- 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 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 administration of routine EPI vaccines.

[1] Acute disseminated encephalomyelitis (ADEM), encephalitis, Guillain-Barre Syndrome, hypotonic hyporesponsive episode (HHE), general 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

- To estimate the incidence of any malaria (including *P. falciparum* malaria) diagnosed by rapid diagnostic test (RDT) and/or microscopy.
- To estimate the incidence of severe malaria (including *P. falciparum* malaria) diagnosed by RDT and/or microscopy.
- To estimate the incidence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- To estimate the prevalence of anaemia among hospitalised children.
- To estimate the incidence of all-cause hospitalisations and hospitalisations attributed to malaria (including *P. falciparum*).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria [including *P. falciparum*]), overall and by gender.

# 4. ENDPOINTS

As per protocol.

## 4.1. Co-Primary endpoints

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of AESI.
- Occurrence of other AEs leading to hospitalisation or death.
- Occurrence of aetiology confirmed meningitis.

## 4.2. Secondary endpoints

As per protocol with more details.

In children living in the study area, prior to implementation of RTS,S/AS01$_E$:

- 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 hospitalisation (including those attributed to an AESI, other AE, meningitis, or malaria) or death.
- Occurrence of febrile convulsions during the 7-day period (Days 0-6) and 1-month period (Days 0-29) following administration of routine EPI vaccine.
- Occurrence of two events used as surveillance quality indicators: abscess at injection site during the 7-day period (Days 0-6) following any routine vaccination and foot positional deformation.

In children included in AS, prior to implementation of RTS,S/AS01$_E$:

- Occurrence of episodes of malaria diagnosed by RDT and/or microscopy
  - Any malaria
  - *P. falciparum* malaria
  - *P. vivax* or other Plasmodium species that cause malaria
  - Severe malaria
  - Severe *P. falciparum* malaria
  - Severe *P. vivax* malaria or other Plasmodium species that cause malaria
  - Cerebral malaria
  - Fatal malaria
  - Fatal *P. falciparum* malaria
- Occurrence of anaemia at hospital entry among hospitalised children
  - All anaemia
  - Severe anaemia
- Occurrence of hospitalisation
  - All causes
  - Hospitalisations for malaria (including *P. falciparum* malaria).
  - Hospitalisations for *P. falciparum* malaria
- Occurrence of death
  - All causes
  - Malaria attributed deaths
  - *P. falciparum* malaria attributed deaths
  - AE attributed deaths

# 5. STUDY POPULATION

As per protocol.

The study population is defined as those children living in the study areas who are < 5 years old.

## 5.1. Total enrolled cohort

The Total enrolled cohort will include all subjects enrolled in the study.

## 5.2. According-to-protocol

The ***According-To-Protocol*** (ATP) cohort will include all evaluable subjects (i.e. those meeting all eligibility criteria).

The elimination codes for the defined populations are listed in the table below:

| Cohort | Elimination codes |
|---|---|
| Total Enrolled cohort | 900*<br>Invalid informed consent or fraudulent data |
| ATP cohort | 2010<br>Inclusion criteria<br>• Subjects' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol.<br>• Written informed consent provided from either the parent(s) or LAR of the subject.<br>• Subject living in the HDSS or equivalent surveillance system area.<br>• For enrolment in the active surveillance: children must be < 18 months of age<br>OR<br>For enrolment in the enhanced hospitalisation surveillance: children must be < 5 years of age and hospitalised at any time during the study.<br>Exclusion criteria<br>• Child in care |
| | 2501<br>Subjects recruited in the group active surveillance 5-17months first DTP:<br>• Subjects without DTP or without DTP vaccine dates available eliminated<br>• Subjects eliminated if ICF signed more than ***10 days*** after 1st DTP<br>• Subjects eliminated if ICF signed at first visit available or after<br>• Subjects for whom the hospitalisation admission date is before 1st DTP and :<br>– If hospital discharge date is known then subjects with ICF signed more than 7 days after hospital discharge are eliminated.<br>– If hospital discharge date is missing with ICF signed more than 7 days after hospital admission are eliminated. |
| | 2502<br>Subjects recruited in the group active surveillance 5-17months catch up:<br>• Subjects eliminated if ICF signed after first available visit<br>• Subjects for whom the hospitalisation admission date is before ICF and:<br>– If hospital discharge date is known then subjects with ICF signed more than 7 days after hospital discharge are eliminated.<br>– If hospital discharge date is missing with ICF signed more than 7 days after hospital admission are eliminated. |
| | 2503<br>Subjects recruited in the group enhanced hospitalisation surveillance (EHS) :<br>• Subjects eliminated if no hospitalisation recorded or without hospitalisation admission dates available<br>• Subjects with ICF before hospitalisation date -1 day are eliminated<br>• Subjects for whom the hospitalisation admission date is before ICF and:<br>– If hospital discharge date is known then subjects with ICF signed more than 7 days after hospital discharge are eliminated.<br>– If hospital discharge date is missing with ICF signed more than 7 days after hospital admission are eliminated. |
| | 2504<br>Subjects recruited in the group active surveillance 6-12 weeks:<br>• Subjects without DTP or without DTP vaccine dates available eliminated<br>• Subjects eliminated if ICF signed more than 10 days after 1st DTP<br>• Subjects eliminated if ICF signed after first visit available |

**This code should be allocated only in very special occasion for fraudulent subject (e.g. lab samples received by error).*

# 6. STATISTICAL METHODS

SAS version 9.4 or above will be used for statistical analysis.

All analyses will be conducted on the ATP cohort, unless otherwise detailed. The analyses will be done also on the Total cohort only if there are more than 5% of eliminated subjects; except for the demography where all the tables will be performed for both cohorts.

Main descriptive statistics (i.e. demographic characteristics) will be computed by study group, gender, EPI vaccine, study site and overall. Moreover, descriptive analysis of safety endpoints (i.e. AESI, Other AEs, meningitis) will be computed for specific sub-populations such as children with haemoglobinopathy and HIV-positive children.

Categorical variables will be summarised by the frequency and the percentage of each category. 95% confidence intervals (CIs) might also be presented and will be described in TFLs part. The following statistics will be presented for continuous variables: number of non-missing observations, mean, standard deviation, median, range (minimum and maximum) and 25$^{th}$ and 75$^{th}$ percentiles where required.

## 6.1. Group definition

The following group names will be used for the statistical analyses:

| Group order in tables | Group label in tables | Group definition for footnote |
|---|---|---|
| *Study Site* * | | |
| 1 | PPD_KE_Kombewa | Kombewa (Kenya) |
| 2 | PPD_GH_Kintampo | Kintampo (Ghana) |
| 3 | PPD_GH_Navrongo | Navrongo (Ghana) |
| *Gender* | | |
| 1 | Female | |
| 2 | Male | |
| 3 | UNK | Unknown |
| *Surveillance* | | |
| 1 | AS | Active surveillance |
| 2 | EHS | Enhanced hospitalisation surveillance |
| *Study group* | | |
| 1 | AS 6-12W | Active surveillance 6-12 weeks |
| 2 | AS 5-17M | Active surveillance 5-17 months |
| 3 | EHS | Enhanced hospitalisation surveillance |
| *EPI Vaccination status (see section 6.8 for definition)* | | |
| 1 | DTP/HepB/Hib vaccinated | Subjects vaccinated with DTP/HepB/Hib vaccine |
| 2 | Unvaccinated | Subjects not vaccinated with DTP/HepB/Hib vaccine |
| *HIV Status* | | |
| 1 | Positive | |
| 2 | Negative | |

| Group order in tables | Group label in tables | Group definition for footnote |
|---|---|---|
| *Haemoglobinopathies* | | |
| 1 | Yes | |
| 2 | No | |

Tables will, in general, be displayed by study group for descriptive tables and for analysis of safety endpoints. When it will not be the case, it will be explicitly mentioned.
* The data from Burkina Faso sites (Nouna and Sapone) will be neither in the interim analysis nor in the final analysis. Final data from Burkina Faso (not cleaned) will be presented in the progress report.

## 6.2. Disposition of subjects

A study flow diagram will be generated to present the number of subjects included in the Total enrolled and ATP cohorts.

Enrolment in each study site will be tabulated by study group.

Subject disposition will be presented by study site, study group and overall by computing:

- Number of enrolled children
- Number (%) of non-eligible children regarding inclusion and exclusion criteria
- Number of ATP children
- Main results
  - Number of subjects with at least one AESI and number of AESI
  - Number of subjects with at least one AE leading to hospitalisation or death and number of AE leading to hospitalisation
  - Number of subjects with at least one meningitis case and number of meningitis cases
  - Number of subjects with at least one episodes of any malaria and number of malaria cases

## 6.3. Analysis of demographics and characteristics at study entry

Demographic characteristics (age at informed consent and age at first visit, gender and household configuration) will be summarised by descriptive statistics per study group and by site. This analysis will be performed on the Total enrolled cohort, as well as on the ATP cohort.

## 6.4. Signs and symptoms, and medical history

- For Active surveillance, signs and symptoms and ***usual*** malaria preventive measures will be tabulated by study group and overall for all visits pooled.
  - The denominator will be the total number of visits and the numerator will be the number of subjects with at least one symptom among the visits.

- For hospitalised children from AS and EHS, malaria preventive measures, risk factors and comorbidity factors will be described by study group and overall for all hospitalisations pooled only: the denominator will be the total number of hospitalisations and the numerator will be the number of subjects with at least one risk among the hospitalisations.

## 6.5. Concomitant medications and vaccination

Medications (verbatim) collected according to protocol will be coded to preferred name using the GSK Drug dictionary.

***Data related to medications and concomitant vaccinations will be available in the corresponding Study Data Tabulation Model (SDTM) (panel Concomitant Medication). A listing of AESI with previous concomitant vaccination (after manual cleaning of typo) will be provided.***

## 6.6. COVID-19 assessment

***COVID-19 AEs (classified by Medical Dictionary for Regulatory [MedDRA] System Organ Class [SOC] and Preferred Term [PT] level for hospitalised cases) will be described along with all other AEs leading to hospitalisation or death (see section 6.9.2.2)***

***Any sensitive analysis due to the COVID-19 pandemic may be part of an additional analysis request if relevant.***

## 6.7. Protocol deviations

***Important protocol deviations and non-important protocol deviations which result in exclusion from the ATP cohort will be summarised.***

***Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important.***

***In addition, separate summaries will be produced for protocol deviations related to the COVID-19 pandemic.***

## 6.8. Exposure description to EPI vaccines

EPI vaccines are those routine vaccines usually given at 6, 10 and 14 weeks of age and which could be DTP, DTP-HepB, DTP-HepB-Hib vaccine. The subjects who received at least one dose of EPI vaccine are the vaccinated subjects.

The coding of vaccine is under the Epidemiologist team (EPI) responsibility (See details described in specific guideline: Vaccine study-specific Coding Guidelines).

The number of subjects who received at least one EPI dose will be described according to study group as well as the number of doses, the source for vaccine history (i.e. individual vaccination cards, vaccination registers at the health care facilities and vaccination data collected during census rounds).

Moreover, the age at each dose administration and the time between doses will also be described using descriptive statistics.

## 6.9. Analysis of co-primary objectives

### 6.9.1. Population

The analysis of co-primary objectives will be done on the ATP cohort and will primarily include subject from AS. A secondary population will include the subjects from the active and enhanced hospitalisation surveillances for the computation of incidence for all children <5 years.

### 6.9.2. Co-primary endpoints

#### 6.9.2.1. AESI

- Each AESI will first be analysed separately after case ascertainment on confirmed cases (hospitalised cases) classified by MedDRA SOC and PT level and case definition, and grouped by body system overall:
  - According to principal investigator (PI) diagnosis (i.e. after first line laboratory ascertainment or second line laboratory if available) ***for progress report (see section 6.9.3.1) and interim analysis***,
  - According to final diagnosis (external expert diagnosis or PI diagnosis if external expert diagnosis not available) ***for interim and final analysis***.

    *Note: The confirmed AESI cases are those AESI with an available ICD-10 code (i.e. variable ICD-10 code not equal to "Not confirmed", as per convention in the case report form [CRF] guidelines).*
- AESI will also be grouped by body system as described in table 3 of the protocol:
  - Nerves and central nervous system: Acute Disseminated Encephalo-Myelitis (ADEM), encephalitis, Guillain-Barre Syndrome, Hypotonic Hyporesponsive Episode (HHE), general 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

#### 6.9.2.2. Other AE leading to hospitalisation or death

Other AE leading to hospitalisation or death are those events different from the pre-defined AESI, meningitis and malaria. These AEs classified by MedDRA SOC and PT level for hospitalised cases will be ***described***:

- According to PI diagnosis corresponding to the diagnosis at discharge ***for progress report (see section 6.9.3.1) and interim analysis,***
- According to final diagnosis (external expert diagnosis or PI diagnosis if external expert diagnosis not available) ***for interim and final analysis***.

***PTs will be grouped into medically relevant groups to provide aggregated incidence rates. Indeed, due to the varied reporting terminologies used, some related or similar medical conditions may be counted separately resulting in partial incidence rate calculation (e.g. bacterial pneumonia and pneumonia, iron deficiency anaemia and anaemia). A manual grouping will be done based on a review of all the MedDRA PTs by the Epidemiologists and a Physician.***

#### 6.9.2.3. Aetiology-confirmed meningitis

Aetiology confirmed meningitis (first line laboratory results ***for progress report*** and final classification based on second line laboratory results and after external panel of experts' review) will not be grouped with other AESI and will be considered as a single endpoint.

### 6.9.3. Incidence of co-primary endpoints

#### 6.9.3.1. Description of the events

The occurrence of the following endpoints will be regularly (every 6 months) reported in progress reports [Progress Report] on the total enrolled cohort for hospitalised cases and outpatient visits when applicable:

- Each AESI according to site diagnosis,
- Other AE leading to hospitalisation or death, according to site diagnosis
- First line laboratory meningitis diagnosis according to site diagnosis following protocol definition (i.e. Bacterial confirmed meningitis, probable meningitis, clinically suspected meningitis).
- Malaria cases reported during outpatient visit or at hospital:
  - Clinically diagnosed Malaria
  - Any uncomplicated malaria (including *P. falciparum* malaria)
  - Any severe malaria (including *P. falciparum* malaria)
  - Severe *P. falciparum* malaria
  - Severe *P. vivax*
  - Cerebral malaria

  - Fatal malaria cases

- Death reported at hospital or at home classified by MedDRA PT from study conclusion.

The number of subjects (%) reporting at least once each endpoint as well as the total number of events listed above and the number of associated outpatient visits/hospitalisations will be presented for both AS and EHS by EPI vaccination status and by gender. MedDRA SOC and PT level will be displayed for those safety endpoints.

Progress reports will include individual listings and statistical tables. The same tables and listings will also be presented for the final report.

Descriptive data in the progress report will also be presented:

- The demographic census will be presented by study site and by age group according to gender and overall.
- The number of subjects enrolled will be presented by study site, by study group and according to EPI vaccination status.
- The evolution of enrolment will be presented separately for each study group.
- Population characteristics (age at informed consent, gender) will be described by study group according to EPI vaccine received.
- The number and percentage of subjects who received the EPI vaccine doses will be summarised for EPI vaccinated subjects by each study group according to gender and overall.

And descriptive analysis of quality indicators (see section 6.10.7) will be done:

- The percentage of subjects reporting abscess at injection site within 7 days (day of vaccination and 6 subsequent days) after each dose of the DTP/HepB/Hib vaccine will be reported for each dose and overall according to gender and overall.
- As negative control, the prevalence of foot positional deformations will be presented according to gender and overall.

Of note, each progress report will be done on uncleaned data and will present cumulative results. The same analysis will be performed for the interim analysis on cumulative cleaned data. ***The final analysis will be done only on confirmed cases according to the protocol case definitions.***

#### 6.9.3.2. Incidence following EPI vaccine or virtual vaccination

Analyses of incidence following EPI vaccine or virtual vaccination will only be performed on children enrolled in the AS ATP cohort for each group (6-12 weeks and 5-17 months).

These analyses will be computed on each confirmed co-primary endpoints (see section 6.9.2) 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. Incidence per 100,000 person-years will be presented by study sites and overall.

Incidence Rates (IRs) after the primary schedule (i.e. combining the 3 doses) and the virtual secondary schedule (i.e. primary schedule and the virtual dose 4) will be presented.

**Individual follow-up period and at risk period**

The total person-years will be computed as the sum of individual follow-up periods expressed in years. The computation of follow-up periods is defined in Table 2.

For each endpoint, the follow-up period will be calculated separately depending on the at-risk period and the vaccine administration. The at-risk period will follow any dose, with a censoring of subjects when they receive the following dose.

**Table 1 Definition of at-risk period for AESI**

| AESI | Risk period identified (for other licensed vaccines)* | Risk period applied |
|---|---|---|
| ADEM | NA | 6 weeks |
| Encephalitis | 6 weeks and 2 weeks | |
| Guillain-Barre Syndrome | 3-5 days to 6-10 weeks | 3 months |
| Generalized convulsive seizures | 0-7 days | 2 weeks |
| Hypotonic Hypo responsive Episode | immediately to 48h | 2 weeks |
| Intussusception | 1 to 7 days | 2 weeks |
| Hepatic Insufficiency | 1-10 days | 2 weeks |
| Renal Insufficiency | 1-10 days | 2 weeks |
| Juvenile Chronic Arthritis | ≤6 months | 6 months |
| SJS & TEN | 1-3 weeks | 6 weeks |
| Henoch Schonlein purpura | NA | 6 months |
| Kawasaki Disease | 1 month | 6 weeks |
| Diabetes mellitus type 1 | ≤6 months | 6 months |
| Anaphylaxis | 0-48 hours | 2 weeks |
| Thrombocytopenia | 12-25 days | 6 weeks |

* from Table 3 of the protocol

Of note:

- The predefined list of AESI with expected at-risk period is available in the current Table 3 of the protocol,
- The at-risk period of 12 months will be used for meningitis,
- For other AEs leading to hospitalisation or death:
  - ***IR will only be computed on the 10 most frequent AEs following the grouping done by the Epidemiologists and a Physician (see section 6.9.2.2)***.

– An at-risk period of 7 days and 30 days will be applied. Other risk periods may be defined with the support of the GSK Safety Physicians and the panel of experts.

**Table 2 Follow-up period definition after each dose**

| Risk period applied | Start | Stop earliest (i.e. date of censoring is whichever occurs first) |
|---|---|---|
| 2 weeks | Reference date* | • Date of first diagnosis of event of interest<br>• Date of death<br>• Date of next dose<br>• Date of end of risk period<br>• Date of last contact**<br>• Date of migration<br>• Date when child reaches 5 years or end of the study |
| 6 weeks | | |
| 3 months | | |
| 6 Months | | |
| 12 Months | | |

*Reference date: see definition detailed in section 7.2.2
** Date of last contact: see definition detailed in section 7.2.13

Notes:

- a child may come back into the study after a certain period of lost-to follow-up. In such a case, the person-year 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). To do so, a migration date will be derived using migration date from:
  - Date of migration:
    - From Study continuation
    - From Study conclusion

      A return date will be derived using return date from:
  - Date of return:
    - From Study continuation
    - From Study conclusion

      In case of several migrations/returns, several migration/return dates will be computed. For such subjects, the last contact date will be computed according to migration/return dates.

      In case of any inconsistencies regarding the migration/return dates, the return will not be considered and the subject will be censored at the first migration date.
- If the ICF is signed after the first reference date, the individual follow-up period will be computed as the difference +1 between the follow-up end date and the ICF date. The follow-up end date remains the same as for subjects with ICF signed before the first reference date.

When AESI will be grouped, in case of multiple cases for a subject, only the first event will be considered in this analysis.

**Management of the at-risk period**

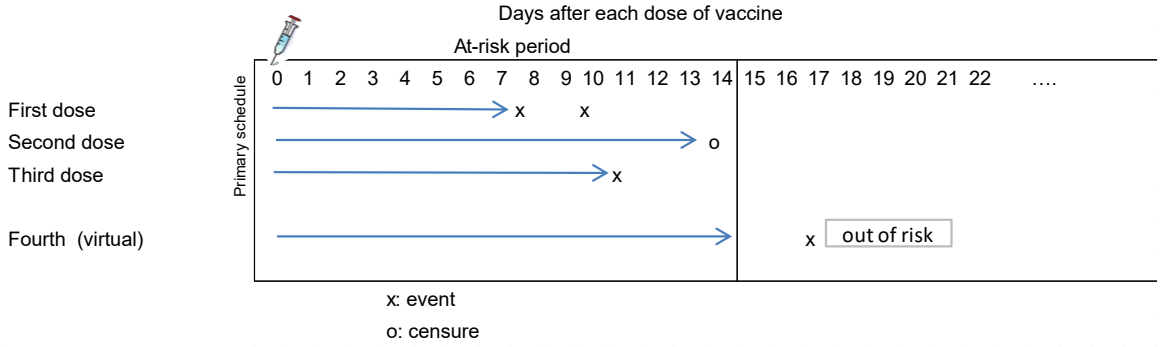
- Events occurring outside of the at risk period (before or after) will be censured for the main analysis. The distribution of the Time to Onset (TTO) of events after EPI vaccine or virtual dose will be described, and additional at-risk periods may be considered based on the results as sensitivity analyses.
- In case an AESI had several at-risk periods, the longest will be considered for analysis:

  Example: Guillain-Barré Syndrome: expected at-risk period from 3-5 days to 6-10 weeks, as a consequence an at-risk period of 3 months will be applied
- In the same way, for the analysis of grouped AESI with different at-risk periods, the longest will be considered:

  Example: Encephalitis (2-6 weeks at risk period) and Generalised convulsive seizure (0-7 days at risk period) as a consequence an at-risk period of 6 weeks will be applied
- In case an AESI occurs after the specified at-risk period, it will be censored at the time-point (e.g.: 2 weeks in the example below) and new at-risk period could be discussed.

<u>First example of AESI with 2 weeks at-risk period</u>:

The following diagram represent a theoretical scenario for one subject presenting a first AESI 7 days after the first dose, a second AESI 9 days after the first dose, a third AESI 10 days after the third dose and a fourth AESI 16 days after the fourth dose.

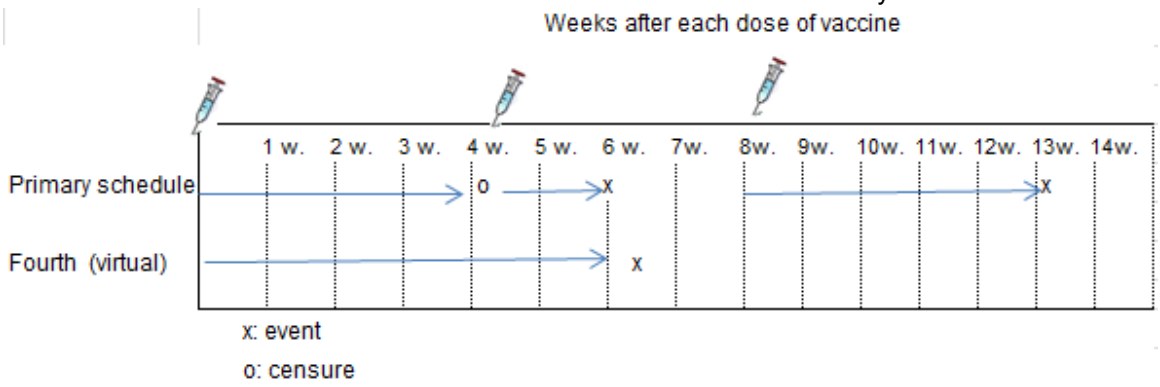



Of note, in case of recurrence of the event after a specified dose, the follow-up will stop at first occurrence.

When computing incidence rate for the primary schedule, the follow-up period corresponding to each dose should be summed. In our example: the follow-up period to consider for the primary schedule is: 7 days + 14 days + 10 days and two events will be considered (the first one after each dose).

<u>Second example of AESI with 6 weeks at-risk period</u>:

The following diagram represent a theoretical scenario for one subject presenting a first AESI 6 weeks (42 days) after the first dose corresponding also to 2 weeks (14 days) after the second dose, a second AESI 5 weeks (34 days) after the third dose and a third AESI more than 6 weeks (45 days) after the fourth dose.




As mentioned earlier, the at-risk period will follow any dose, with a censoring of subjects when they receive the following dose. Then in our example the follow-up period to consider for:

- First dose: 28 days with no event*
- Second dose: 14 days with one event
- Third dose: 34 days with one event
- Primary schedule: 28 days + 14 days + 34 days with two events considered.
- Virtual fourth dose: censoring at 6 weeks
- Secondary schedule: 28 days + 14 days + 34 days + 42 days with two events.

  ** Note: In case no event occurred between doses, the exact number of days between the two doses will be considered to compute the follow-up period.*

**Incidence rates over all study sites**

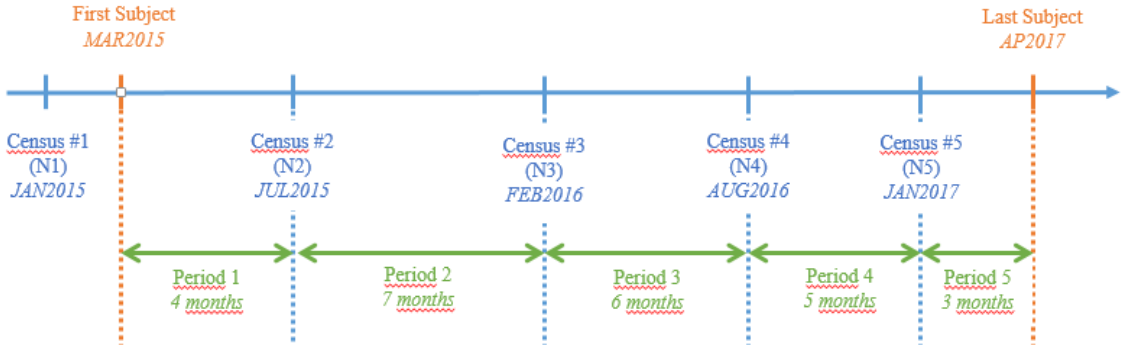
The crude incidence rate (unadjusted) over all sites will be computed. If relevant, the adjusted overall incidence rate will be computed considering the study sites as clusters.

### 6.9.3.3. Incidence in children < 5 years

The IR of each and any AESI, of each and any other AE leading to hospitalisation or death (classified by the MedDRA SOC and PT level) and of aetiology confirmed meningitis will be estimated in all children < 5 years per 100,000 person per year. A 95% CI will be computed per year and overall using an exact method for a Poisson variable.

The numerator will be the number of cases of specified events (i.e. AESI) during the study period (in both AS and EHS grouped) and the denominator will be the person-years contribution of children in all communities < 5 years of age. The denominator will be computed using the census data. A census done at least once a year will provide the total number of children under 5 years.

For example, considering 5 census done between January 2015 and January 2017, a first subject recruited in March 2015 and a last subject recruited in April 2017:




The person-year (PY) will be computed as:

PY = N1*Period1 + N2*Period2 + N3*Period3 + N4*Period4 + N5*Period5

Contrary to the computation of IR following EPI vaccine or virtual vaccination where only the first event is counted in the numerator, for IR in children < 5 years, in case a subject had more than once the same AESI, all events will be counted in the numerator.

Confidence intervals [CI] will be computed using the exact method [Clopper, 1934].

**Management of first year of inclusion:**

During the first year of inclusion (i.e. 2016), recruitment was done according to Protocol Amendment 3 where children had to be less than 3 years old with a corresponding census. As a consequence, IR in children < 5 years will be computed after the application on field of the Protocol Amendment 4:

- ***Kintampo: 12 June 2017 in AS and 22 May 2017 in EHS***
- ***Kombewa: 9 March 2017***
- ***Navrongo: subjects entered directly under protocol amendment 4 (25 September 2017)***

The method to compute incidence will be described in a technical annex of the specific Mock TFL for the final analysis.

### 6.9.4. Cumulative probability analysis

Kaplan-Meier curves presenting the cumulative probability of having at least one confirmed co-primary endpoint following EPI vaccine or virtual vaccination will be displayed.

This analysis will be performed on children enrolled in the AS ATP cohort.

The cumulative probability of presenting each event will be given with its 95% CI:

- After the primary schedule,
- After the secondary schedule.

In case an event occurs after several doses, only the first event will be taken into account.

## 6.10. Analysis of secondary safety objectives

### 6.10.1. Population

The same population as for the co-primary objectives (see Section 6.9.1) will be used.

### 6.10.2. Meningitis cases

#### 6.10.2.1. Meningitis cases monitoring

As described in section 6.9.1, the number of cases of meningitis as well as the cumulative number of cases will be tabulated in the progress report for all meningitis diagnosis at the site level (based on first line laboratory results).

#### 6.10.2.2. Incidence rate 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 used to compute IR. The meningitis cases will be analysed grouped as follows:

- Probable meningitis,
- Aetiology confirmed, and/or probable meningitis,
- Aetiology confirmed, probable and/or clinically suspected meningitis.

The IR (and 95% CI) of each definition of meningitis cases will be estimated with the same approach as for the co-primary endpoints (described in Section 6.9.3.2).

For IR following EPI vaccine, the at-risk period applied will be 12 months after each vaccine administration and same approach as described in section 6.9.3.3 will be used to compute IR for children less than 5 years.

### 6.10.3. Cerebral malaria

The IR (and 95% CI) of cerebral malaria will be estimated with the same approach described in Section 6.9.3. Incidence following EPI vaccine or virtual vaccination with a 12 month risk period will be derived and Time-to-Onset will be computed.

### 6.10.4. Analysis of risk factors

Analysis of potential risk factors of the below secondary safety endpoints will only be done on hospitalised events from ATP-Active surveillance for IR following EPI vaccine or virtual vaccination on primary schedule and virtual secondary schedule only (ie: primary schedule and virtual dose 4 only) by means of univariate and multivariate Poisson regression models for the following confirmed (final diagnosis) endpoints:

- ***Each AESI separately***

- Aetiology confirmed meningitis,
- Cerebral malaria,
- Death.

For those endpoints, if possible, a model with study site considered as random effect will be performed as sensitive analysis. The methods are described in section 7.5.1 and in section 7.5.2.

### 6.10.5. Cause of hospitalisation (including AESI, other AE, meningitis and malaria) and death

Causes of hospitalisation (including AESI, other AE, classified by MedDRA SOC and PT level as well as meningitis and malaria) will be analysed grouped as follows:

- Hospitalisations (all causes)
- Hospitalisation for malaria (including *P. falciparum* malaria)
- Hospitalisation for *P. falciparum* malaria

In the same way, descriptive analysis of causes of death classified by MedDRA will be done overall and by gender grouped as follows:

- Deaths – all cause
- Malaria attributed deaths (including *P. falciparum* malaria)
- *P. falciparum* malaria attributed deaths
- Deaths attributed to an AESI or other AE (i.e. other than meningitis, AESI, malaria)

Descriptive analysis of the cause of hospitalisation (overall) and death (overall and by gender) will consist in computing the number of cases, person-year per 100,000 and IR (with 95% CI).

IR of all cause of hospitalisation and death will be computed following EPI vaccine or virtual vaccination (at risk period of 12 months) as described in section 6.9.3.2 and for children < 5 years as described in section 6.9.3.3. Of note, death IR per gender in children < 5 years will be computed after the first year of recruitment. Indeed, census per gender will be available after the application on field on the Protocol Amendment 4.

Note that malaria subtype will be defined using outpatient and hospitalisation visits. In case of death occurring at home malaria subtype may be unknown.

### 6.10.6. Febrile convulsions

- Descriptive analysis

  Data about febrile convulsion (definition in Section 7.2.7) within 7 days (day of vaccination and 6 subsequent days) and within 30 days (day of vaccination and 29 subsequent days) of EPI vaccine will be presented. ***Separate listings*** will include the diagnostic certainty level as defined in Job Aid, the duration of seizures in minutes when applicable, the time from vaccination and number of seizures.

- The IR of febrile convulsions will be computed as described in section 6.9.3.2. Of note, two at-risk periods will be considered: 0-6 and 7-29 days.

***Of note, risk period might be revised if deemed necessary at the time of the analysis.***

### 6.10.7. Surveillance indicator analysis

***This analysis will be done only in children enrolled in AS.***

***Abscess at the injection site (positive control), reported during outpatient visits and at hospital within 7 days of EPI vaccine will be described.***

The prevalence of Foot positional deformations as a birth defect (negative control) reported during outpatient visits and at hospital, will be computed.

Abscess at the injection site and foot positional deformations reported during home visits will only be described.

## 6.11. Analysis for other secondary objectives

These analyses will be performed only on children enrolled in the AS ATP cohort for each group (6-12 weeks and 5-17 months).

### 6.11.1. Analysis population

Primary analysis will be performed on the other secondary endpoints (i.e. malaria, anaemia, hospitalisation and death as described in Table 4) at one year post last dose of the primary schedule in order to anticipate further comparisons to be done with the EPI-MAL-003 study (i.e. indirect, total and overall effects computation):

- D3 → D3 + 1Y: one year after the third dose (before 12 months of age) of EPI vaccine or virtual vaccination evaluated from third dose.

Additional analyses will be performed on the other endpoints:

  – D3 → D4 + 1Y: one year after the visit mimicking the 4$^{th}$ dose (i.e. Month 32) evaluated from the 3$^{rd}$ dose (before 12 months of age) of EPI vaccine or virtual vaccination.

  – D3 → D3 + 2Y: two years after the 3$^{rd}$ dose of EPI vaccine or virtual vaccination evaluated from 3$^{rd}$ dose of EPI vaccine or virtual vaccination

- D1 → D4 + 2Y: two years after the visit mimicking the 4th dose (i.e. Month 44) evaluated from the 1st dose of EPI vaccine or virtual vaccination
- D3 → D4 + 2Y: two years after the visit mimicking the 4th dose (i.e. Month 44) evaluated from the 3rd dose of EPI vaccine or virtual vaccination.

### 6.11.2. Derivation of incidence rate and prevalence

- For all endpoints listed in Table 4 incidence rate will be calculated by dividing the number of all cases over the follow-up period by person-year as defined in the table.

  If a subject had several cases during the period defined, all episodes will be reported.

  The number of person-years will be computed as the sum of subjects follow-up period expressed in years.

**Table 3 Follow-up period definition for other secondary endpoints**

| Analysis | Start | Stop (earliest) |
|---|---|---|
| D3 → D3 + 1Y | Third dose or virtual vaccination* | • One year after third dose<br>• Date of death<br>• Date of last contact**<br>• Date of migration<br>• Date when child reaches 5 years |
| D3 → D4 + 1Y | Third dose or virtual vaccination* | • One year after virtual fourth dose<br>• Date of death<br>• Date of last contact**<br>• Date of migration<br>• Date when child reaches 5 years |
| D3 → D3 + 2Y | Third or virtual vaccination* | • Two years after third dose<br>• Date of death<br>• Date of last contact**<br>• Date of migration<br>• Date when child reaches 5 years |
| D1 → D4 + 2Y | First dose or virtual vaccination* | • Two years after virtual fourth dose<br>• Date of death<br>• Date of last contact**<br>• Date of migration<br>• Date when child reaches 5 years |
| D3 → D4 + 2Y | Third dose or virtual vaccination* | |

* Virtual vaccination: for 5-17 month study group or unvaccinated children
** Date of last contact: lost-to follow-up

The prevalence rate for anaemia will be computed by dividing the number of all cases by the number of enrolled children.

## Table 4 Incidence rate and prevalence calculations for other secondary objectives (children enrolled in active surveillance)

| Endpoints | Numerator | Denominator |
|---|---|---|
| **Any malaria** | # cases of any malaria during the follow-up time of each analysis<br>Source: Outpatient visits and hospitalisations at all health care facilities | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Any *P. falciparum* malaria** | # cases of any malaria due to *P. falciparum* during the follow-up time of each analysis<br>Source: Outpatient visits and hospitalisations at all health care facilities | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Severe malaria** | # cases of severe malaria during the follow-up time of each analysis<br>Source: Outpatient visits and hospitalisations at all health care facilities | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Severe *P. falciparum* malaria** | # cases of severe malaria due to *P. falciparum* during the follow-up time of each analysis<br>Source: Outpatient visits and hospitalisations at all health care facilities | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Cerebral malaria** | # cases of cerebral malaria during the follow-up time of each analysis<br>Source: Hospitalisations | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Death – all cause** | # deaths (due to any cause) during the follow-up time of each analysis<br>Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Malaria attributed deaths** | # cases of deaths with malaria listed as a contributing cause during the follow-up time of each analysis<br>Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register | Person-years contribution of enrolled children during the follow-up time of each analysis |
| ***P. falciparum* Malaria attributed deaths** | # cases of deaths with malaria due to P. falciparum listed as a contributing cause during the follow-up time of each analysis<br>Source: Regular home visits; outpatient visits and hospitalisations at all health care facilities, completion visit; HDSS register | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **All cause hospitalisation** | # of children hospitalised during the follow-up time of each analysis<br>Source: Hospitalisations | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Malaria attributable hospitalisation** | # of children hospitalised during the follow-up time of each analysis where malaria is listed as the primary diagnosis<br>Source: Hospitalisations | Person-years contribution of enrolled children during the follow-up time of each analysis |
| ***P. falciparum* Malaria attributable hospitalisation** | # of children hospitalised during the follow-up time of each analysis where *P. falciparum* malaria is listed as the primary diagnosis<br>Source: Hospitalisations | Person-years contribution of enrolled children during the follow-up time of each analysis |
| **Anaemia in hospitalised children** | # cases of anaemia<br>Source: Hospitalisations | Number of enrolled children |
| **Severe anaemia in hospitalised children** | # cases of severe anaemia<br>Source: Hospitalisations | Number of enrolled children |

As done for safety endpoints, analysis of risk factors will be conducted by means of univariate and multivariable Poisson regression models for ***any malaria, severe malaria and cerebral malaria***. The methods are described in Section 7.5.1. The covariates and their select method are described in Section 7.5.3.

## 6.12. Summary of analyses by endpoints

The following table summary the analyses done by endpoints described in the previous sections.

## Table 5 List of analyses by endpoints

| | Description of events | Incidence following primary and secondary schedule | Incidence for children < 5 years | Cumulative probability | Analysis of risk factors on IR following primary/secondary schedule | Incidence following: D3 → D3 + 1Y, D3 → D4 + 1Y, D3 → D3 + 2Y, D1 → D4 + 2Y, D3 → D4 + 2Y | Analysis of risk factors on IR: D3 → D3 + 1Y | Prevalent rate: D3 → D3 + 1Y, D3 → D4 + 1Y, D3 → D3 + 2Y, D1 → D4 + 2Y, D3 → D4 + 2Y |
|---|---|---|---|---|---|---|---|---|
| **AESI according to Final diagnosis** | | | | | | | | |
| AESI (by MedDRA SOC & PT) | ○/● | - | - | - | - | - | - | - |
| AESI by case definition as listed in CRF | ○/● | ○ | ● | ○ | ○* | - | - | - |
| AESI grouped by body-system | ○/● | ○ | ● | - | - | - | - | - |
| **Other AE leading to hospitalization or death according to Final diagnosis** | | | | | | | | |
| Other AE leading to hospitalisation or death (by MedDRA SOC & PT) | ○/● | - | - | - | - | - | - | - |
| Other AE leading to hospitalisation or death (Aggregated) | - | ○ | ● | - | - | - | - | - |
| **Meningitis according to Final diagnosis** | | | | | | | | |
| Aetiology confirmed meningitis | ○/● | ○ | ● | ○ | ○* | - | - | - |
| Aetiology confirmed, and/or probable meningitis | ○/● | ○ | ● | - | - | - | - | - |
| Probable meningitis | ○/● | ○ | ● | - | - | - | - | - |
| Aetiology Confirmed and/or probable and/or suspected meningitis | ○/● | ○ | ● | - | - | - | - | - |
| **Malaria according to Final diagnosis** | | | | | | | | |
| Any Malaria | ○/● | - | - | - | - | ○ | ○ | - |
| *P. falciparum* Malaria | ○/● | - | - | - | - | ○ | ○ | - |
| Severe Malaria | ○/● | - | - | - | - | ○ | ○ | - |
| *P. falciparum* severe Malaria | ○/● | - | - | - | - | ○ | ○ | - |
| Cerebral Malaria | ○/● | ○ | ● | ○ | ○* | ○ | ○ | - |
| **Death (overall and by gender)** | | | | | | | | |
| Death all cause | ○/● | ○[a] | ● | ○ | ○* | ○ | - | - |
| Death due to an AESI (all grouped) | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Death due to another AE (all grouped) | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Death due to meningitis | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Death due to malaria (including P. falciparum malaria) | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Death due to P. falciparum malaria | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| **Hospitalisation** | | | | | | | | |
| Hospitalisation all causes | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Hospitalisation due to malaria (including P. falciparum malaria) | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| Hospitalisation due to P. falciparum malaria | ○/● | ○[a] | ● | ○ | - | ○ | - | - |
| **Anaemia** | | | | | | | | |
| Anaemia | ○/● | - | - | - | - | - | - | ○ |
| Severe anaemia | ○/● | - | - | - | - | - | - | ○ |
| **Febrile convulsions** | | | | | | | | |
| Febrile convulsions | ○/● | ○ | - | - | - | - | - | - |
| **Surveillance indicator** | | | | | | | | |
| Foot positional deformations as a birth defect | ○ | - | - | - | - | - | - | - |
| Abscess at the injection site | ○ | - | - | - | - | - | - | - |

● Analysis to be done for AS and EHS
o Analysis to be done only for AS
* Sensitivity analysis using site as random effect

Primary objective
Secondary Safety objective
Secondary other objective

# 7. STATISTICAL CALCULATIONS

## 7.1. Methodology for computing confidence intervals

Except specify otherwise, all confidence intervals [CI] will be two sided 95% CI computed using the exact method [Clopper, 1934].

The asymptotic 95% CIs for a mean within a group will be calculated when applicable.

## 7.2. Derived and transformed data

Programming specifications for the derivation of data are supporting the SAP.

### 7.2.1. Age

Age ***in days*** at time of enrolment in the study will be computed as the difference between the date of enrolment (date of ICF) and the date of birth.

Calendar age will be expressed in months and will be computed based on (the number of days/365.25)*12.

The age will be categorised as followed:

- 0-5: less than 6 months
- 6-11: from 6 months to <1 year

  1 - <2 years could also be used
- 12-23: 1 - <2 years
- 24-35: 2 - <3 years
- 36-47: 3 - <4 years
- 48-59: 4 - <5 years

### 7.2.2. Reference date

The reference date is defined as:

- For the 6-12W study group:
  - Date of vaccination for the DTP/HepB/Hib vaccine dose received
  - Virtual vaccination: virtual dose 4 one week before Visit 6 (i.e. Month 20) mimicking study schedule in the subsequent EPI-MAL-003
- For the 5-17M study group (as they do not follow study visits according to EPI vaccine administrations schedule) in order to mimic study procedures in the subsequent EPI-MAL-003, the virtual vaccinations are:
  - Virtual dose 1: one week before first visit (i.e. Month 0)

- Virtual dose 2: one week before Visit 2 (i.e. Month 1)
- Virtual dose 3: one week before Visit 3 (i.e. Month 2)
- Virtual dose 4: one week before Visit 6 (i.e. Month 20).

  Note: For the 5-17M 1st DTP group, the first visit (V1) will be at the age of approximately 6 months. In case an event occurred after ICF signature but before V1, the event will not be included in the computation of IR following EPI vaccine or virtual vaccination, but the event will be included in the computation of IR in children <5 years.

### 7.2.3. Date of occurrence

The dates of occurrence of events are defined as follows depending on the endpoint:

- Suspected or confirmed AESI and meningitis reported at hospital:
  - Onset date of event
- Suspected AESI and suspected meningitis reported during outpatient visit (see section 7.3 for worst case allocation sensitivity analysis):
  - Admission date at outpatient visit
- Other AE leading to hospitalisation or death:
  - Onset date of event if AE is the primary diagnosis
  - Admission date at hospital otherwise
- Suspected or confirmed malaria cases:
  - Onset date of event for hospitalised cases
  - Admission date at outpatient visit otherwise
- Death:
  - Date of death reported in study conclusion

### 7.2.4. Time to onset

For the computation of IR following DTP/HepB/Hib vaccine or virtual vaccination, the TTO will be computed as [the difference between the date of first occurrence of study endpoint (e.g. AESI) and the reference date + 1].

TTO will be expressed in days.

### 7.2.5. Specifics sub-groups

The following sub-groups of analysis will be derived as:

- Children with haemoglobinopathies, if at any time during the study the condition is reported in at least one of the below sections:
  - Any known pre-existing conditions reported either at visit 1 or during hospitalisation

  - Comorbidity factors reported during hospitalisation
  - Other diseases reported during hospitalisation with ICD-10 codes = D55.0, D57.X(X=0-8) , D56.X(X=0-9)

***Otherwise, status will be reported as "No".***

- HIV-positive children, if at any time during the study the condition is reported in at least one of the below sections:
  - Any known pre-existing conditions reported either at visit 1 or during hospitalisation
  - Diagnosis recorded during outpatient visit
  - Risk factors reported during hospitalisation
  - Other diseases reported during hospitalisation with ICD-10 codes = B20-B24

***Otherwise, status will be reported as "HIV-negative children".***

### 7.2.6. AESI

As mentioned in Section 6.9.2, confirmed AESI reported at hospitalisation are coded using MedDRA Dictionary and presented by SOC and PT. The coding is based on ICD-10 code reported by the investigator (see Vaccine study-specific Coding Guidelines).

### 7.2.7. Febrile convulsions

***As per study protocol (section 9.2.5.4), febrile convulsions are those events reported during hospitalisation in AESI sections only (i.e. General Convulsive Seizure) with ICD-10 codes = R56.0.***

***Note: R56.0 reported in section other AE should not be considered as febrile convulsion as per protocol case definition.***

### 7.2.8. Management of consecutive visits and/or hospitalisations

#### 7.2.8.1. AESI, Meningitis and other AE

For cases reported at hospital, events in one subject with the same preferred term and with the same onset date or onset date + 1 day will be considered as the same event. In such case, they will contribute to several hospitalisations and one event.

*Remarks:*

1. For other AE leading to hospitalisation or death, if the AE is not the primary diagnosis the hospital admission date will be considered (indeed, the onset date is only available for primary diagnosis).
2. For meningitis a worst case allocation is applicable. In case two or more hospitalisations occurred for different protocol definitions of meningitis with the same onset date or onset date + 1, the event considered will be the worst according to the following order (starting from worst):
   - Bacterial confirmed meningitis / Aetiology confirmed meningitis

- Probable meningitis
- Clinically suspected meningitis
- Suspected meningitis without diagnosis done by the site yet (applicable for progress report)
- Suspected meningitis ruled out afterward

3. This rule is applicable if their onset dates are complete.

#### 7.2.8.2. Malaria cases

In the same way, to avoid counting the same malaria episode more than once, episodes in the same subject with a difference between admission dates for outpatient visit or between onset dates for hospitalised cases of ≤ 14 days and with the same specie(s) (identified either with rapid diagnostic test or slide reading), will be considered as one event. A worst case allocation is attributed according to the following order (starting from worst):

- Severe malaria (with the same species)
- Uncomplicated malaria (with the same species)
- Clinically diagnosed malaria
- Suspected malaria

*Remarks:*

1. In case two or more consecutive visits/hospitalisations, with less than 14 days between each visit and/or hospitalisation, only one event will be considered also (even if there is more than 14 days between the first and the last visit and/or hospitalisation).
2. Malaria episodes can only be combined if their outpatient visit admission date or their onset dates are complete.

### 7.2.9. Definition of malaria cases

***For final analysis, only malaria per protocol will be considered (i.e. uncomplicated and severe malaria, including cerebral malaria).***

#### 7.2.9.1. Uncomplicated malaria

*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.

#### 7.2.9.2. Severe *P. falciparum* malaria

Severe malaria was defined according to the following two definitions along the study:

| **Definition 1** [WHO, 2010] | **Definition 2** [WHO, 2015], from protocol amendment 4 |
|---|---|
| *P. falciparum* parasitaemia > 0 detected by microscopy and/or RDT<br>AND<br>One or more of the following, occurring in the absence of an identified alternative cause:<br>Impaired consciousness: a Blantyre coma score < 3 in children;<br>Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;<br>Multiple convulsions: more than two episodes within 24 h;<br>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).<br>Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);<br>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;<br>Renal impairment: plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L;<br>Jaundice: plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL; | *P. falciparum* parasitaemia > 0 detected by microscopy and/or RDT<br>AND<br>One or more of the following, occurring in the absence of an identified alternative cause:<br>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;<br>Prostration: generalised weakness so that the person is unable to sit, stand or walk without assistance;<br>Multiple convulsions: more than two episodes within 24 h;<br>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).<br>Hypoglycaemia: blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL);<br>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;<br>Renal impairment: plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L; |

| **Definition 1** [WHO, 2010] | **Definition 2** [WHO, 2015], from protocol amendment 4 |
|---|---|
| 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;<br><br>Significant bleeding: including recurrent or prolonged bleeding from the nose,gums or venepuncture sites; haematemesis or melaena;<br><br>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);<br><br>Hyperparasitaemia: *P. falciparum* parasitaemia > 10%). | Jaundice: plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL;<br><br>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;<br><br>Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena;<br><br>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);<br><br>Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500,000/µL). |

#### 7.2.9.3. Severe *P. vivax* malaria

Severe *P. vivax* malaria is defined as for severe *P. falciparum* malaria when *P. vivax* parasitaemia > 0 detected by microscopy and/or RDT but with no parasite density thresholds.

#### 7.2.9.4. Cerebral malaria

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.

### 7.2.10. Definition of anaemia

Cases of anaemia will be defined as follow:

- All anaemia: haemoglobin <11g/dL.
- Severe anaemia: haemoglobin <7g/dL .

### 7.2.11. Hospitalisation

- Hospitalisations (all causes)
- Hospitalisation for malaria (including *P. falciparum* malaria)

  A hospitalised subject with malaria (including *P. falciparum* malaria)
- Hospitalisation for *P. falciparum* malaria

  A hospitalised subject with *P. falciparum* malaria

### 7.2.12. Deaths

- Deaths – all causes

  A fatality (of any cause).
- Malaria attributed deaths (including *P. falciparum* malaria)

  A fatality for which malaria (including *P. falciparum* malaria) is listed as a contributing cause of death.
- *P. falciparum* malaria attributed deaths

  A fatality for which
  - Malaria is listed as a contributing cause of death
  - And the malaria type is identified as *P. falciparum*.
- Deaths attributed to an AE
- Deaths attributed to an AESI
- Meningitis attributed death

***Of note, as cause of death is a free text reported by the investigator on the Study Conclusion form, a specific guideline explaining the process to retrieve the above categories was prepared (***EPI-MALARIA-002 VS AME (115055) General study information study specific coding term retrieval and supply for MedDRA coding_version 2.0_20190108***)***

Number of outpatient visits per centre

The number of outpatient visits per centre will be computed as the sum of outpatient visits that occurred for the children enrolled in the same centre.

### 7.2.13. Last contact date

The last contact date will be derived as:

- For deceased subjects the last contact date will be set as the death date.
- For subjects who have finished their participation in the study and for whom their participation did not finish prematurely (i.e. "Did the study participant finish its participation in the study prematurely" equal No) the last contact date will be set as the last contact date from study conclusion CRF page
- For the other subjects (i.e. "Did the study participant finish its participation in the study prematurely" not equal No) the last contact date will be defined as the latest date among:
  - Date of consent
  - Date of reconsent
  - Last date of hospitalisation
  - Last discharge date of hospitalisation
  - Last check-up after discharge
  - Last date of outpatient visit
  - Last home visit
  - Date of enrollment of EPI-MAL-003 study
  - ***Date of RTS,S/AS01$_E$ vaccine***
  - Date of migration (From Study continuation or from Study conclusion)

Notes:

- The last contact date recorded in study conclusion CRF page will not be used for this scenario (i.e. when "Did the study participant finish its participation in the study prematurely" not equal No).
- The last contact date will not be computed using start and end date of symptoms associated with events

In addition:

- For subjects enrolled with protocol amendment 4 or subjects enrolled with protocol amendment 3 and who signed the ICF addendum related to protocol amendment 4, the last contact date should not be after the child reaches 5 years ***or 44 months follow-up after visit 1 of the last child enrolled in AS per site whichever comes first:***
  - ***Kombewa: 7 April 2022***
  - ***Kintampo: 27 April 2022***
  - ***Navrongo: 19 July 2022***

- For subjects enrolled with protocol amendment 3 who did not sign the ICF addendum related to protocol amendment 4 (meaning that the reason for not signing the addendum is different than "Study participant enters directly with Protocol Amendment 4"), the last contact date should not be after the child reaches 3 years or 24 months follow-up per site whichever comes first:
  - ***Kombewa: 25 January 2018***
  - ***Kintampo: 7 February 2018***
  - ***Navrongo started directly under protocol amendment 4***

## 7.3. Handling missing data

***For incidence rate computation, the missed visits will be considered as:***

- ***for the AS 5-17 months group***

  ***If the three first home-visits planned according to the schedule are missing, the first home-visit will be imputed as:***

- ***AS 5-17 months first DTP: Date of birth + 6 months***
- ***AS 5-17 months catch-up: Date of ICF***
- ***for the AS 6-12 weeks group: no imputation of missed visits as DTP vaccination dates will be considered for the computation of the follow-up.***

***Of note, the number of missed home-visits (without imputation) will be displayed on the flowchart section of the study report.***

## 7.4. Number of decimals

The following decimal description will be used for the analyses.

| **Parameters** | **Number of decimal digits** |
|---|---|
| % of count, including LL & UL of CI | 1 (***except for 100% in which case no decimal will be displayed***) |
| p-value | 3 |
| Minimum, maximum, range, ***Q1, Q3*** | Number of decimals in the raw data |
| Mean, median | Number of decimals in the raw data +1 |
| SD | Number of decimals in the raw data +2 |

LL = Lower Limit UL = Upper Limit CI = Confidence Interval
SD = Standard deviation

## 7.5. Statistical models

### 7.5.1. Fixed effect Poisson regression model

#### 7.5.1.1. Rationale

Analysis of risk factors for incident endpoints will be done using the person-time method described above.

The effect of the covariates on the outcomes of interest will be evaluated based on the relative incidence rates (incidence rate ratios) obtained by means of Poisson regressions.

Both univariate and multivariable Poisson regression models will be used. Incidence rate ratio will be the measure of association used to estimate the relative risk of the outcome due to covariates.

#### 7.5.1.2. Method

The Poisson regression model expresses the natural logarithm of the event or outcome of interest as a linear function of a set of predictors. The dependent variable is the number of events ($Y$). The model will include the covariates $X_1 \ldots X_n$ , the study site [Z] as a fixed effect, and the log-transformed total person-time ($PY$).

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

The coefficients $\beta_1 \ldots \beta_n$ and $\beta_z$ are the coefficients associated to covariates $X_1 \ldots X_n$ and study sites, respectively. The risk ratio will be derived as the exponential of the coefficient associated with the covariate status and its 95% Wald CI.

Poisson regression will be conducted using the SAS GENMOD procedure:

```
PROC GENMOD data=<filename> ;
  CLASS X1 […]  Xn Z;
  MODEL Y= X1 […]  Xn 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 overdispersion.

In case of overdispersion, 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 overdispersion is still a problem, another alternative approach considering a negative binomial distribution model will be discussed considering scientific inputs.

Of note, the same procedure PROC GENMOD will be adapted by specifying option DIST=negbin in the model statement:

```
PROC GENMOD data=<filename> ;
 CLASS X1 […]  Xn Z;
 MODEL Y= X1 … Xn Z / OFFSET=Ln_PY DIST=negbin LINK=log ;
RUN;
```

### 7.5.2. Random effect poisson regression model

As sensitive analysis Mixed-Poisson model including study site as random-effect will be conducted using the SAS GLIMMIX procedure.

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

### 7.5.3. Covariates

#### 7.5.3.1. Potential confounding variables

Patient characteristics and potential confounding variables will be based on the ***first home visit or first hospitalisation***.

The category of covariates will be presented in the TFLs template part.

##### *7.5.3.1.1. Individual level covariates*

For all enrolled study participants:

- **General covariates:**
  - Demographic parameters:
    - Age
    - Gender
    - Study site
    - Household configuration
    - Neighbourhood of residence
  - Medical history:
    - Signs and symptoms
    - Developmental delay or physical disabilities, known pre-existing conditions and risk factors

  - Health behaviour:
    - Usual health care seeking place
    - Distance to the usual health care provider
- **Malaria related covariates**: Malaria preventive measures
  - use of bednets,
  - indoor residual spraying,
  - seasonal malaria chemoprevention
- **Comorbidity**
  - known haemoglobinopathies,
  - known HIV infection

#### 7.5.3.2. Forced-in covariates

As described in section 7.5.1, some clinical covariates will be forced-in multivariable models related to safety endpoints and related to impact endpoints.

##### *7.5.3.2.1. Forced-in covariates for safety endpoints*

- Demographic parameters:
  - Age
  - Gender
  - Study site
- Health behaviour:
  - Usual health care seeking place
  - Distance to the usual health care provider

***Other forced-in covariates may be included at the time of the final analysis.***

##### *7.5.3.2.2. Forced-in covariates for other secondary endpoints*

The same covariates as for safety endpoints.

***Other forced-in covariates may be included at the time of the final analysis.***

#### 7.5.3.3. Summary

The following table summarises the models and covariates used for each endpoint.

**Table 6 Covariates used in the models according to each endpoint**

| Endpoint | Population | Model | Forced-In covariates | Individual level covariates | | |
|---|---|---|---|---|---|---|
| | | | | General covariates | Comorbidity | Malaria specific covariates |
| AESI | AS ATP | Fixed effect Poisson models | o | o | o | |
| Meningitis | AS ATP | Fixed effect Poisson models | o | o | o | |
| Cerebral malaria | AS ATP | Fixed effect Poisson models | o | o | o | |
| Malaria | AS ATP | Fixed effect Poisson models | o | o | o | o |
| Deaths (All causes) | AS ATP | Fixed effect Poisson models | o | o | o | o |

#### 7.5.3.4. Strategy for covariates selection

For multivariable Poisson models, the following strategy for covariates selection will be applied.

The model will include time-independent covariates at study entry from EPI-MAL-002.

The covariates are described in section 7.5.3.1.

Covariates occurring in less than 5% of the subjects (percentage will be computed over subjects both in 6-12 weeks and 5-17 months group) will not be included in the model. Of note, models will be run if a minimum number of cases of each endpoint are observed (at least 10 cases in total).

The predefined clinically relevant covariates described in section 7.5.3.2 will be forced into the models.

Covariates selection will be done using statistical significance. Confounders will be included in the multivariable models if univariate p-value will be less than 20%.

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 (cutoff level = 10). The method is described in the following section 7.5.3.5.

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

#### 7.5.3.5. Method for assessing co-linearity

##### *7.5.3.5.1. Fitting weights for generalised linear models*

The computation of the fitting weights will be conducted using the SAS GENMOD procedure.

For Poisson regression models the syntax will be:

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

#### *7.5.3.5.2. Assess variance inflation factor*

A weighted regression will be done with the complete set of covariates (including the forced-in covariates) using the weights computed at the previous step. This regression will be conducted using the SAS REG procedure, the option VIF gives the variance inflation factor:

```
PROC REG data=out ;
 WEIGHT W;
 MODEL Y= X Z / VIF ;
RUN;
```

A variance inflation factor higher than 10 indicates a co-linearity issue regarding the concerned covariate. The decision to drop the covariate will be made on order of clinical importance.

#### *7.5.3.5.3. Variables transformation for the weighted regression*

Categorical covariates with at least 3 categories will be transformed into dummy variables to be used in the SAS REG procedure.

Example:

The covariate Z could take the 3 categories values: 1, 2 and 3.

3 dummy variables will be created:

Z1=1 if Z =1 else Z1=0;

Z2=1 if Z =2 else Z2=0;

Z3=1 if Z =3 else Z3=0;

If we choose the Z=1 as the reference category, the weighted regression will be:

```
PROC REG data=out ;
 WEIGHT W;
 MODEL Y= X Z2 Z3 / VIF ;
RUN;
```

The choice of the reference category could have an influence on the variance inflation factor. It is recommended to choose the category with the larger fraction of the subjects.

Discrete variables and dichotomous variables will be left unchanged in the model.

# 8. CONDUCT OF ANALYSES

## 8.1. Sequence of analyses

| Description | Analysis ID (SDD & CARS sub-folder) |
|---|---|
| First Progress Report | E1_02 |
| …. | E1_03 |
| Interim analysis | ***E1_07*** |
| Final analysis | E1_01 |

## 8.2. Statistical considerations for interim analyses

### 8.2.1. Selection of subjects

This interim analysis will be done with clean data* collected on a sub-group of subjects from AS only having 6 months of follow-up following the administration of dose 3 of EPI vaccine (6-12 weeks group), or 6 months after Visit 3 (5-17 months group); corresponding to Visit 5.

No adjustment for controlling the alpha level was planned.

** 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 cut-off date was defined as 5 October 2018.

The subjects from AS selected are those:

- with available Visit 5 ≤ 5 October 2018
- with theoretical Visit 5 ≤ 5 October 2018:
- when Visit 5 is missing, a theoretical Visit 5 is computed based on ICF as
  - AS 6-12 Weeks or AS 5-17 catch-up:

    Inform consent date + 1 week + 8 months + 2weeks
  - AS 5-17 months 1st DTP:

    Inform consent date + 6 months + 8 months + 2weeks

Moreover, subjects from AS prematurely withdrawn (from any cause) before Visit 5 who should have had Visit 5 before the cut-off date are included in the interim analysis using the following rules:

- Visit 1 before 5 February 2018
- Visit 2 before 5 March 2018 if Visit 1 missing
- Visit 3 before 5 April 2018 if Visit 1 and Visit 2 missing
- Visit 4 before 20 May 2018 if Visit 1, Visit 2 and Visit 3 missing

- If all the above visits are missing
  - AS 6-12W or AS 5-17 catch-up: ICF before 5 February 2018
  - AS5-17 1st DTP: ICF before 5 February 2018 minus 6 months

It must be mentioned the last contact (see section 7.2.13) applicable for the interim analysis should be <= Visit 5 or theoretical Visit 5.

Of note, the selection of the sub-group of subjects included in the interim analysis is done by the study-set up analyst.

### 8.2.2. Selection of endpoints

The interim analysis will concern co-primary safety objectives and the main other secondary objectives (at 6 months post dose 3 of EPI vaccine for the purpose of this interim):

- To estimate the incidence of AESI, and of other AE leading to hospitalisation or death, in children, prior to implementation of RTS,S/AS01$_E$.
- To estimate the incidence of aetiology confirmed meningitis, in children, prior to implementation of RTS,S/AS01$_E$.
- To describe the causes of death, overall and by gender.
- To estimate the incidence of any malaria (including *P. falciparum* malaria) diagnosed by rapid diagnostic test (RDT) and/or microscopy.
- To estimate the incidence of severe malaria (including *P. falciparum* malaria) diagnosed by RDT and/or microscopy.
- To estimate the incidence of cerebral malaria (malaria diagnosed by RDT and/or microscopy).
- To estimate the mortality rate (all-cause mortality and deaths attributed to malaria (including *P. falciparum*), overall and by gender.

Description of surveillance quality indicator will also be part of the interim analysis.

A specific TFL dedicated to the Interim Analysis (IA) described all the analysis to be provided.

The following table summarises the analyses done by endpoint for the IA.

## Table 7 List of analyses by endpoints for IA

**EPI-MAL-002 : Summary of interim analysis**

| | Description of events | Incidence following EPI vaccine or virtual vaccination<br><br>After each dose, primary and secondary schedule | Incidence following:<br><br>D3 → D3 + 6 Months |
|---|---|---|---|
| **AESI:** | | | |
| **Suspected AESI** | | | |
| AESI by case definition as listed in CRF | o | - | - |
| AESI grouped by body-system | o | - | - |
| **Confirmed AESI according to PI (after 1st or 2nd line lab)** | | | |
| AESI (by MedDRA SOC & PT) | o | - | - |
| AESI by case definition as listed in CRF | o | - | - |
| AESI grouped by body-system | o | - | - |
| **Confirmed AESI according to final diagnosis Overall** | | | |
| AESI (by MedDRA SOC & PT) | o | o | - |
| AESI by case definition as listed in CRF | o | o | - |
| AESI grouped by body-system | o | o | - |
| **Confirmed AESI according to final diagnosis by level of certainty** | | | |
| AESI by case definition as listed in CRF | o | o | - |
| **Other AE leading to hospitalization or death** | | | |
| **According to PI diagnosis** | | | |
| Other AE leading to hospitalisation or death (by MedDRA SOC & PT) | o | - | - |
| **According to Expert diagnosis** | | | |
| Other AE leading to hospitalisation or death (by MedDRA SOC & PT) | o | o | - |
| **Meningitis** | | | |
| **According to PI (after 1st )** | | | |
| Aetiology confirmed meningitis | o | - | - |
| Aetiology confirmed, and/or probable meningitis | o | - | - |
| Probable meningitis | o | - | - |
| Aetiology Confirmed and/or probable and/or suspected meningitis | o | - | - |
| **According to PI (after 2nd )** | | | |
| Aetiology confirmed meningitis | o | - | - |
| Aetiology confirmed, and/or probable meningitis | o | - | - |
| Probable meningitis | o | - | - |
| Aetiology Confirmed and/or probable and/or suspected meningitis | o | - | - |
| **According to Final (Expert)** | | | |
| Aetiology confirmed meningitis | o | o | - |
| Aetiology confirmed, and/or probable meningitis | o | o | - |
| Probable meningitis | o | o | - |
| Aetiology Confirmed and/or probable and/or suspected meningitis | o | o | - |
| **Malaria** | | | |
| **According to PI diagnosis** | | | |
| Any Malaria | o | - | - |
| *P. falciparum* Malaria | o | - | - |
| Severe Malaria | o | - | - |
| *P. falciparum* severe Malaria | o | - | - |
| Cerebral Malaria | o | - | - |
| **According to Expert diagnosis** | | | |
| Any Malaria | o | - | o |
| *P. falciparum* Malaria | o | - | o |
| Severe Malaria | o | - | o |
| *P. falciparum* severe Malaria | o | - | o |
| Cerebral Malaria | o | o | o |
| **Death (overall and by gender)** | | | |
| Death all cause | o | o | o |
| Death due to an AESI (all grouped) | o | o | o |
| Death due to another AE (all grouped) | o | o | o |
| Death due to meningitis | o | o | - |
| Death due to malaria (including P. falciparum malaria) | o | o | o |
| Death due to P. falciparum malaria | o | o | o |
| **Surveillance indicator** | | | |
| Foot positional deformations as a birth defect | o | - | - |
| Abscess at the injection site | o | o | - |

# 9. CHANGES FROM PROTOCOL

- ***Risk factors of other AE leading to hospitalisation or death will not be done by means of univariate and multivariable Poisson regressions as for AESI, meningitis and malaria.***

  ***Indeed, from a clinical point of view such models will not be relevant in the context of EPI-MAL-002. Those models will be done in the before-after comparison in EPI-MAL-003 study.***

  ***Descriptive analyses of risk factors will be done as planned.***

  – ***Aggregated variables recorded in EPI-MAL-005 study will be part of the analysis of EPI-MAL-003 study including comparison of EPI-MAL-002 and -003 data. Those aggregated variables will not be included as risk factors of malaria in EPI-MAL-002 study.***

  – ***Handling of missing data is not relevant in the context of EPI-MAL-002 study. Therefore, Section 9.7.8.1 of the protocol will not apply.***

  – ***Version 17 terminology of the statistical catalogue will be used for the final analysis leading to a minor impact: in the Study Report, "subject" will be replaced by "participant". The adaptation is already done in the SAP/TFLs***

# 10. REFERENCES

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