GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A prospective, multi-centre, cohort study to assess the burden of dengue illness in household members (aged between 6 months and 50 years) from selected communities in Southeast Asia and Latin America
eTrack study number and Abbreviated Title	200318 (EPI-DENGUE-007 BOD)
Scope:	All available data pertaining to the above study
Date of Statistical Analysis Plan	Final: 24 May 2019
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Epidemiologist, Director) PPD (Clinical and Epidemiology Project Lead) PPD (Scientific Writer) PPD (peer reviewer statistician)
Approved by:	PPD (Lead Biostatistician) PPD (Lead statistical analyst) PPD (Epidemiologist, Director) PPD (Clinical and Epidemiology Project Lead) PPD (Lead Scientific Writer) delegating to PPD PPD (Statistician)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 05 March 2019)

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LIST OF ABBREVIATIONS

ATP	According-To-Protocol
CI	Confidence interval
CTRS	Clinical Trial Registry Summary
DE	Design effect
DENV	Dengue virus
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
FHP	Family Health Physician Program
GEE	Generalized estimating equations
GSK	GlaxoSmithKline
HCT	Hematocrit
ICC	Intra-cluster correlation
IgG	Immunoglobulin type G
IgM	Immunoglobulin type M
LAR	Legally Acceptable Representative
LL	Lower limit of the confidence interval
NS1	Non Structural 1
RT-qPCR	Reverse Transcriptase quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SDC	Suspected dengue case
TFL	Tables Figures and Listings annexed to SAP
UL	Upper limit of the confidence interval
WHO	World Health Organization

1. DOCUMENT HISTORY

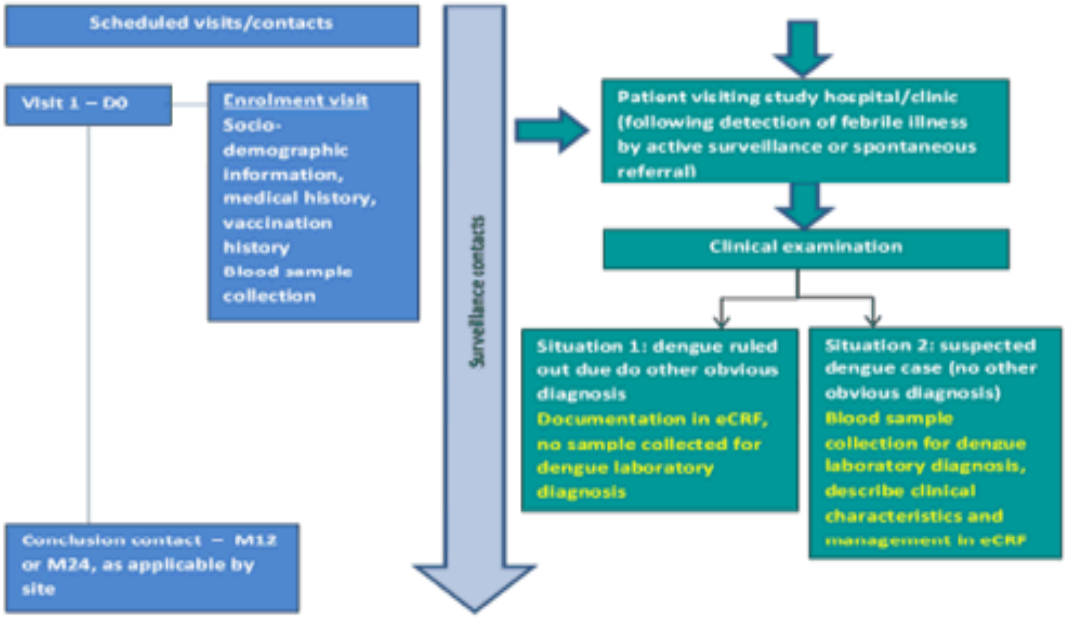
Date	Description	Protocol Version
24 MAY 2019	First version	Mexico: Amendment 1: 28 JAN 2016 Philippines: Amendment 3: 24 JUL 2017

2. STUDY DESIGN

2.1. Study design overview

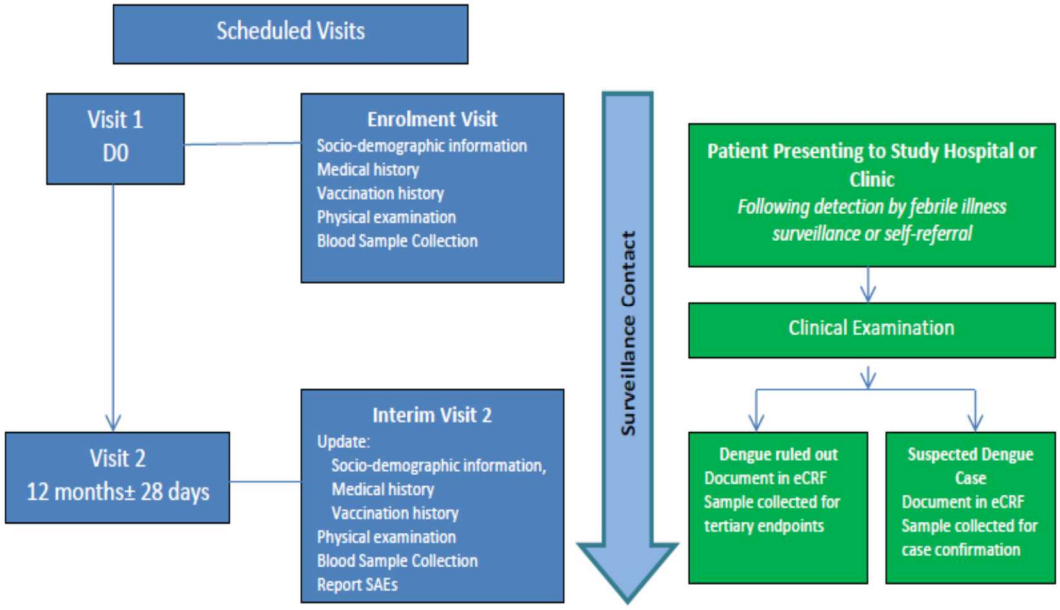
- **Type of design**: Prospective, multi-country, multi-centre, household-based, cohort study/surveillance study.
- **Study population:** Subjects aged between 6 months and 50 years at the time of enrolment living in geographically-defined communities in Latin America and Southeast Asia. The study population comprised household members. The study population should have between 30% and 50% of adults (aged 18 years or above) per site
- **Recruitment:** The appropriate recruitment strategy was selected by each participating site. Two approaches have been considered: a school-based approach and a community-based approach without school involvement. The recruitment period should have preferably occurred outside the period of peak incidence of dengue, based on the local epidemiology of dengue in the past years.
- **Duration of longitudinal follow-up and number of visits**: The study duration was planned to be 24 months for each participating site. Subjects were planned to have a scheduled visit at enrolment, one visit at Month 12 and a conclusion visit at Month 24. The Month 12 and Month 24 visits may occur via a telephone contact for the Mexican site. The number of visits in case of febrile illness, referred as “suspected symptomatic dengue case”, varied by subject.
- **Type of study:** self-contained.
- **Data collection**: Electronic Case Report Form (eCRF).
- **Study termination:** in December 2017, GSK decided to deprioritise the development of the dengue purified inactivated vaccine (DPIV) candidate and to terminate the study EPI-DENGUE-007. This decision was made due to the scientific challenges and development risks associated with the candidate vaccine. Therefore, only two sites participated to the study, one in Mexico and one in Philippines. The site in Mexico conducted the study as planned per protocol Amendment 1. The site in Philippines conducted the study as per protocol Amendment 3 but the study was terminated at Visit 2 (Month 12). The planned sites in Malaysia and Thailand were not initiated before the decision of study termination was taken, so no subjects were enrolled in these countries. From the 1750 subjects planned to be enrolled in the study, only 850 subjects were finally enrolled in the study.

- **Schematic representation of the scheduled visits – Mexico**



The conclusion contact took place at Month 24 for the Mexico site

- **Schematic representation of the scheduled visits – Philippines**



2.2. Study population

This study planned to enrol approximately 1750 subjects aged between 6 months and 50 years at the time of enrolment from households from different selected communities and schools within the study sites, with about 300 to 500 subjects expected per study site.

2.2.1. Selection of study sites

One study site in Mexico and one study site in Philippines were initiated for this study.

2.2.2. Selection of communities and schools

The following criteria were considered as guidance for selecting the communities and schools:

- Areas which are known to be endemic for dengue with high rates of transmission in most recent years.
- Easy access for the study population to a healthcare centre that can evaluate SDC (fast track) and manage the enrolled subjects.
- Safe access by study personnel.

In addition, the following criteria was considered as guidance for selecting schools, in case the school based approach was selected for recruitment:

- Of sufficient size to allow the enrolment target of 300-500 subjects (children and adults) per site in one geographically-defined community.

2.2.3. Selection of households and subjects

The number of households depended on the number of subjects enrolled per household. For a site enrolling 500 subjects, the number of households would likely range between 125 (assuming 4 subjects on average per household) and 250 (assuming 2 subjects on average per household).

The recruitment strategy was selected by each participating site. The two study sites used the community-based approach without school involvement.

- **For the school-based approach**

Recruitment was to be initiated in primary and/or secondary schools. The parent(s)/ LAR(s) of the student attending participating schools were to be asked to allow voluntarily participation of their child/ward. The parent(s)/LAR(s) of these students were also to be invited to enrol himself/herself/themselves (if ≤ 50 years) and their younger/older child who may not be attending the study school(s). Other household members were to be invited to participate in the study (if ≤ 50 years).

Recruitment was to be organised by study staff, preferably at participating schools (primary and/or secondary) or designated facility (e.g. healthcare centre, local community centre, etc.). If any member of a given household refused to participate in the study, it did not preclude inclusion of other household members. Study staff could also have conducted home visits for recruitment but collection of blood sample was done preferably at a designated facility.

- **For the community-based approach (without school involvement)**

Recruitment was organised by study staff at the household level and/or at other designated facilities (e.g. healthcare centre, local community centre, etc.), using various modes of communication (e.g.: public announcements or community meetings to inform about the study). Study staff could also have conducted home visits for recruitment but collection of blood sample was done preferably at a designated facility.

Whichever approach was chosen, the various modes of communication used for recruitment were reviewed and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to the local legislation (for e.g.: public announcements or community meetings to inform about the study).

2.3. Dengue case detection

Suspected cases in the study may arise from two sources:

1. Through enhanced passive surveillance
2. As a result of active surveillance between scheduled visits

2.3.1. Case detection through enhanced passive surveillance

- This form of surveillance was key in maximising the likelihood to detect SDC early, during the course of illness. Study personnel instructed subjects/subject's parent(s)/LAR(s)/ designate (if applicable) to contact the study personnel or come to a designated study healthcare centre/hospital for medical evaluation in case of febrile illness (preferably within 5 days of onset of febrile illness).

2.3.2. Case detection through active surveillance

Between scheduled visits, detection of SDC in the cohort were performed using active surveillance of acute febrile illness and enhanced passive surveillance.

- **Active surveillance**: Households were contacted regularly to enquire about the occurrence of febrile illness among the study subjects. Preferably, the frequency of contacts was once per week. In sites with marked dengue seasonality, the frequency of contact may have been twice per month during periods of low transmission of dengue. These periods may have been modified upon decision of the central study team based on available epidemiological information. The mode of contact may have included phone calls and/or house visits. In addition to the regular phone contact, some sites may have opted to check the school absenteeism log and contact the household of the children who are absent.

- If febrile illness was identified during active surveillance, an appointment was arranged at the designated study healthcare centre/ hospital as soon as possible (preferably within 5 days following the onset of symptoms).

A household visit may have been planned if the subject cannot come to the designated healthcare centre/hospital. This situation should have, however, remained exceptional.

2.4. Dengue seasons

Dengue season:

Study site number	Study site name	Dengue season 2017, 2018
219902	Mexico	1st July to 30th October of each year
219497	Philippines	1st May to 30th November of each year

3. OBJECTIVES

3.1. Primary objective

- To estimate the overall incidence rate of reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR)-confirmed symptomatic DENV infection in a multi-centre cohort of household members aged 6 months to 50 years.

3.2. Secondary objectives

- To estimate the incidence rate of virologically confirmed (through RT-qPCR or NS1) and probable (based on serological evidence) symptomatic DENV cases, separately and combined - by age, gender, site, serotype (if applicable) and anti-DENV IgG serological status at enrolment.
- To estimate the prevalence of anti-DENV immunoglobulin G (IgG) antibodies against dengue in the study population, overall and by age and site (at enrolment), for all participants and among dengue cases (confirmed and probable).
- To describe clinical presentations of dengue cases (confirmed and probable).

3.3. Tertiary objectives

- To describe the spatial and temporal distribution of dengue cases (confirmed and probable) among cohort participants in the study areas and analyse determinants of spatio-temporal transmission (e.g. environmental, entomological, socio-demographic or ecological factors).
- To describe the DENV, and other flaviviruses (i.e. Japanese Encephalitis Virus [JEV; mostly relevant in Southeast Asia]) or West Nile Virus [WNV; mostly relevant in Latin America]) neutralising antibody profile in a subset of subjects.
- To explore other infectious aetiologies than dengue in subjects with episodes of febrile illness referred to as “suspected dengue case” (chikungunya, Zika, influenza, leptospirosis).

- To explore determinants of past dengue infection and dengue illness.
- To further characterise the immune status at enrolment (e.g. antibody avidity, etc.).

Tertiary objectives will not be analysed (refer to Section 10).

4. ENDPOINTS

4.1. Primary endpoint

- RT-qPCR confirmed symptomatic DENV infection (all DENV types) during the study period.

4.2. Secondary endpoints

- DENV-type specific confirmed symptomatic DENV infection.
- Virologically confirmed (by RT-qPCR or NS1) and probable (based on serological evidence) symptomatic DENV infection.
- Status for anti-DENV IgG at enrolment (indicative of past DENV infection).
- Symptoms and severity of symptomatic dengue.

4.3. Tertiary endpoints

Exploratory objectives may be assessed based on, but not limited to the following endpoints:

- Spatial coordinates of the houses of participating households and of dengue cases and date of symptoms onset (applicable only for symptomatic cases).
- Neutralising antibodies titres against DENV 1-4.
- Neutralising antibody titres against other flaviviruses (such as JEV and WNV).
- Other infectious aetiology than dengue in subjects with episodes of febrile illness referred to as “suspected dengue cases” (chikungunya, Zika, influenza, leptospirosis).
- Determinants of past dengue infection and dengue illness.
- Characteristics of immune status against DENV infection.

5. ANALYSIS SETS

5.1. Definition

The following analysis sets are defined:

Analysis Set	Description
Total cohort	All subjects enrolled in the study
Total cohort without subjects with code 900	All subjects from the Total cohort without elimination codes 900
ATP cohort	All subjects from the Total cohort without subjects with code 900 and who met all inclusion/exclusion criteria

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each analysis set.

5.2.1. Elimination from Total cohort without subjects with code 900

Code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects eliminated from Total cohort without subjects with code 900.

5.2.2. Elimination from ATP cohort

Code 900 (invalid informed consent or fraudulent data) and code 2010 (Protocol violation linked to the inclusion/exclusion criteria) will be used for identifying subjects eliminated from ATP cohort.

5.3. Important protocol deviation not leading to elimination from Analysis set

Refer to the Periodic Review of Protocol deviation documents stored in C.A.R.S./Epidemiology/DENGUE/Studies/007 BOD/05 Site Management/05.04 Site Management/05.04.06 Protocol Deviations.

6. DENGUE CASE CLASSIFICATION

The following classification of suspected dengue case (SDC) was used in this study.

6.1. Suspected symptomatic dengue case

Acute febrile illness measured as ≥ 38.0°C with a thermometer by any route or recent history of febrile illness (onset in the past 8 days) reported by the subject/the parent(s)/LAR(s)/ designate (if applicable) of the subject for at least two consecutive days (a duration of approximately 36-48 hours) and of less than 7 days duration, which may be accompanied by other dengue symptoms or signs and does not have a defined focus or an obvious reason unrelated to dengue (based on physician judgement).

Note: Besides fever, other dengue associated signs and symptoms include but are not limited to: upper respiratory tract symptoms like cough, nasal congestion, runny nose and dyspnoea, gastrointestinal symptoms and febrile convulsion in infants/older children and fatigue, headache, pain behind the eyes, abdominal pain, nausea, vomiting, muscle ache, joint ache, diffuse rash on the trunk, itching of skin (pruritis) in adults/adolescents.

A number of infectious and non-infectious diseases mimic dengue and severe dengue. Physicians should be careful not to rule out dengue diagnosis too quickly, when the differential diagnosis cannot be accurately made. Early symptoms of dengue may include gastrointestinal and upper respiratory symptoms and may be misdiagnosed as diarrhoeal diseases or other diseases with flu-like symptoms. The WHO handbook for clinical management of dengue provides a list of conditions that mimic the febrile phase and the critical phase of dengue infection.

A SDC presenting at the health care facility within 5 days following the onset of symptoms (i.e. day of symptoms onset and the next 4 days) will be defined as an ‘early presenter’. A SDC presenting at the health care facility 6 days or more after the onset of symptoms will be defined as ‘late presenter’. Both early and late presenters will have a scheduled visit at the study healthcare centre including blood sampling for laboratory diagnosis.

Seven consecutive calendar days without fever (body temperature ≥ 38.0°C), in the absence of antipyretic medication, are required to separate two episodes of SDC.

6.2. Laboratory confirmation

6.2.1. RT-qPCR confirmed symptomatic DENV infection

A SDC confirmed by RT-qPCR

6.2.2. A virologically confirmed symptomatic DENV infection

A SDC confirmed by RT-qPCR or NS1.

6.2.3. Probable dengue case

A SDC with:

- DENV RT-qPCR negative or not performed (late presenter)

and

- DENV NS1 negative or undetermined (early or late presenter)

and

- Anti-DENV IgM positive with a rapid immunochromatographic (ICT) assay or an ELISA assay

Or

- Anti-DENV IgG positive (rapid ICT assay or 'capture ELISA' assay)

7. STATISTICAL ANALYSES

SAS software will be used for statistical analysis.

Note that data derivation rule and statistical methods are described in Section 12 and will not be repeated below.

Continuous variables will be summarized with number of non-missing observations, mean, standard deviation (SD), median, minimum, maximum, 25th and 75th percentiles. Categorical variables will be summarized with frequency tables; numbers and percentages for each level will be given.

If an elimination code 900 is attributed, then all the analyses planned to be done on the Total cohort will be done on the Total cohort without subjects with code 900, except Template 5 from EPI-DENGUE-007 BOD (200318) TFL (24-MAY-2019) DRAFT.

The final analysis will be performed on the following study sites using data up to the specified study visits covered up to study termination:

Study sites name	Number of enrolled subjects	Study visits covered at study termination	Dengue season covered at study termination
Mexico	350	Visit 1 to Visit 3	2017, 2018
Philippines	500	Visit 1 to Visit 2	2018

The laboratory results (POS/NEG/IR=invalid result/EQV=equivocal (i.e. level of measured Dengue IgG Ab is not enough to conclude of a Dengue infection)) will be available at the scheduled visits for the following tests:

- Dengue Virus Ab.IgG by ELISA (v_id= 3789.005) will be available at Visit 1 for Mexico site
- Dengue Virus Ab.IgG by ELISA (v_id= 3789.005) will be available at Visit 1 and 2 for Philippines site

The laboratory results (POS/NEG/IR) will be available in case of SDC, at first visit, for the following tests:

Assays	Method	Early presenters	Late presenters
DENV RT-qPCR: • Dengue Virus Type 1 RNA (v_id= 3415.005) • Dengue Virus Type 2 RNA (v_id= 3415.006) • Dengue Virus Type 3 RNA (v_id= 3415.007) • Dengue Virus Type 4 RNA (v_id= 3415.008)	RT-qPCR	Yes	Yes
DENV NS1	RAPIDIMM	Yes	Yes
Anti-DENV IgM	RAPIDIMM	Yes	Yes
Anti-DENV IgG	RAPIDIMM	Yes	Yes
Hematology / Biochemistry		Yes	Yes

RAPIDIMM = rapid immunochromatographic assay

7.1. Analysis of demographics/baseline characteristics

The number of subjects enrolled into the study will be tabulated by study site and overall on the Total cohort.

The number of subjects enrolled per household will be tabulated by study site and overall on the Total cohort.

The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal by study site, age category and overall on the Total cohort.

The distribution of the subjects in each cohort and reasons for exclusion will be tabulated by study site and overall.

- Minimum and maximum visit dates will be tabulated by study site and overall on the Total cohort.

Demographic characteristics (age at Visit 1 and gender) will be summarized using descriptive statistics by study site and overall on the Total cohort and on the ATP cohort.

Summary of history of dengue at Visit 1 will be summarized by study site and overall on the ATP cohort.

7.2. Description of ad-hoc visits

The analyses will be performed on the ATP cohort.

The distribution of ad-hoc visits with suspicion of dengue and ad-hoc visits without suspicion of dengue will be tabulated by study site, month and overall. Distribution of ad-hoc visits by month will also be displayed graphically by study site.

Ad-hoc visits without suspicion of dengue will be listed with the following characteristics: study site, ad-hoc visit date, subject number, age in year at ad-hoc visit, gender and diagnosis.

7.3. Characteristics of the suspected dengue cases

The analyses will be performed on the ATP cohort.

SDC will be listed with the following characteristics: study site, date of first visit for SDC, subject number, household number, dengue episode number, age at first symptom onset, gender, time interval between fever onset and first visit for SDC (in days), time interval between first symptoms onset and first visit for SDC (in days), early/late classification (based on interval between date of symptoms onset and date of first visit for SDC), date of blood sample, laboratory results at first visit for SDC, dengue classification (virologically confirmed, probable, other SDC), Dengue Virus Ab.IgG antibodies (ELISA) at Visit 1, hospitalization (Yes/No), at least 1 WHO 2009 warning signs (Yes/No), at least 1 WHO 2009 criteria for severe dengue (Yes/No) and most likely diagnosis (investigator opinion).

Distribution of suspected dengue cases type (early/late presenters) by month will be displayed graphically by study site and overall.

The following characteristics will be summarized for each category of dengue cases (Virologically, probable, other SDC):

- Temperature at first visit: <37.5, ≥ 37.5, >38, >38.5, >39, >39.5, >40
- Clinical symptoms at onset, from first and returned visits: frequency and proportion of cases with each symptom
- Final classification of the episode (hospitalisation (yes/no), at least one WHO 2009 warning signs (yes/no), at least one WHO 2009 criteria for severe dengue (yes/no), most likely diagnosis according to investigator opinion (dengue, chikungunya, influenza, malaria rotavirus or other enteric infection, other infection disease or non-infectious disease)).

7.4. Analysis of incidences

The analyses will be performed on the ATP cohort.

The following analyses will be performed by study site and overall:

- Incidence proportion of RT-qPCR confirmed symptomatic dengue infection during the study period.
- Incidence proportion of virologically confirmed symptomatic dengue infection during the study period.
- Incidence proportion of probable symptomatic dengue infection during the study period.
- Incidence proportion of virologically confirmed or probable symptomatic dengue infection during the study period.
- The numerator will be the number of subjects with at least one specified event reported during the study period. The denominator will be the number of subjects in the ATP cohort.

95% CI accounting for clustering effect will be computed on all estimated incidence proportions. The method for estimating the CIs is described in Section 12.1.

- The proportion, with 95%CI, of subjects with Dengue Virus Ab.IgG positive result (ELISA) at Visit 1 will be tabulated by study site and age category.

7.5. Analysis of tertiary objectives

- Tertiary objectives will not be analysed.

7.6. Analysis of serious adverse events

Serious adverse events related to study procedures reported during the study period will be listed.

8. ANALYSIS INTERPRETATION

All analyses are descriptive.

9. CONDUCT OF ANALYSES

9.1. Sequence of analyses

The final analysis will be performed when all data have been collected and cleaned.

Study progress reports were generated during the study conduct to follow study progress using specified tables and using the study database as source data.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)* requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	SR, CTRS	No	No	Refer to EPI-DENGUE-007 BOD (200318) TFL (24-MAY-2019) DRAFT.docx
Study progress reports	E1_02	Monitoring	No	No	Refer to EPI-DENGUE-007 BOD (200318) Additional Analysis Request E01_02 Study Progress Report.docx

9.2. Statistical considerations for interim analyses

No interim analyses were planned.

10. CHANGES FROM PLANNED ANALYSES

The cohorts were clarified and the Total cohort without subjects with code 900 was added.

Due to study termination:

- Medical history and vaccination history for Japanese Encephalitis and Yellow Fever will not be summarised.
- Tertiary objectives will not be analysed.
- Refer to Section 7 for the laboratory tests performed. Those not performed will therefore not be analysed. In addition, no GMTs will be computed as only qualitative laboratory results (positive/negative) will be available.
- Incidence proportions will be computed instead of incidence rates for the primary and secondary objectives. Sub-analyses by season/year, by age category, gender, serotype and dengue serological status at the beginning of the analysis period will not be performed due to the low number of virologically confirmed or probable symptomatic dengue infection reported during the study period. In addition, analysis of incidences will only be performed on the ATP cohort.
- The proportion of subjects with Dengue Virus Ab.IgG positive result (ELISA) at Visit 1 will not be summarized among dengue cases (confirmed and probable) due to the low number of virologically confirmed or probable symptomatic dengue infection reported during the study period.
- The statistical methodology to estimate the CI for proportions accounting for clustering effect will not use stratification by center for the analyses on overall centers (refer to Section 12.1).

11. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

Refer to the document entitled EPI-DENGUE-007 BOD (200318) TFL (24-MAY-2019) DRAFT.docx.

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

- Age categories:

Group order in tables	Group label in tables	Group definition for footnote
1	6 months-<12 months	From the 6th month birthday up to and including the day before the 1st year birthday
2	1-4 years	From the 1st year birthday up to and including the day before the 5th year birthday
3	5-8 years	From the 5th year birthday up to and including the day before the 9th year birthday
4	9-17 years	From the 9th year birthday up to and including the day before the 18th year birthday
5	18-50 years	From the 18th year birthday up to and including the day before the 51th year birthday

- Study sites (named center in the database):

Group order in tables	Group label in tables	Group definition for footnote
1	Mexico	No footnote
2	Philippines	

- Ad-hoc visits:

Group order in tables	Group label in tables	Group definition for footnote
1	Non SDC	Ad-hoc visits without suspicion of dengue
2	SDC	Ad-hoc visits with suspicion of dengue

- Symptomatic dengue confirmation status:

Group order in tables	Group label in tables	Group definition for footnote
1	Virologically confirmed	Symptomatic dengue cases confirmed by RT-qPCR or NS1
2	Probable	Probable symptomatic dengue cases
3	Other SDC	Symptomatic dengue cases not classified as virologically confirmed or probable

- Early/late presenter classification:

Group order in tables	Group label in tables	Group definition for footnote
1	Early presenter	Suspected dengue cases presenting at the health care facility within 5 days of symptoms onset
2	Late presenter	Suspected dengue cases presenting at the health care facility 6 days or more after symptoms onset

12. DATA DERIVATION RULE AND STATISTICAL METHODS

12.1. Methodology for computing CI

All confidence intervals (CIs) will be two-sided 95% CI.

This study will use cluster sampling (i.e. households within centers), inducing a potential clustering effect of the households and/or centers.

Individuals within a household are expected to have a more similar risk of infection compared to individuals from different households. For example, individuals living in the same household are more likely to share similar risk of being exposed to DENV infected mosquitoes. Similarly, subjects within a center may have a more similar risk of infection compared to individuals from different centers.

Therefore, CIs for proportions will account for clustering of observations. The 95% CIs will be based on generalized estimating equations (GEE) logistic regression model with robust variance estimate [Liang, 1986]:

- For an analysis by center, households will be considered as the clusters in the model.
- For an analysis on overall centers, the model with the highest estimated design effect (DE) among those using either households or centers as clusters will be used.
- SAS code:

```
PROC GENMOD DATA=xxx descending;
  CLASS cluster;
  MODEL event = / dist=bin link=logit;
  REPEATED subject= cluster / type=exch;
RUN;
```

Note that if the DE estimated from the selected GEE model is less than 1, then the classical logistic regression model will be used (GENMOD without cluster statement).

The design effect (DE), assessing the impact of clustered data on the variance of the estimated proportions (thus on the the precision of the estimated proportions), will be estimated as follows:

$$DE = \frac{\text{estimated variance accounting for the cluster sampling from GEE model}}{\text{variance estimated under the assumption of simple random sampling}}$$

If the proportion is 0% or 100%, or if all subjects used to compute the proportion are from the same cluster, then ICC, DE and 95%CI will not be estimated.

12.2. Data presentation

The following decimal description will be used for the analyses:

Display Table	Parameters	Number of decimal digits
Dengue cases	Incidence proportion, including LL & UL of CI	2
Dengue cases	Percentage	1
Demographic characteristics/ baseline characteristics	Percentage, mean, median, standard deviation, minimum, maximum, Q1, Q3	1

CI = confidence interval
LL = lower limit of the confidence interval
SD = standard deviation
UL = upper limit of the confidence interval
Q1/Q3 = 25th and 75th percentiles

12.3. Handling missing data

No data handling will be performed in case of missing data.

12.4. Data derivation

12.4.1. Date derivation

SAS date derived from a character date: in case day is missing, 15 is used. In case day and month are missing, 30 June is used.

12.4.2. Age

- Age: age at the reference activity is computed as the number of units between the date of birth and the reference activity, expressed in months/years.

When age at reference activity is to be displayed in months/years, it will be calculated as the number of complete calendar months/years between the date of birth and the date of reference activity. For example:

- DOB = 10JUN2017, Date of vaccination = 09JUL2018 -> Age = 12 months
- DOB = 10JUN2017, Date of vaccination = 10JUL2018 -> Age = 13 months
- DOB = 10SEP1983, Date of reference = 09SEP2018 -> Age = 34 years
- DOB = 10SEP1983, Date of reference = 10SEP2018 -> Age = 35 years

12.4.3. Time interval

Time interval between 2 visits is expressed in days. It is the number of days between the 2 visit dates. Therefore, the time interval is of 0 day if the 2 visit dates are the same.

Time interval expressed in years will be computed as follows: time interval expressed in days/365.25.

12.4.4. Duration

Duration of an event is expressed in days. It is the number of days between the start and the stop dates + 1. Therefore, duration is 1 day for an event starting and ending on the same day.

12.4.5. SDC confirmed by RT-qPCR

A SDC will be considered as confirmed by RT-qPCR if at least one Dengue Virus Type 1, 2 3 or 4 RNA result is POS.

12.4.6. Classification of severity of dengue

Criteria for dengue with warning signs (WHO 2009): at least one of the following should be present (i.e. criteria box ticked in the eCRF):

- Abdominal pain or tenderness,
- Persistent vomiting (three or more emesis in a period of one hour, or five or more in a period of six hours),
- Clinical fluid accumulation (peri-orbital, facial or lower limb oedema as reported by the study physician, or pleural effusion, ascites or gall-bladder wall thickening ≥3 mm as observed via X-ray radiography or ultrasonography),
- Mucosal bleed (any of the following: hemoptysis, epistaxis, gingival bleeding, melena, hematemesis, hematuria, menorrhagia, vaginal bleeding, or subconjunctival hemorrhage as observed by a study physician or reported by the patient),
- Liver enlargement (liver enlarged >2 cm below the edge of the ribs as palpated by a study physician),
- Increase in HCT concurrent with rapid decrease in platelet count (interpreted as any HCT >20% over baseline with platelet 50,000/mm3),
- Lethargy (Glasgow coma scale score <15 for children aged 5 years or more or Blantyre coma scale <5 for children under 5, as evaluated by a study physician) and restlessness.

Criteria for severe dengue (WHO 2009): dengue with at least one of the following criteria (i.e. criteria box ticked in the eCRF):

- Severe Plasma Leakage leading to Shock (DSS)[1], Fluid accumulation with respiratory distress[2],
- Severe Bleeding[3],
- Severe organ involvement;
- Liver: AST or ALT ≥ 1000 IU/L,
- Central nervous system: impaired consciousness[4] ,
- Failure of heart and other organs[5].

12.4.7. Fever at the visit

The status of fever at the visit for suspicion of dengue will be derived from the fever tick box of the eCRF from the list of main signs.

12.4.8. Safety

For analysis of serious adverse events related to study procedures, all enrolled subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.

13. REFERENCES

[Liang KY and Zeger SL]. Longitudinal Data Analysis Using Generalized Linear Models. *Biometrika*, 73, 13–22 (1986)

[1] A clinical state of reduced perfusion to end-organs (such as the skin), defined as presence of a weak pulse, and/or narrowing of pulse pressure, and/or hypotension for age and one of the following: 1) Cold, clammy skin, 2) Increased capillary refill time, 3) Peripheral cyanosis, 4) Skin mottling

[2] defined as respiratory discomfort, dyspnea, respiratory failure, or increased respiratory rate of >60 breaths/min for ages <2 months; >50 breaths/min for ages 2 months to 1 year; >40 breaths/min for ages 1 to 5 years; >30 breaths/min for ages 5 to 8 years; and >20 breaths/min for those older than 8 years);

[3] As evaluated by clinician WHO Grade 2 or above: haematemesis, melena, menorrhagia or clinical drop in haemoglobin requiring whole blood or packed red cell transfusion;

[4] Any reduction in coma score that may be accompanied by convulsions and/or meningism and/or abnormal neurological signs

[5] For renal impairment: Stage 2 Acute Kidney Injury defined as serum creatinine increase of 100% over baseline or calculated norm for age/gender/race)