| GlaxoSmithKline | **Statistical Analysis Plan** |
|---|---|
| **Detailed Title:** | A prospective, epidemiological, interventional, multi-country based, cohort study to assess the disease burden of respiratory syncytial virus (RSV) associated, suspected lower respiratory tract infections (LRTIs) in newborns, from birth up to 2 years of age and population attributable risk percent of RSV LRTI on the development of wheeze and asthma from birth up to 6 years of age. |
| **eTrack study number and Abbreviated Title** | 200150 (EPI-RSV-005 BOD) |
| **Scope:** | All data during epoch 1 pertaining to the above study from birth to 2 year of age. |
| **Date of Statistical Analysis Plan** | Amendment 1 Final: 18-May-2018 |
| **Co-ordinating author:** | PPD (Statistician)<br>PPD (Statistician) |
| **Reviewed by:** | PPD (Clinical and Epidemiology Project Lead)<br>PPD (Lead statistician)<br>PPD (Lead statistical analyst)<br>PPD (Statistician)<br>PPD (Statistician)<br>PPD, Clinical Read-Out Team Leader<br>PPD (Scientific writer)<br>PPD (Regulatory Affair)<br>PPD (SERM physician)<br>PPD (Public disclosure representative) |
| **Approved by:** | PPD (Clinical and Epidemiology Project Lead)<br>PPD (Lead statistician)<br>PPD (Lead scientific writer)<br>PPD (Lead statistical analyst) |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **CI** | Confidence Interval |
| **CP** | Concept Protocol |
| **CRF** | Case Report Form |
| **CSR** | Clinical Study Report |
| **CTRS** | Clinical Trial Registry Summary |
| **DE** | Design Effect |
| **eCRF** | electronic Case Report Form |
| **EL.U/ml** | ELISA unit per milliliter |
| **Eli Type** | Internal GSK database code for type of elimination code |
| **ELISA** | Enzyme-linked immunosorbent assay |
| **ER** | Emergency Room |
| **ES** | Exposed Set |
| **FAS** | Full Analysis Set |
| **FN** | False Negative |
| **FP** | False Positive |
| **GCP** | Good Clinical Practice |
| **GMC** | Geometric mean antibody concentration |
| **GMT** | Geometric mean antibody titer |
| **GP** | General Practitioner |
| **GSK** | GlaxoSmithKline |
| **HIV** | Human Immunodeficiency Virus |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonization |
| **IEC** | Independent Ethics Committee |
| **ILI** | Influenza-like Illness |
| **IRB** | Institutional Review Board |
| **IU/ml** | International units per milliliter |
| **LAR** | Legally Acceptable Representative |
| **LL** | Lower Limit of the confidence interval |
| **LLOQ** | Lower Limit Of Quantification |
| **LRTI** | Lower Respiratory Tract Infection |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **mL** | Milliliter |
| **N.A.** | Not Applicable |
| **NH** | Northern Hemisphere |
| **NPV** | Negative Predictive Value |
| **OTC** | Over-The-Counter |
| **P** | Percentile |
| **PCR** | Polymerase Chain Reaction |

| | |
|---|---|
| **PD** | Protocol Deviation |
| **PPS** | Per Protocol Set |
| **PPV** | Positive Predictive Value |
| **RDE** | Remote Data Entry |
| **RR** | Respiratory Rate |
| **RSV** | Respiratory Syncytial Virus |
| **RTI** | Respiratory Tract Infection |
| **RT-qPCR** | Reverse transcription-quantitative real time polymerase chain reaction |
| **RVP** | Respiratory Viral Panel |
| **SAE** | Serious Adverse Events |
| **SaO2** | Blood Oxygen Saturation |
| **SAP** | Statistical Analysis Plan |
| **SBIR** | Randomization System on Internet |
| **SD** | Standard Deviation |
| **SDV** | Source Document Verification |
| **SH** | Southern Hemisphere |
| **SPM** | Study Procedure Manual |
| **SR** | Study Report |
| **TFL** | Tables Figures and Listings |
| **TN** | True Positive |
| **TOC** | Table of Content |
| **TP** | True Negative |
| **UL** | Upper Limit of the confidence interval |
| **URTI** | Upper Respiratory Tract Infection |
| **US** | United States |
| **WHO** | World Health Organisation |

# 1. DOCUMENT HISTORY

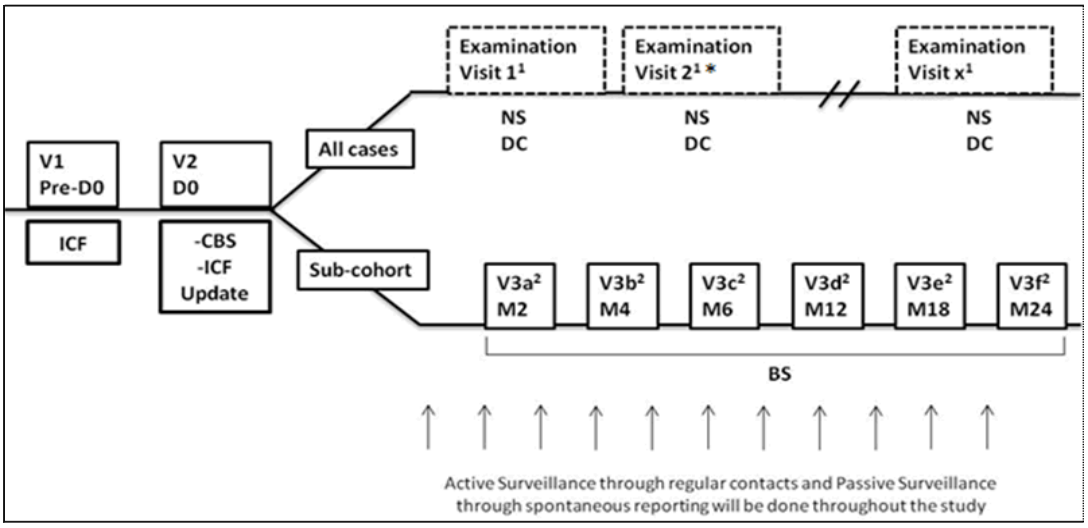
| Date | Description | Protocol Version |
|---|---|---|
| 17-JUL-2015 | First version | Amendment 2 Final - 06-JUL-2016 |
| 18-MAY-2018 | Amendment 1 | Amendment 3 Final - 15-DEC-2017 |

# 2. STUDY DESIGN

## 2.1. Design summary

In the primary study, subjects were to be followed-up from birth up to the age of 2 years for RSV LRTI. Episodes of wheeze and diagnoses of asthma were also documented.

**Figure 1 Study design diagram for the primary study (from birth up to the age of 2 years for detection of RSV LRTI)**




V = Visit; D = Day; M = Month
ICF = Informed Consent Form; CBS = Cord Blood Sample; NS = Nasal Swab; DC = Diary Card; BS = Blood Sample
[1] An examination visit (off-site/site) is to occur for new or worsened, potential LRTI case as identified during active or passive follow-up contact. The examination visit needs to occur as soon as possible and no later than 72 hours after the potential LRTI was identified during a follow-up contact. Each subject may have none, single or multiple examination visits over the course of the study.
[2] A sub-cohort of subjects will be randomized for a single blood draw to occur at one of the six possible time points and will have a Visit 3 corresponding to this time point (if still participating at that time); either V3a at 2, V3b at 4, V3c at 6, V3d at 12, V3e at 18 or V3f at 24 months.
* All follow up procedures associated with V2 (e.g. ICF) must be performed within 5 working days after birth.

- Type of design: Prospective, epidemiological, interventional, multi-country, cohort study.
- Study population:
  - A cohort of approximately 2400 infants will be included in the study at birth and followed-up up to 2 years of age.
  - A sub-cohort of subject will be randomized for a single blood draw to one of the time point at 2, 4, 6, 12, 18 or 24 months of age as described in Table 1.

**Table 1 Blood sample collection**

| Time point | Seroprevalence sub-cohort Number of allocated subjects* |
|---|---|
| 2 months | 200 |
| 4 months | 200 |
| 6 months | 250 |
| 12 months | 300 |
| 18 months | 450 |
| 24 months | 600 |
| **Total** | 2000 |

Note: Only one blood sample will be withdrawn from each subject in this sub-cohort.
*Number of subjects selected per time point is calculated based on the required number of subjects for adequate analysis considering an accumulating drop-out of subjects. Actual numbers might be less due to drop-outs and exclusion of subjects with gestational age <36 weeks..

- Type of study: Self-contained.
- Data collection: Electronic case report form (eCRF).
- Biological samples (Primary Study only):
  - Cord Blood collected from all participating subjects, at birth.
  - Nasal swabs collected from subjects with potential LRTI.
  - Serum collected from a sub-cohort of subjects, excluding those born at a gestational age of less than 36 weeks. Sampling time points for this sub-cohort will be randomly allocated as specified in Table 1.
- Duration of the study: Approximately 2 years for each participant enrolled in the primary study and an additional (approximately) 3 to 4 years for each participant enrolled in the extension study.
  - Epoch 1 (Primary Study): Begins at birth (Visit 1) and ends at the age of approximately 2 years (Visit or contact at 2 years).
  - Epoch 2 (Extension Study): Begins with the first contact for the extension study (at approximately age 2 years); ends with the contact at approximately the sixth birthday. Table 2 presents the study groups and epochs foreseen in the study.

**Table 2 Study groups and epochs foreseen in the study**

| Study Groups | Number of subjects | Age (Min/Max) | Epoch 1 | Epoch 2 |
|---|---|---|---|---|
| Primary | Approximately 2400 | 0 days - 2 years | x | |
| Extension | Maximum 2400 | Approximately 2 years to 6 years | | x |

* Data collection will also occur from medical charts retrospectively for those who have a gap period between the end of the primary study and providing re-consent for the extension.

Surveillance Plan:

- Surveillance for RSV Lower Respiratory Tract Infection (RSV LRTI), wheeze and asthma during the Primary Study period.
- Surveillance for wheeze and asthma during the extension study period.
- Safety Follow-up:
- Study procedure related Serious Adverse Events (SAEs) to be reported throughout the study.

This comprehensive analysis has been structured according to the endpoints per protocol. The table below summarises for the reader where analyses are presented. Full details of endpoints are given in section 4.

**Table 3 Analyses topics summary**

Please note that the extension analyses are not described in this SAP.

| Analysis | Endpoint | Endpoints listed in section | Analysis presented in section |
|---|---|---|---|
| Incidence | Co-primary | 4.1 | 6.6.1 |
| | Secondary | 4.2 | 6.6.26.6.2 |
| | Tertiary | 4.3 | 6.6.3 |
| Health care utilization | Co-primary | 4.1 | 6.7 |
| Performance of case definitions | Co-primary | 4.1 | 6.8.1 |
| | Tertiary | 4.3 | 6.8.2 |
| Neutralizing antibodies over time and protection against RSV disease | Secondary | 4.2 | 6.9.1<br>6.9.2 |
| | Tertiary | 4.3 | 6.9.3 |
| Other viruses and RSV infections | Tertiary | 4.3 | 6.10 |
| Compliance with protocol | Tertiary | 4.3 | 6.11 |

Please note that the extension analyses are not described in this SAP.

## 2.2. Discussion of the study design

The multi-country design of both the primary and extension studies will provide robust, multinational estimates of the incidence of RSV-associated LRTI during the first two years of life and assess the amount of wheeze and asthma that may be attributable to those early RSV-LRTI infections.

### 2.2.1. Primary study

The Primary study will determine the incidence and associated healthcare utilization of RSV-associated LRTIs in infants from birth up to the age of 2 years, and assess the performance of a new LRTI case definition and severity scale. Using a cohort representing the general population of newborn infants, the study is designed to identify RSV-associated LRTI cases at any severity, and will not be limited to those that require hospitalization and/or other essential medical care. This will provide a comprehensive and accurate measure of the overall burden of disease, whereas many previous case-control or hospital-based cohort studies were limited to the hospitalized cases of RSV-associated LRTI.

The association of other respiratory viruses with RSV-associated LRTI and/or severe LRTI, and the impact of potential RSV risk factors on the incidence and severity of RSV-associated LRTI will also be explored. In order to assess and adjust for other potential confounders in the various analyses, data on the subjects' demography and lifestyle factors will be collected at baseline, and followed up quarterly for changes, during the regular follow-up contacts.

# 3. OBJECTIVES

## 3.1. Co-primary objectives

- To determine the total health burden* of RSV-associated RTI with a suspicion of involvement of the lower respiratory tract.

**Health burden refers to burden of the disease imposed on the study population in terms of incidence of the disease and associated healthcare utilization in any healthcare setting.*

- To assess the performance of the LRTI case definition and severity scale for RSV associated cases.

## 3.2. Secondary objectives

In a cohort of infants followed-up from birth up to 2 years of age;

- To determine the total health burden of non-RSV-associated RTI with a suspicion of involvement of the lower respiratory tract.
- To evaluate the association between RSV-associated LRTI, RSV-associated severe LRTI and RSV neutralizing antibodies in the baseline cord blood samples collected from subjects, at birth.
- To determine the prevalence of RSV infection, at 2, 4, 6, 12, 18 and 24 months in a randomly selected sub-cohort of subjects by assessing antibodies in serum.
- To assess the between calendar year variability in the incidence rates of RSV-associated LRTI.

## 3.3. Tertiary objectives

In a cohort of infants followed-up from birth up to 2 years of age;

- To explore the association of co-infections with the incidence of RSV-associated LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale) using xTAG™ respiratory viral panel (RVP) fast assay.
- To explore the association of RSV and other respiratory viruses with the incidence of LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale) using xTAG™ RVP Fast assay.
- To explore the association of RSV viral load with the incidence of RSV-associated RTI, LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale).
- To explore the impact of changes to the symptoms and threshold levels of symptoms in the LRTI case definition and severity scale.

- To assess the impact of potential RSV risk factors (e.g. complications at birth, family history of respiratory disease, living environment and household composition, breast feeding, passive smoking, day care attendance) on the incidence and severity of RSV-associated LRTI.
- To explore the impact of variations in cord-blood sample collection variables on the stability of test results.
- To assess the natural decay of maternal antibody levels using a single follow-up blood sample collected from a randomly selected sub-cohort of subjects at 2, 4, 6, 12, 18 and 24 months.

# 4. ENDPOINTS

## 4.1. Co-primary endpoints

- Occurrence of RSV as confirmed by RT-qPCR.
- Occurrence of different types of healthcare utilization*.

** Healthcare utilization includes primary, secondary and tertiary care settings such as self-care with OTC drugs, GP visits, ER visits, hospital visits, etc.*

- Occurrence of LRTI/severe LRTI as classified by the LRTI case definition and severity scale.
- Occurrence of LRTI/severe LRTI as classified by the existing comparator LRTI case definition by WHO and by Nokes et al.

## 4.2. Secondary endpoints

- Levels of RSV neutralizing antibodies in the cord blood samples collected at birth.
- Levels of RSV neutralizing antibodies in the blood samples collected at 2, 4, 6, 12, 18 and 24 months.
- Occurrence of LRTI/severe LRTI cases as classified by the LRTI case definition and severity scale, in the subgroups of subjects recruited from Months 1-6 and 13-18.

## 4.3. Tertiary endpoints

- Occurrence of RSV and other respiratory viruses as confirmed by xTAG™ RVP Fast assay:
  - Parainfluenza virus type 1, 2, 3, and 4
  - Human Metapneumovirus
  - Rhinovirus
  - Adenovirus
  - Bocavirus

  - Coronavirus - 229E, OC43, NL63, HKU1
  - RSV
  - Influenza A, including subtypes H1 and H3
  - Influenza B
- RSV viral load as determined by RSV RT-qPCR.
- Occurrence of any symptom identified in cases of potential LRTI.
- Cord-blood sample collection variables including collection and storage times and temperatures.
- Occurrence of potential risk factors including complications at birth, family history of respiratory disease, living environment and household composition, breastfeeding, passive smoking and day-care attendance.

# 5. ANALYSIS SETS

## 5.1. Definition

### 5.1.1. Screened cohort

The screened cohort will include all subjects screened for the study. This cohort will include all subjects with an ICF signed before birth. All subjects who signed the ICF before birth. All the aggregated information (anonymous) for these subjects will be collected in a logbook.

### 5.1.2. Total enrolled cohort

The total enrolled cohort will include all subjects enrolled in the study, without ICF issues (ICF signed before birth and re-signed after birth).

### 5.1.3. Per-protocol Set (PPS)

Note that in order to align to ICH and cDISC terminology the According To Protocol (ATP) cohort as stated in the protocol has been renamed Per-Protocol Set (PPS) respectively.

The PPS will include all subjects meeting all elimination criteria up to the time of their censoring (study termination), either at study completion or prematurely as drop-out (e.g. withdrawn consent, lost-to-follow-up, lack of compliance).

### 5.1.4. Total sub-cohort

All subject randomized to a blood sampling visit and with available result for blood sampling for either RSV A or RSV B.

### 5.1.5. Sub-cohort in PPS

The PPS sub-cohort will include subjects for whom a blood sample result will be available (at Month 2, 4, 6, 12, 18 or 24). Analyses will be done on the PPS sub-cohort from the total cohort defined in section 5.1.2, as well as from the PPS defined in section 5.1.3.

## 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 set.

### 5.2.1. Elimination from Total enrolled cohort

Code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES

### 5.2.2. Elimination from Per-protocol analysis Set (PPS)

#### 5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions

| Code | Condition under which the code is used |
|---|---|
| 900 | Invalid informed consent or fraud data |
| 200/2010 | Protocol violation (inclusion/exclusion criteria) |

### 5.2.3. Elimination from Total sub-cohort

#### 5.2.3.1. Excluded subjects

| Code | Condition under which the code is used |
|---|---|
| 900 | Invalid informed consent or fraud data |
| 200/2010 | Protocol violation (inclusion/exclusion criteria) |
| 2500 | Subjects not randomize to a blood sampling visit |
| 2502 | Serological results were not available for subjects at visit 3 who had a BS as randomized from SBIR |

### 5.2.4. Elimination from Per Protocol Set Sub-cohort (PPS Sub-cohort)

#### 5.2.4.1. Excluded subjects

A subject will be excluded from the PPS sub-cohort analysis under the following conditions.

| Code | Condition under which the code is used |
|---|---|
| 900 | Invalid informed consent or fraud data |
| 200/2010 | Protocol violation (inclusion/exclusion criteria) |
| 2500 | Subjects not randomize to a blood sampling visit |
| 2501 | Blood sample taken but: non-compliance with blood sampling schedules |
| 2502 | Serological results were not available for subjects at visit 3 who had a BS as randomized from SBIR |

## 5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

Not applicable.

# 6. STATISTICAL ANALYSES

## 6.1. Derived and transformed data

### 6.1.1. Case definitions

The different case definitions are summarized in the following table (see section 11.2.1 for detail description of case definition):

**Table 4 Summary of case definitions**

| Endpoint | Case definition |
|---|---|
| RSV asymptomatic[1] | Infants with no history of cough OR<br>runny nose OR<br>blocked nose, AND<br>Confirmed RSV infection[4] |
| RSV RTI | [Infant with history of cough OR<br>Runny nose OR<br>Blocked nose] AND<br>Confirmed RSV infection |
| RSV RTI with suspicion of involvement of LRT | From surveillance contact:<br>[Infant with history of cough OR runny nose OR<br>blocked nose] AND<br>[History of wheezing or grunting, OR<br>History of fast breathing, OR<br>History of flaring of nostrils, OR<br>History of chest wall indrawing, OR |

| Endpoint | Case definition |
|---|---|
| | History of shortness of breath], AND<br>[Confirmed RSV infection<br>OR<br>Self-referral to examination to assessment], AND<br>Confirmed RSV infection |
| RSV hospitalization* | Infant hospitalized AND<br>Confirmed RSV infection[5] |
| RTI with suspicion of involvement of LRT (all cause) | From surveillance contact:<br>[Infant with history of cough OR runny nose OR<br>blocked nose] AND<br>[History of wheezing or grunting, OR<br>History of fast breathing, OR<br>History of flaring of nostrils, OR<br>History of chest wall indrawing, OR<br>History of shortness of breath], AND<br>[Confirmed RSV infection<br>OR<br>Self-referral to examination to assessment] |
| **GSK 2013** | |
| RSV LRTI* | [Infant with history of cough OR runny nose OR<br>blocked nose] AND<br>[$SpO_2$ < 95% OR<br>RR increase] AND<br>Confirmed RSV infection[4] |
| RSV LRTI hospitalization | Meeting the case definition of RSV LRTI and associated with hospitalization |
| RSV severe LRTI* | Infant with RSV LRTI AND<br>SpO2 < 92% OR<br>[Difficulty breathing leading to:<br>Irritability/agitation, OR<br>Lethargy/sleepiness, OR<br>Lower chest wall indrawing, OR<br>Reduced/no vocalization, OR<br>Apnoea > 20 seconds, OR<br>Cyanosis, OR<br>Stop feeding well/dehydration] |
| RSV severe LRTI hospitalization | Meeting the case definition of RSV severe LRTI and associated with hospitalization[6] |
| **Nokes 2004** | |
| RSV LRTI* | [Infant with history of cough OR<br>difficulty breathing] AND<br>[[$SpO_2$ < 90% AND clinical diagnosis of LRTI or bronchiolitis]<br>OR<br>RR increase OR<br>Lower chest wall indrawing] AND<br>Confirmed RSV infection[4] |
| RSV LRTI hospitalization | Meeting the case definition of RSV LRTI and is associated with hospitalization |
| RSV severe LRTI* | Infant with RSV LRTI AND<br>At least one of the following two<br>• $SpO_2$ < 90% AND clinical diagnosis of LRTI or bronchiolitis<br>• Lower chest wall indrawing |

| Endpoint | Case definition |
|---|---|
| RSV severe LRTI hospitalization | Meeting the case definition of RSV severe LRTI and is associated with hospitalization |
| **WHO 2015** | |
| RSV LRTI* | [Infant with history of cough OR Difficulty breathing[2]] AND [$SpO_2$ < 95% OR RR increase[3]] AND Confirmed RSV infection[4] |
| RSV LRTI hospitalization | Meeting the case definition of RSV LRTI AND associated with hospitalization |
| RSV severe LRTI* | Infant with RSV LRTI AND [$SpO_2$ < 93%, OR Lower chest wall indrawing] |
| RSV severe LRTI hospitalization* | Meeting the case definition of RSV severe-LRTI, AND associated with hospitalization |
| LRTI (all cause) | [Infant with history of cough OR Difficulty breathing[2]] AND [$SpO_2$ < 95% OR RR increase[3] ] |
| Severe LRTI (all cause) | Infant with LRTI AND [$SpO_2$ < 93%, OR Lower chest wall indrawing] |
| **Exploratory definitions** | |
| RSV LRTI | [Infant with Cough OR Difficulty breathing] AND [$SpO_2$ < 95% OR RR increase OR Lower chest wall indrawing] AND Confirmed RSV infection[4] |
| RSV LRTI hospitalization | Meeting the case definition of RSV LRTI AND associated with hospitalization |
| RSV severe LRTI | Infant with RSV LRTI AND $SpO_2$ < 93% |
| RSV severe LRTI hospitalization | Meeting the case definition of RSV severe-LRTI AND associated with hospitalization |
| RSV very severe LRTI | Meeting the case definition of RSV LRTI AND $SpO_2$ < 90% |
| RSV very severe LRTI hospitalization | Meeting the case definition of RSV very severe-LRTI AND associated with hospitalization |

[1]Surveillance mechanism not designed to detect cases meeting this endpoint.
[2] Based on history reported by parents/LARs and includes difficulty breathing associated with nasal obstruction
[3] RR defined as ≥ 60/minute (< 2 months of age); ≥ 50/minute (2 to 11 months of age); ≥40/minute (12 to 24 months of age)
[4] RSV infection confirmed on nasal swab positive for RSV A or B by quantitative polymerase chain reaction (qPCR)
[5] RSV sampling and testing is based on medical judgment of medical practitioner or driven by algorithm
[6]Hospitalization is defined as a medical decision requiring infant admission for observation or treatment

### 6.1.2. RSV

Geometric means and positivity status for RSV viral loads will be derived according to the following table:

**Table 5 Derivation rule for GMT calculation of RSV viral load**

| Component | Raw result | Derivation for GM calculation | Derivation for positivity status |
|---|---|---|---|
| RSV-A | <LLOD | LLOD /2 | NEG |
| | ≥ LLOD | Exact value | POS |
| RSV-B | < LLOD | LLOD /2 | NEG |
| | ≥ LLOD | Exact value | POS |

The thresholds used for the derivation are detailed in the following table:

**Table 6 Derivation rule for positivity status of RSV viral load**

| Component | Method | Unit | LOD |
|---|---|---|---|
| RSV-A | RT-qPCR | copies of RSV RNA per mL | 1123 |
| RSV-B | RT-qPCR | copies of RSV RNA per mL | 1467 |

The subject will be considered to be RSV positive when the RSV infection will be confirmed on nasal swab by quantitative polymerase chain reaction (PCR) using both RSV-A (fields [LABO_RES.COMPONEN] = “RSV-A” and [LABO_RES.METHOD] = “QRTPCR” and [LABO_RES.RAWRES]) and RSV-B (field [LABO_RES.COMPONEN] = “RSV-B” and [LABO_RES.METHOD] = “QRTPCR” and [LABO_RES.RAWRES]) tests.

The subject will be considered as positive if one or both tests are positive.

A RSV-A test will be considered:

- Positive if [LABO_RES.RAWRES] ≥ 1123 copies/ml
- Negative if [LABO_RES.RAWRES] < 1123 copies/ml

A RSV-B test will be considered

- Positive if [LABO_RES.RAWRES] ≥ 1467 copies/ml
- Negative if [LABO_RES.RAWRES] < 1467 copies/ml

*Please note that the RSV01 test will not be considered to derive RSV status for primary objectives.*

### 6.1.3. RSV neutralising antibody

Geometric means for RSV neutralising antibodies will be derived according to the following table:

**Table 7 Derivation rule for GMT calculation of RSV neutralizing Antibody**

| Assay | Raw result | Derivation for GMT calculation |
|---|---|---|
| RSV-A neutralising Antibody | <8 | 4 |
| | ≥8 | Exact value |
| RSV-B neutralising Antibody | <6 | 3 |
| | ≥6 | Exact value |

Seropositivity status for RSV neutralising antibodies in cord blood samples will be derived according to the following table:

**Table 8 Derivation rule for seropositivity status of RSV neutralizing Antibody in cord blood samples**

| Assay | Raw result | Derivation for seropositivity status |
|---|---|---|
| RSV-A neutralising Antibody in cord blood | < 8 | NEG |
| | ≥ 8 | POS |
| RSV-B neutralising Antibody in cord blood | < 6 | NEG |
| | ≥ 6 | POS |

Seropositivity status for RSV neutralising antibodies in blood samples will be derived according to the following table:

**Table 9 Derivation rule for prevalence of infection of RSV neutralizing Antibody in blood samples**

| Assay | Raw result | Derivation for infection status |
|---|---|---|
| RSV-A neutralising Antibody in blood sample month 2, 4, 6, and 12 | < 2 fold of expected value* | Non infected |
| | ≥ 2 fold expected value | Infected |
| RSV-A neutralising Antibody in blood sample month 18 and 24 | < 8 | Non infected |
| | ≥ 8 | infected |
| RSV-B neutralising Antibody in blood sample month 2, 4, 6, and 12 | < expected value | Non infected |
| | ≥ expected value | Infected |
| RSV-B neutralising Antibody in blood sample month 18 and 24 | < 6 | Non infected |
| | ≥ 6 | infected |

*Expected value is calculated using Natural decay model.

## 6.1.4. Cox model

### 6.1.4.1. Gestational age at birth

The gestational age at birth will be categorized as followed:

- Less or equal to 36 weeks
- More than 36 weeks

### 6.1.4.2. Birth weight

The birth weight will be categorized as followed:

- Less than 2.5 kg
- More or equal to 2.5 kg

### 6.1.4.3. Apgar at 5 mins of age

The Apgar at 5 mins of age will be categorized as followed:

- 0-3 inclusive,
- 4–6 inclusive,
- 7 or greater

### 6.1.4.4. Family history of respiratory disease

The subject will be considered to have family history of respiratory disease if at least one of its first degree relative (i.e. mother father or sibling) has respiratory disease.

### 6.1.4.5. Time of birth relative to the transmission season

The transmission season period is defined:

- from April to September in the North hemisphere
- from October to March in the South hemisphere
- all year long in the tropical hemisphere

A summary of transmission season is displayed in the following table.

**Table 10 Summary of transmission season by country**

| Country | Hemisphere | Transmission season period |
|---|---|---|
| Canada | North hemisphere | April 1 to September 30 |
| United States | North hemisphere | April 1 to September 30 |
| Finland | North hemisphere | April 1 to September 30 |
| Argentina | South hemisphere | October 1 to March 31 |
| South Africa | South hemisphere | October 1 to March 31 |
| Thailand | Tropical hemisphere | All year long |
| Bangladesh | Tropical hemisphere | All year long |
| Honduras | Tropical hemisphere | All year long |

All subjects from tropical hemisphere will be considered to be born within the season.

Subjects from North hemisphere will be considered to be born within the season if they are born between April and September. Subjects from South hemisphere will be considered to be born within the season if they are born between October to March.

#### 6.1.4.6. Father and mother's highest education

Education level is categorized as:

- High education Yes: Higher education/University (educational program more than 3 years), and Higher education (educational program 3 years or less)
- No: Secondary school and less than secondary school

#### 6.1.4.7. Number of people living in the household at month 3

Number of people living in the household are categorized as

- 1 – 3, inclusive
- 4 – 6, inclusive
- $\geq 7$

#### 6.1.4.8. Number of children (< 18) living in the household at month 3

Number of children living in the household are categorized as:

- 0
- 1 – 2, inclusive
- $\geq 3$,

#### 6.1.4.9. Other

- Age of the subject at time of the LRTI case will be expressed in months and will be computed as the difference between the start date of the LRTI case and the date of birth.
- Age of the subject at time of blood sample collection will be expressed in months and will be computed as the difference between the sample collection date and the date of birth.
- Age of the mother at the time of childbirth will be expressed in years and will be computed as the difference between the birth date of the subject and the birth date of the mother.
- Duration of the study for each subject will be computed as the difference between the date of last contact (i.e., active or passive surveillance contact or the date of the censoring) and the date of enrolment (date when ICF was first signed by the subject's parent[s]/LAR[s]).

## 6.2. Data Presentation

The following decimal description will be used for the analyses.

**Table 11 Decimal points in analyses**

| Display Table | Parameters | Number of decimal digits |
|---|---|---|
| All summaries | % of frequency, including LL & UL of CI | 1 |
| All summaries | % frequency, including LL & UL of CI | 1 |
| All summaries | Mean, median, minimum, maximum | 1 |
| All summaries | SD | 2 |
| All summaries | *P*-value | 3 |

## 6.3. Subgroup definition

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

| Sub-group order in tables | Sub-group label in tables | Sub-group definition for footnote |
|---|---|---|
| *Country* | | |
| 1 | AR | Subjects from Argentina |
| 2 | BD | Subjects from Bangladesh |
| 3 | CA | Subjects from Canada, |
| 4 | FI | Subjects from Finland |
| 5 | HN | Subjects from Honduras |
| 7 | SA | Subjects from South Africa |
| 8 | TH | Subjects from Thailand |
| 9 | US | Subjects from US |
| *Age category* | | |
| 1 | 0-5M | 0 - < 6 months |
| 2 | 6-11M | 6 - < 12 months |
| 3 | 0-11M | 0 - < 12 months |
| 4 | 12-17M | 12 - < 18 months |
| 5 | 18-23M | 18 - < 24 months |
| 6 | 12-23M | 12 - < 24 months |
| 7 | 0-23M | 0 - < 24 months |
| *Monthly age category* | | |
| 1 | 0M | Less than 1 month of age |
| 2 | 1M | 1 - < 2 month of age |
| 3 | 2M | 2 - < 3months of age |
| 4 | 3M | 3 - < 4 months of age |
| 5 | 4M | 4 - < 5 months of age |
| 6 | 5M | 5 - < 6 months of age |
| *Birth period* | | |
| 1 | Born during the transmission season | Born during the transmission season |
| 2 | Born out of the transmission season | Born out of the transmission season |
| *Follow up in transmission season in first 6 month of life* | | |
| 1 | ≤3 months | ≤3 months of life in transmission season |
| 2 | >3 months | >3 months of life in transmission season |
| *Sub-cohort groups* | | |
| 1 | BS 2M | Subjects with blood sample at 2 months |
| 2 | BS 4M | Subjects with blood sample at 4 months |
| 3 | BS 6M | Subjects with blood sample at 6 months |
| 4 | BS 12M | Subjects with blood sample at 12 months |
| 5 | BS 18M | Subjects with blood sample at 18 months |
| 6 | BS 24M | Subjects with blood sample at 24 months |

Tables will, in general, be displayed by study group for descriptive tables and for incidence computation.

Please note that age intervals are overlapping as we are interested to calculate endpoints also during the first and second year of life.

## 6.4. General considerations calculations of incidence

When mentioned below in the upcoming analyses sections, analysis by subgroups will include:

- Country
- Age interval:
  - 0-5M
  - 6-11M
  - 0-11M
  - 12-23M
  - 0-23 M
- Age interval by months for the first 6 months

## 6.5. Analysis of demographics/baseline characteristics

The distribution of subjects enrolled among the study sites will be tabulated at least overall and by country. The distribution of subjects of the PPS sub-cohort will be described for the various time points.

The demographic, medical status, family history, lifestyle characteristics, medical care and medications collected for the enrolled subjects will be summarized at least overall.

The surveillance visit and examination visit information, and the laboratory results will be described:

- Frequency tables will be generated for categorical variable such as country.
- Mean, median, standard deviation will be provided for continuous data such as age.

## 6.6. Incidence analysis

### 6.6.1. Analysis of co-primary objectives: incidence of RSV respiratory disease

For this objective, the analysis will be based on PPS.

For clarity the analysis of RSV disease incidence is summarised in the table below showing endpoints and analytic methods.

For each of the following endpoints you could find the case definitions in Table 4:

- RSV RTI with suspicion of involvement of LRT
- WHO RSV LRTI
- WHO RSV LRTI hospitalisation
- WHO RSV severe LRTI
- WHO RSV severe LRTI hospitalisation
- WHO RSV hospitalisation

**Table 12 Summary of RSV incidence analyses for primary objectives**

| Endpoints | Incidence analysis method | Subgroup |
|---|---|---|
| RSV RTI with suspicion of involvement of LRT<br>WHO RSV LRTI<br>WHO RSV severe LRTI<br>RSV hospitalisation<br>WHO RSV LRTI hospitalisation<br>WHO RSV severe LRTI hospitalisation | Incidence rates of first episode<br>Cumulative probability of first episode (Kaplan Meier) | Overall, by country, by age intervals, by transmission interval |
| RSV RTI with suspicion of involvement of LRT<br>WHO RSV LRTI<br>WHO RSV severe LRTI<br>RSV hospitalisation<br>WHO RSV LRTI hospitalisation<br>WHO RSV severe LRTI hospitalisation | Proportion affected by all new episodes | Overall and by country, by age intervals |
| RSV RTI with suspicion of involvement of LRT<br>WHO RSV LRTI<br>WHO RSV severe LRTI<br>RSV hospitalisation<br>WHO RSV LRTI hospitalisation<br>WHO RSV severe LRTI hospitalisation | Incidence proportion of first episode | Overall and by country, by monthly age |

For each endpoints listed in the previous table the 95% CI will be computed as described in section 11.1.2 depending on the age category considered and the method listed in the analysis column. Kaplan-Meier curves presenting the cumulative probability of first episode will be displayed overall and by country. The cumulative probability of presenting first episode will be given with its 95% CI at the end of the follow-up.

### 6.6.2. Analysis of secondary objective: incidence of all cause respiratory disease

The analysis will be based on PPS and will be done on the first episode of all cause RTIs occurring during the age interval considered.

The incidence will be computed overall and by age category:

- 0-5 months
- 6-11 months
- 0-11 months
- 12-23 months
- 0-23 months

Incidences rates will be calculated using the same approach describe in section 11.1.1 for first episode of RTI with a suspicion of involvement of the lower respiratory tract, WHO LRTI and WHO severe LRTI and LRTI hospitalization.

### 6.6.3. Analysis of tertiary objectives: potential risk factors for RSV disease

For this objective, the analysis will be based on PPS.

The incidence, overall and by country, of first events of RSV-LRTI, RSV severe LRTI, RSV non severe LRTI (WHO definition) will be analysed using a Cox regression.

The following risk factors will be considered in the model:

- **General:**
  - Country of birth
  - Gender (as recorded in demography of extension phase)
  - Time of birth relative to the transmission season (see section 6.1.4.5)
- **Characteristics at birth:**
  - Gestational age at birth (see details section 6.1.4.1)
  - Birth weight (see details section 6.1.4.2)
  - Apgar at 5 mins of age (see details section 6.1.4.3)
  - Caesarian section
- **Family history:**
  - First degree relative with family history of asthma (see details section 6.1.4.4)
- **Living environment and household composition:**
  - Highest education level of the mother (see details section 6.1.4.6)
  - Highest education level of the father (see details section 6.1.4.6)
  - Number of people living in the household at month 3 (see details section 6.1.4.7)

- Number of other children ( <18 years old) living in the household at month 3 (see detail section 6.1.4.8)
- Subject in regular close contact with toddlers at month 3
- The child live in a surrounding where people smoke daily at month 3
- Breast feeding *

** Time dependent covariate; status is yes of subject ever breastfed from DOB until the end of breastfeeding given in the surveillance visit. Last day of month will be imputed for any partial date of breastfeeding end date.*

As described in the section 11.1.5, covariates with univariate p-value less than 0.1 will be included in the multivariable model. The number of covariates included in the model will depend on the number of events (at least 10 events per covariates).

Please note that the multivariable model will be performed only if the number of events is sufficient (at least 10 events per covariates). In addition, depending on the data, other models could be explored or the model could be simplified.

## 6.7. Health care utilization analysis

For this objective, the analysis will be based on PPS.

Descriptive statistics of the different types of healthcare utilization associated with disease severities will be produced by age interval and by country.

Please note that the heath care utilization reported here are only including medical care that subject were seeking outside the site clinics.

The number and percentage of all episodes(including recurrent) leading to outpatient visit, emergency room visit, Inpatient Admission-Non-Intensive Care, Inpatient Admission-ICU and No physician consultation outside site clinic will be displayed according for WHO RSV LRTI and WHO RSV severe LRTI cases.

The distribution (means and SD) of the number of days the usual care giver or another person took care of the child without missing work, the number of days a person had to stay home specifically because of the illness instead of going at work, and the number of days a person was hired to care for the child specifically because of the illness, will be displayed according to WHO RSV LRTI and WHO RSV severe LRTI status.

For clarity the type of health care utilization for RSV disease episodes is summarised in the table below showing endpoints and analytic methods.

**Table 13 Summary of health care utilization for RSV disease episodes for primary objectives**

| Subgroup | Case definition | Endpoints | Event considered |
|---|---|---|---|
| By age categories and by country | • WHO RSV LRTI<br>• WHO RSV severe LRTI | • The number and proportion of episodes classified by<br>  Outpatient visit<br>  Emergency Room visit<br>  Inpatient Admission (non intensive care)<br>  Inpatient Admission (intensive care)<br>  No consultation other than site clinic<br>  Other<br>• By episodes the mean and SD of:<br>  The number of days the usual care giver or another person took care of the child without missing work<br>  The number of days a person had to stay home specifically because of the illness instead of going at work<br>  The number of days a person was hired to care for the child specifically because of the illness | • All events including recurrent events |

## 6.8. Performance of case definitions analysis

### 6.8.1. Analysis of co-primary objectives: Measures of agreement

For this objective, the analysis will be based on subjects among PPS by RSV case status – Case and Non-case. This analysis will be done considering all new events including recurrent events.

Statistical analysis of agreement will be performed to compare the different case definitions of RSV- LRTI/severe LRTI and RSV hospitalization status – hospitalized and non-hospitalized.

Three 2x2 contingency tables will be provided and the following measures of agreement (with 95% CI) will be calculated:

**Table 14 Comparison of two classifications for RSV LRTI**

| RSV-associated cases | | Classification of reference | |
|---|---|---|---|
| | | Case | Non Case |
| Alternative classification (LRTI, severe LRTI) | Case | True positive (TP) | False positive (FP) |
| | Non case | False negative (FN) | True Negative (TN) |

- Sensitivity: TP/ (TP+FN)
- Specificity: TN/ (TN+FP)
- Positive predictive value (PPV): TP/ (TP+FP)
- Negative predictive value (NPV): TN/ (TN+FN)
- Proportion of overall agreement, which is the proportion of cases similarly classified: (TP + TN)/ (TP+FP+FN+TN).
- Cohen's kappa coefficient. The magnitude of the kappa coefficient represents the proportion of agreement greater than that expected by chance.

Such tables will be done for the comparison of each of the 4 LRTI case definitions: WHO, GSK, Nokes, and exploratory (see Table 4) according to the case ascertainment: Case vs Non case, by severity and RSV hospitalization status. Note that GSK, Nokes, and exploratory case definitions (alternative classification) will be compared to WHO case definition (reference classification) but only GSK (reference classification) and Nokes (alternative classification) will be compared to each other.

### 6.8.2. Analysis of tertiary objectives: case definitions and association with total RSV viral load

Please note that the association of RSV viral load with the incidence of RSV-associated RTI, LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale) could not be studied since only positive subjects for RSV will have a viral load > LOD.

For this objective, instead a descriptive analysis, based on PPS, will be done considering the 3 age interval:

- 0-11 Months
- 12-23 Months
- 0-23 Months

Two analyses will be realized, on the first episode and on all episodes including recurrent episodes occurring during the age interval considered.

Descriptive analyses (mean, median, min, max) of the total viral load assessed by the RSV RT-qPCR of first event of RSV RTI, RSV LRTI and severe LRTI cases, with overlapping and non-overlapping disease severity, will be tabulated by age interval for the following endpoints:

- All RSV positive nasal swab samples (see details 6.1.2)
  - RSV asymptomatic
  - RSV RTI
  - WHO RSV LRTI,
  - WHO RSV Severe LRTI
  - RSV asymptomatic (Excluding RSV RTI, WHO RSV LRTI, and WHO RSV severe LRTI)
  - RSV RTI (Excluding WHO RSV LRTI, and WHO RSV severe LRTI)
  - WHO RSV LRTI (excluding WHO severe LRTI)
- Any RSV hospitalisation (see details 11.2.1.8)
  - RSV hospitalization
  - WHO RSV LRTI hospitalization
  - RSV hospitalization (excluding WHO RSV LRTI hospitalization and WHO RSV severe LRTI hospitalization)
  - WHO RSV LRTI hospitalization (excluding WHO RSV severe LRTI hospitalization)
  - WHO RSV severe LRTI hospitalization

The total RSV viral load will be computed by adding the viral load from RSV A tests and the viral load from RSV B tests.

## 6.9. Neutralizing antibodies over time and protection against RSV disease analysis

### 6.9.1. Analysis of secondary objective: Association between RSV disease and cord blood neutralizing antibodies

The analysis will be based on PPS and will be done considering the 2 age intervals:

- 0-2 months
- 0-5 months

The analysis will be realized only on the first episode (and not recurrent events) occurring during the considered age interval using a stepwise approach.

**Step 1: Descriptive analysis:**

Descriptive analyses (seropositivity rate with 95% CIs, geometric mean, median, min, max) of RSV neutralizing antibodies in the baseline cord blood samples will be presented by WHO RSV LRTI and WHO RSV severe LRTI case status; and with overlapping and non-overlapping disease severity.

In addition, descriptive analyses (seropositivity rate with 95% CIs, geometric mean, median, min, max) of RSV neutralizing antibodies in the baseline cord blood samples will be analysed according to the following endpoints:

- All RSV positive nasal swab samples (see details 6.1.2)
  - WHO RSV LRTI
  - WHO RSV LRTI (excluding WHO RSV severe LRTI)
  - WHO RSV severe LRTI
- Descriptive analyses (mean, median, min, max) of the total viral load of RSV according to the quartiles of neutralizing antibodies detected in the cord blood will be described.

**Step 2: Cox models:**

The impact of the level of RSV neutralizing antibodies in the baseline cord blood samples on the incidence of first event of WHO RSV-LRTI and WHO RSV-severe LRTI separately will be assessed through Cox models.

Univariate and multivariable Cox models will be presented. The following covariates may be considered in the multivariable model

- General:
  - Country of birth
  - Gender
  - Time of birth relative to the transmission season
- Characteristics at birth:
  - Gestational age at birth
  - Birth weight
  - Apgar at 5 mins of age
  - Caesarian section
- Family history:
  - First degree relative with family history of asthma

- Living environment and household composition:
  - Highest education level of the mother
  - Highest education level of the father
  - Number of people living in the household at month 3
  - Number of other children ( <18 years old) living in the household at month 3
  - Subject in regular close contact with toddlers at month 3
  - The child live in a surrounding where people smoke daily at month 3
  - Breast feeding *

** Time dependent covariate; status is yes of subject ever breastfed from DOB until the end of breastfeeding given in the surveillance visit. Last day of month will be imputed for any partial date of breastfeeding end date.*

Covariates with univariate p-value less than 0.1 will be included in the multivariable model. The number of covariates included in the model will depend on the number of events (at least 10 events per covariates).

Please note that the multivariable model will be performed only if the number of events is sufficient (at least 10 events per covariates). In addition, depending on the data other models could be explored or the model could be simplified.

**Step 2-a: RSV neutralizing antibodies classified as a binary variable: Seropositive and seronegative:**

In a first step, the RSV neutralizing antibodies in the baseline cord blood samples will be introduced in the model as binary variable. If the effect of RSV neutralizing antibodies as binary variable is significant we process to the next step.

**Step 2-b: RSV neutralizing antibodies classified as semi-quantitative variable: Quartiles**

In a second step, the RSV neutralizing antibodies levels will be introduce in the model using quartiles. And the Cox models will be performed as describe in the previous paragraph (RSV neutralizing antibodies as quantitative variable – Step 2-a). If the effect of neutralizing antibodies as semi quantitative variable is significant, we proceed to next step.

**Step 2-c: RSV neutralizing antibodies classified as continuous variable:**

In a third step, the RSV neutralizing antibodies levels might be treated as continuous variable in Cox models to evaluate how each unit of neutralizing antibody level change impacts on the above clinical outcomes. The Cox models will be performed as describe in the previous section (with log of RSV neutralizing antibodies as quantitative variable). For the subjects with antibody level below the LLOQ, a value of LLOD/2 will be imputed.

The model with best fit using log like-hood criteria will be selected.

Note that depending on the results, a quantitative association between RSV-associated LRTI, RSV-associated severe LRTI and RSV neutralizing antibodies in the baseline cord blood samples could be further explored and described more in details in a separate Additional Analysis Request.

### 6.9.2. Analysis of secondary objective: prevalence of RSV infection at 2, 4, 6, 12, 18 and 24 months

The analysis will be based on PPS sub-cohort for this objective.

Descriptive analyses (seropositivity rate with 95% CIs, geometric mean, median, min, max) of RSV neutralizing antibodies at 2, 4, 6, 12, 18 and 24 months will be presented.

Prevalence of infection will be determined at the time of the analysis based on the measured antibody titer *vs*. the expected antibody level at the time of sampling based on the individual baseline (cord blood) value and the average, modelled decay rate for subjects with blood sampling at time point 2, 4, 6, and 12 month. RSV infection is defined as titers 2-fold higher than expected value. For subjects with blood sampling during second year of life, a sample with positive result will count as prevalence of infection.

All exact 95% CI will be two-sided, based on the Clopper-Pearson based on a mathematical relationship (see Fleiss et al (2003), p. 25) between the F distribution and the cumulative binomial distribution.

### 6.9.3. Analysis of tertiary objective: natural decay of maternal neutralizing antibodies

The analysis will be based on total sub-cohort subject with blood sampling at month 2, 4, 6, and 12 for this objective.

The decay of maternal antibody levels over time will be analysed graphically and by a linear regression of the log of maternal antibody levels. A true, natural decay curve will be explored by stochastically reducing the sample to uninfected subjects only. The following steps will be taken to identify, confirmed and suspected infected subjects to eliminate these from the sample;

STEP 1: Subjects with an RSV positive ***nasal swab*** during the study before time of sampling will be eliminated. Note that such subjects are removed from the analysis because they are infected by RSV; as a consequence their antibody levels are no longer maternal antibody levels.

STEP 2: Run the model and compute expected value based on the decay curve for each subjects

STEP 3: Subjects with an antibody titer at the sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected, eliminated and the decay curve refined.

STEP 4: Step 3 is repeated up to 5 times until the most accurate decay curve is established.

The natural decay of antibody will be determined using linear regression between the log of antibody level (Y) and time t (age in months) with subject as a random effect. Indeed, all subjects have RSV neutralizing antibodies measured at birth (cord blood). And, each subject of the Total sub-cohort will be randomly selected to be sampled for RSV neutralizing antibodies at one of the following time points: 2, 4, 6, and 12 months. For the natural decay model, subjects will have maximum 2 RSV neutralizing antibodies measures, one at birth and one either at 2 months or 4 or 6 or 12 months.

A table will describe the decay rate and half-life statistics of the natural decay model.

A descriptive table will describe the serology status (positive/negative) according to the natural decay analysis.

A sensitivity analysis of the decay curve will be explored in sub-sample consisting of the subjects born 'off-season' as these have the lowest likelihood of having been infected.

Please note that additional exploratory analysis could be perform depending on the data and that the decay analysis could be adapted depending on the number of samples < LLOQ for each time points, especially for the later time points. Specific analysis of the twins could be explored if the number of twins reaches at least 50 subjects. Additional models such as models including a $t^2$ term or some covariates could be explored.

## 6.10. Analysis of other viruses and RSV infection

### 6.10.1. Analysis of tertiary objective: incidence of other respiratory viruses as cause of LRTI and severe LRTI

The number and percentage of cases for each respiratory virus identified for all WHO LRTI and WHO severe LRTI. For each respiratory virus infection, number and percentage will be summarized by single or co-infection status.

The number and percentage of cases associated with each of the other respiratory viruses, with at least one other a respiratory virus, 1, 2, or more than 2 additional viruses, will be described for WHO LRTI and WHO severe LRTI.

The percentage will be computed using the number of cases (associated with each of the other respiratory viruses, with at least one other a respiratory virus, 1, 2, or more than 2 additional viruses) divided by the total number of case for a given endpoint.

This analysis will be performed at less than 3 month, between 3 – 5 month, 6 -11 month, and 12 – 23 months and by country.

Other respiratory viruses include Influenza A (subtypes H1 and H3); Influenza B; Parainfluenza virus type 1, 2, 3, and 4; Human Metapneumovirus; Rhinovirus/Enterovirus; Adenovirus; Bocavirus and Coronavirus - 229E, OC43, NL63, HKU1. The analyses will be performed for each viral type and aggregated viral types, for example, viral type of parainfluenza will combine parainfluenza virus type 1, 2, 3 and 4.

### 6.10.2. Analysis of tertiary objective: co-infections with RSV

For cases of WHO RSV LRTI and WHO RSV severe LRTI the number and percentage of cases associated with at least one other respiratory virus, 1, 2, or more than 2 viruses will be described. The number and percentage of cases associated with each of the other respiratory viruses will be described.

This analysis will be performed at less than 3 month, between 3 – 5 month, 6 -11 month, and 12 – 23 months and by country.

## 6.11. Evaluation of cord blood collection variables, disease surveillance and protocol procedures

### 6.11.1. Analysis of tertiary objective: cord blood collection, storage and processing

The objective is to assess the effect of cord blood collection, and storage and processing on the neutralizing antibody level in the cord blood.

Number and percentage of subjects follow each cord-blood collection, storage, and processing categories will be calculated. Descriptive statistics of geometric mean, standard deviation, median, and range will be calculated for neutralizing antibody level in the cord blood for each of the collection, storage, and processing category.

The duration between collection and completion of processing will be calculated. Scatter plots will be used to assess the association between the duration of processing and cord blood antibody levels.

### 6.11.2. Analysis of tertiary objective: evaluation of surveillance and protocol procedures

The objective of these sets of analysis is to evaluate the practical implementation of the surveillance system across the countries.

The number and percent of surveillance contacts resulted in an exam visit will be summarized by country. The number and percent of exam visit following under each duration period after surveillance contact is summarized by country. The number of exam visit associate with a surveillance contact is summarized by country. The number and percent of visit with collection of nasal swab is summarized by country. And the number and percent of nasal swab under each duration period after onset of coughing or difficult breathing is summarize by country.

# 7. ANALYSIS INTERPRETATION

Analyses will be descriptive with the aim to characterise overall occurrences, patterns and potential differences between groups in the endpoints related to the objectives. No hypothesis testing will be performed.

The tertiary objective 'To explore the impact of changes to the symptoms and threshold levels of symptoms in the LRTI case definition and severity scale' will be assessed if we detect potential areas of improvement of the LRTI case definition and severity scale, such as clearly under or overestimated incidence rates of LRTI/ severe LRTI compared to the rates in the literature or a lack of discriminative power between severe and non-severe cases. This decision will not be taken on specific pre-defined thresholds.

# 8. CONDUCT OF ANALYSES

## 8.1. Sequence of analyses

An interim analysis has been performed after data lock at the end of recruitment (expected after 18 months) or in June 2015 whichever occurs first, on the data collected for the subjects recruited in the first year of the study (approximately 1600).

Final analysis will be performed on all the data collected and cleaned in the study until 2 years of life.

The analyses will be release in a stepwise manner.

A first DBF will include all data except RVP results followed by a first statistical report. The results will be released according to a priority order defined with the team. A second DBF will add the RVP results which will be analysed in a second step and included in the statistical report.

## 8.2. Statistical considerations for interim analyses

A statistical analysis for the interim analysis has been performed on all the data collected and cleaned for the subjects recruited in the first year of the study, at the end of recruitment (expected after 18 months) or in June 2015 whichever occurred first.

The interim analysis has been purely descriptive, no adjustment of the type I error was foreseen.

Due to issue regarding the swab sample analysis, an additional analysis has been done in July 2017 to study the incidence.

# 9. CHANGES FROM PLANNED ANALYSES

- Due to the number of subjects with examination visit but without surveillance visit:
  - RSV LRTI endpoints computed using data from examination visit were added to the endpoint RSV-associated RTI with a suspicion of involvement of the lower respiratory tract definition computed using data from surveillance visit
  - The delay between LRTI identification and swab sample is not considered in the case definition
  - The subgroup analysis by collection time of swabs (72 hours/48 hours from the start date of the case (date of the call), 72 hours/48 hours from the reported onset of symptoms) has been removed
- In protocol it is suggested to analyse by country and then pool by hemisphere and region. Pooling across such diverse settings is not developing strong messages about RSV incidence and therefore we limit our subgroup analysis to by country. Where the protocol described overall incidence we have preferred to only do pooled incidence across countries by year of life. This aids meaningful interpretation and minimises tables.
- In the analysis of the key healthcare utilization and health outcomes: the hospitalization status, intensive care unit attendance, clinical diagnosis of bronchiolitis or pneumonia, death has been replaced by: outpatient visit, emergency Room visit, inpatient Admission (non intensive care), innpatient Admission (intensive care), no consultation other than site clinic and other.
- In the analysis of the performance of case definition, the key health outcome does not include intensive care unit attendance, clinical diagnosis of bronchiolitis or pneumonia and death. Instead, hospitalization status according to WHO, GSK, Nokes, and exploratory case definition will be used for the analysis.
- The incidence rates of RSV-associated LRTI/severe LRTI as classified by the GSK and Nokes case definition are not computed.
- Incidence rate of all cause RTI provided instead of per protocol non-RSV associated RTIs as RSV RTIs are subset of all cause RTI. Hence analysis of all cause RTIs is more relevant and conventional in epidemiological studies.
- Descriptive statistics of the different types of healthcare utilization will not be provided among non-RSV-associated RTI with a suspicion of involvement of the lower respiratory tract, overall and by subgroups.
- The risk factor analysis will be done using a Cox regression model and not a Poisson regression model to be consistent with the analysis performed in clinical trials.
- The sensitivity analysis will not be performed on the total enrolled cohort.
- The analysis of the impact of changes to the symptoms and threshold levels of symptoms in the LRTI case definition and severity scale will not be done by age category

- The date of study conclusion for subjects lost to follow-up will be the date of conclusion given in the CRF and will not be derived according to number of missed visits.
- Only first episode within a given age interval is considered for the computation of incidence. The incidence of event is computed using 3 different calculation methods: incidence rate, proportion affected, and incidence proportion. See section 11.1.1 for detail of calculation
- Sub-group of analysis for birth period outside or within transmission season will not be performed. Instead, the analysis will be based on the first 6 month of subject's life, and will be done considering 2 categories: <= 3 months and > 3 months. The incidence rate of RSV associate LRTI, severe LRTI, and hospitalization will be computed by country.
- Incidence and performance of case definition analysis (measures of agreement) will be performed using exploratory case definitions in anticipation of update to WHO case definitions.
- Analyses of cord blood collection using and not using recommended procedures will not be done. Instead, descriptive statistics for cord blood collection variables and cord blood levels of RSV A and B neutralizing antibodies according to cord blood collection variables will be provided. Additional analyses will be performed to evaluate disease surveillance and protocol procedures and include summary of number and percent of surveillance contacts followed by an exam visit, the duration between surveillance contact and exam visit, and duration between nasal swap and onset of symptoms.

# 10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The list of final report tables, listing and figures are available in the TOC document.

# 11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

## 11.1. Statistical Method References

### 11.1.1. Computation of incidence rates

For each endpoint, the incidence rate (IR, number of episodes/endpoints per 100 person-years) will be calculated by dividing the number of subjects reporting first episode over the follow-up period by the total person-year. A 95% CI will be computed using an exact method for a Poisson variable as described below.

The person-time at risk for an event of interest (e.g. RSV-LRTI) will be calculated as the time between the date of birth and the end of the at-risk period or the earliest of the followings:

- Date of first diagnosis of event of interest (e.g. first episode of RSV-LRTI);
- Date when child reaches 2 years;
- Date of last contact (lost-to follow-up, defined as no contact by the subject's parent(s)/LAR(s) over the period of 3 planned contacts and/or 2 months and after a final attempt has been made by mail. Once this has been reached, the subject is censored at the time of last contact);
- Date of death.

### 11.1.2. Exact confidence intervals (CIs)

The exact confidence interval within a group for an incidence rate (per 100 person-years):

To estimate the confidence limit of the incidence rate, the exact Poisson confidence limit will be used [Clopper, 1990]:

If *n* is the number of subjects presenting a given characteristic among these *Ny* subjects per year, the true incidence rate can be estimated by *(n/Ny)*100*. Its exact *(1- )%* confidence interval is obtained from:

*CINV( /2,2*n)/2/Ny*100* as the lower boundary

and

*CINV((1- /2),2*(n+1))/2/Ny*100* as the upper boundary.

where *CINV(probability, degrees of freedom)* returns the inverse of the chi-squared probability distribution and is the type I error rate.

### 11.1.3. Computation of proportion affected

Proportion affected will be computed as the number of subject who had at least one episode in the age interval divided by the total number of subjects at start of the age interval. A 95% CI will be computed using an exact method for a Poisson variable.

### 11.1.4. Computation of incidence proportion

Incidence proportion will be computed as the number of subjects had first episode in the age interval divided by the number of subject at risk of event at the beginning of the age interval. A subject that has an event will no longer consider of at risk, i.e. subjects with event in 0 – 1 month are excluded from denominator for future monthly incidence calculation. A 95% CI will be computed using an exact method.

### 11.1.5. Cox regression models

Cox regression models will be performed for the univariate analyses in order to obtain unadjusted hazards ratios of the determinants of interest.

In addition, a multivariable Cox regression model will be performed in order to estimate the relative contribution of each potential risk factor adjusting for the simultaneous effects of the other covariates. The model will include: time-independent covariates (e.g., country, gender etc.) and time-dependent covariates, breast feeding. Covariates selection will be done using statistical significance. Potential risk factors will be included in the multivariable models if univariate p-value will be less than 0.1.

The Table 15 details the time dependent status of the potential risk factors:

**Table 15 Time dependent status of the covariates**

| Potential risk factor | Time-dependent |
|---|---|
| Country of birth | No |
| Gender | No |
| Birth period | No |
| Gestational age at birth | No |
| Birth weight | No |
| Apgar at 5 mins of age | No |
| First degree relative with family history of asthma | No |
| Quartiles of cord blood maternal antibodies for RSV A | No |
| Quartiles of cord blood maternal antibodies for RSV B | No |
| Highest education level of the mother | No |
| Highest education level of the father | No |
| Number of people living in the household at month 3 | No |
| Number of other children (<18 years old) living in the household at month 3 | No |
| Subject in regular close contact with toddlers at month 3 | No |
| The child live in a surrounding where people smoke daily at month 3 | No |
| Breast feeding | Yes |

Results from the multivariable Cox model will include hazards ratios (with 95% CI).

The number of covariates included in the model will depend on the number of events (at least 10 events per covariates).

Please note that the multivariable model will be performed only if the number of events is sufficient (at least 10 events per covariates). In addition, depending on the data other models could be explored or the model could be simplified.

## 11.2. Standard data derivation

### 11.2.1. Case definitions

#### 11.2.1.1. Any cause RTI

The subject will be defined as RTI positive when he is presenting one or more of the following items:

- Cough reported in interview during the examination visit or Dica (fields [EXAM_VS.SYMP_CAT]=”Cough” and [EXAM_VS.SYMP_REP]=”Y”)
- Runny nose reported in interview during the examination visit or Dica (fields [EXAM_VS.SYMP_CAT]=” Runny nose” and [EXAM_VS.SYMP_REP]=”Y”)
- Blocked nose reported in interview during the examination visit or Dica (fields [EXAM_VS.SYMP_CAT]=” Blocked nose” and [EXAM_VS.SYMP_REP]=”Y”)

##### *11.2.1.1.1. Start of date of RTI case*

The start date of the case is defined as the first day of symptoms (i.e. cough, or Runny nose or Blocked nose) based on definitions described in section 11.2.1.1. In case of missing data, for one or 2 of the symptoms, the missing data will be imputed using the earliest date between the non-missing start date for RTI symptoms for this event.

##### *11.2.1.1.2. End date of RTI case*

End date of the case is defined as the point at which the subject is considered symptom-free of symptoms.

In case of missing data, for one or 2 of the symptoms, the missing data will be imputed using the latest date between the non-missing end date for RTI symptoms for this event.

#### 11.2.1.2. RSV RTI

RSV RTI status will be defined positive when the subject is RTI positive (see section 11.2.1.1) **AND** RSV positive (see section 6.1.2).

#### 11.2.1.3. All cause RTI with suspicion of involvement of lower respiratory tract

The status RTI with suspicion of involvement of LRTI will be assessed using data from surveillance visit and data from examination visit.

The subject will be considered positive for RTI with suspicion of involvement of LRTI:

- positive for RTI at surveillance visit AND positive for a suspicion of involvement of LRTI at surveillance visit
- AND/OR when the subject has attended an examination visit (whatever LRTI final assessment)

The subject will be defined as positive for RTI at surveillance visit when he is presenting one or more of the following items:

- Did or does the child cough? (fields [SRV_RTI.CATEGORY] ="Cough" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** did or doe s the child have runny nose? (fields [SRV_RTI.CATEGORY] ="Runny nose" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** did or doe s the child have a blocked nose? (fields [SRV_RTI.CATEGORY] ="Blocked nose" and [SRV_RTI.QUEST_YN]=Y")

The subject will be considered positive for a suspicion of involvement of LRTI when he subject has attended an examination visit (whatever LRTI final assessment) or when he has one or several of the following items is reported in interview during the surveillance visit:

- Did or does the child make noises like wheezing or grunting when breathing? (fields [SRV_RTI.CATEGORY] ="Wheezing or grunting" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** did or does the child breathe faster than normal? (fields [SRV_RTI.CATEGORY] ="Breathe faster" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** did or does the child flare his/ her nostrils when breathing? (fields [SRV_RTI.CATEGORY] ="Flare Nostrils" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** did or does the child use his/ her muscles in chest and neck when breathing? (fields [SRV_RTI.CATEGORY] ="Use muscles" and [SRV_RTI.QUEST_YN]=Y")
- **And/or** was or is the child short of breath? (fields [SRV_RTI.CATEGORY] ="Short of breath" and [SRV_RTI.QUEST_YN]=Y")

#### 11.2.1.4. LRTI

##### *11.2.1.4.1. Any LRTI (WHO definition)*

The subject will be defined as LRTI positive according to WHO definition when he is presenting:

- history of cough or difficulty breathing,
- and a measured oxygen saturation < 95% or an increase of respiratory rate.

For derivation purposes we are characterizing 2 groups of items:

- Component A which gathers items used to derive history of cough and difficulty breathing,
- Component B which gathers the oxygen saturation and respiratory rate.

**Component A:**

The subject will be considered positive for Component A when one or several of the following items are reported in interview during the examination visit:

- Cough reported in interview during the examination visit or Dica (fields [EXAM_VS.SYMP_CAT]="Cough" and [EXAM_VS.SYMP_REP]="Y")
- **And/or** difficulty breathing as defined in section 11.2.2.1

  *Please note that the 2 symptoms: blocked nose and runny nose are not considered here for the derivation, indeed even if in the table 1 note 1 the case definition mentioned "Based on history reported by parents/LARs and includes difficulty breathing associated with nasal obstruction". (in fact it relates to how the data is intended to be collected in future trials where the mother is asked does the child have difficulty breathing yes or no. It is meant to qualify that if the child's breathing difficulty is due to only blocked nose if the mother says its difficulty breathing it is. However, in this study we don't have the question difficulty breathing and so we cannot know whether the blocked nose was or not associated with difficulty breathing in the mothers view)*

**Component B:**

The subject will be considered positive for Component B when one or both of the following statement is reached:

- Blood Oxygen Saturation <95% (field [CLN_SGN2.BLSAT_V])
- **And/or** Increased Respiratory rate as defined in section 11.2.2.2

  *Please note that Blood Oxygen Saturation and respiratory rate are measured during the examination visit.*

The subject will be defined as LRTI positive according to WHO definition when he is positive for Component A **AND** positive for Component B.

#### *11.2.1.4.2. Severe LRTI (WHO definition)*

Severe LRTI status will be defined positive when the subject is LRTI positive (see section 11.2.1.4.1) **AND** present one or both of the 2 following items:

- Blood Oxygen Saturation <93% (field [CLN_SGN2.BLSAT_V])

- **AND/OR** Any chest indrawing present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Chest indrawing" and [CLN_SIGN.SIGN_YN]="Y")

*Please note that the chest indrawing symptom used to define severity is the one measured by the medical team during the examination visit.*

#### *11.2.1.4.3. Any LRTI (GSK case definition)*

The subject will be defined as LRTI positive according to GSK case definition when he is presenting:

- RTI as defined in section 11.2.1.1

  **AND** at least one or both of the following:

  - Blood Oxygen Saturation <95% (field [CLN_SGN2.BLSAT_V])
  - **And/or** Increased Respiratory rate as defined in section 11.2.2.2

#### *11.2.1.4.4. Severe LRTI (GSK case definition)*

Severe LRTI status according to GSK case definition will be defined positive when the subject is LRTI positive according to GSK case definition (see section 11.2.1.4.3) **AND** present at one of the following items:

- Blood Oxygen Saturation <92% (field [CLN_SGN2.BLSAT_V])
- **AND/OR** Irritability/agitation present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Irritability" and [CLN_SIGN.SIGN_YN]="Y")
- **AND/OR** Lethargy/sleepiness present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Lethargy" and [CLN_SIGN.SIGN_YN]="Y")
- **AND/OR** Any chest indrawing present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Chest indrawing" and [CLN_SIGN.SIGN_YN]="Y")
- **AND/OR** Reduced/no vocalisation present at examination visit (fields [CLN_SIGN.SIGN_CAT]="No vocalisation" and [CLN_SIGN.SIGN_YN]="Y")
- **AND/OR** Apnoea > 20 sec present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Apnoea" and [CLN_SIGN.SIGN_YN]="Y" and [CLN_SIGN.APNOEA20]="Y")
- **AND/OR** Cyanosis present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Cyanosis" and [CLN_SIGN.SIGN_YN]="Y")
- **AND/OR** Stop feeding well present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Stop feeding" and [CLN_SIGN.SIGN_YN]="Y").

*Please note that the symptom used to define severity is the one measured by the medical team during the examination visit.*

#### *11.2.1.4.5. Any LRTI (Nokes definition)*

The subject will be defined as LRTI positive according to Nokes definition when he is presenting:

- history of cough or difficulty breathing,
- and at least one of the following:
  - Fast breathing, or
  - Indrawing, or
  - Low oxygen saturation (< 90%) by pulse oxymetry when accompanied by a clinical diagnosis of LRTI or bronchiolitis.

For derivation purposes we are characterizing 2 groups of items:

- Component A which gathers items used to derive history of cough and difficulty breathing,
- Component B which gathers Fast breathing, Indrawing, Low oxygen saturation (< 90%) by pulse oxymetry when accompanied by a clinical diagnostic of LRTI or bronchiolitis.

**Component A:**

The subject will be considered positive for Component A when one or several of the following items is reported in interview during the examination visit:

- Cough reported in interview during the examination visit or Dica (fields [EXAM_VS.SYMP_CAT]=”Cough” and [EXAM_VS.SYMP_REP]=”Y”)
- **And/or** difficulty breathing as defined in section 11.2.2.1

**Component B:**

The subject will be considered positive for Component B when at least one of the following statements is reached:

- Increased Respiratory rate as defined in section 11.2.2.2
- **AND/OR** Any chest indrawing present at examination visit (fields [CLN_SIGN.SIGN_CAT]=”Chest indrawing” and [CLN_SIGN.SIGN_YN]=”Y”).
- **AND/OR** Low oxygen saturation (< 90%) by pulse oxymetry (field [CLN_SGN2.BLSAT_V]) associated with clinical diagnostic of respiratory infection. (fields [CLN_DIAG.DIAG_YN]=”Y”)

#### *11.2.1.4.6. Severe LRTI (Nokes definition)*

The subject will be considered positive Severe LRTI according to Nokes definition when the subject is LRTI positive according to Nokes case definition (see section 11.2.1.4.5) and when at least 2 of the following statements are reached:

- Any chest indrawing present at examination visit (fields [CLN_SIGN.SIGN_CAT]="Chest indrawing" and [CLN_SIGN.SIGN_YN]="Y").
- **AND/OR** Low oxygen saturation (< 90%) by pulse oxymetry (field [CLN_SGN2.BLSAT_V]) associated with clinical diagnostic of respiratory infection. (fields [CLN_DIAG.DIAG_YN]="Y")

#### *11.2.1.4.7. Start date of LRTI case*

The start date of the case is defined as the first day of symptoms (e.g. cough, or difficulty breathing) based on definitions.

In case of missing data, for one or more of the symptoms, the missing data will be imputed using the earliest date between the non-missing start date of LRTI symptoms for this event.

#### *11.2.1.4.8. End date of LRTI case*

End date of the case is defined as the point at which the subject is considered symptom-free of symptoms (e.g. cough, or difficulty breathing).

In case of missing data, for one or more of the symptoms, the missing data will be imputed using the latest date between the non-missing end date of LRTI symptoms for this event.

### 11.2.1.5. RSV RTI with suspicion of involvement of lower respiratory tract

The RSV status will be assessed at the examination visit, and the status RTI with suspicion of involvement of LRTI will be assessed using data from surveillance visit and data from examination visit.

The subject will be considered positive for RSV RTI with suspicion of involvement of LRTI:

- When he is positive for RSV (see section 6.1.2)
- AND positive for RTI with suspicion of involvement of LRTI (see section 11.2.1.3)

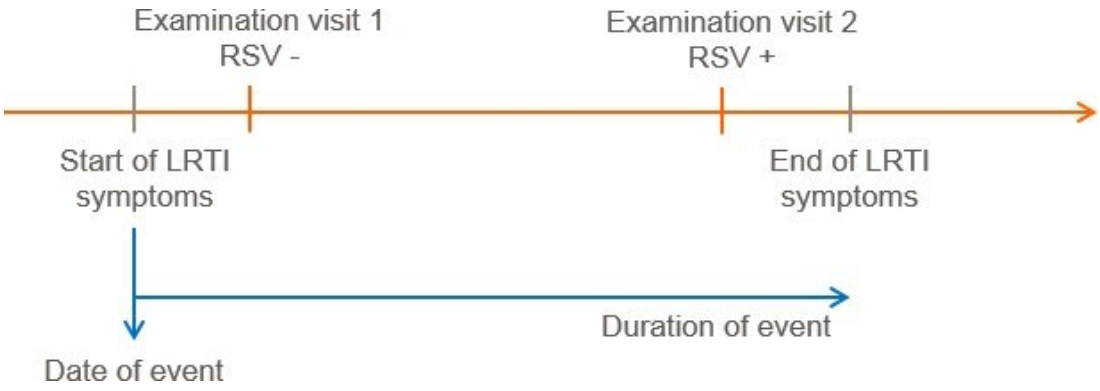
#### 11.2.1.6. RSV-LRTI

RSV-LRTI status will be defined positive when the subject is RSV positive (see section 6.1.2) **AND** LRTI positive according to each of the LRTI case definitions (WHO see section 11.2.1.4.1, GSK see section 11.2.1.4.3, Nokes see section 11.2.1.4.5). In addition an exploratory RSV LRTI was defined see Table 4 Summary of case definitions. 4 RSV-LRTI statuses will be defined:

- RSV-LRTI according to WHO definition
- RSV-LRTI according to GSK definition
- RSV-LRTI according to Nokes definition
- RSV-LRTI according to Exploratory definition

The Figure 2 shows how is derived the start date of event and its duration according to the start date and duration of the corresponding LRTI event.

**Figure 2 Derivation of RSV-LRTI events date and duration according to the the corresponding LRTI event**




#### 11.2.1.7. RSV severe LRTI

RSV Severe LRTI status will be defined positive when the subject is RSV positive (see section 6.1.2) **AND** Severe LRTI positive according to each of the Severe LRTI case definitions (WHO see section 11.2.1.4.2, GSK see section 11.2.1.4.4, Nokes see section 1). In addition an exploratory case definition for RSV severe LRTI was defined in Table 4. 4 RSV Severe LRTI statuses will be defined:

- RSV Severe LRTI according to WHO definition
- RSV Severe LRTI according to GSK definition
- RSV Severe LRTI according to Nokes definition
- RSV Severe LRTI according to Exploratory defintion

#### 11.2.1.8. RSV hospitalization

RSV hospitalization status will be defined positive when the subject is RSV positive (see section 6.1.2) **AND** if he has been hospitalized after examination visit.

The subject will be considered to be hospitalized if the medical attendance is defined as one of the following:

- Inpatient clinic (Hospitalisation) - Intensive care (field [MED_ATD.MEDATD_TXT]="Inpatient clinic (Hospitalisation) - Intensivecare")
- Inpatient clinic (Hospitalisation) - Medium care (field [MED_ATD.MEDATD_TXT]="Inpatient clinic (Hospitalisation) - Medium care")
- Inpatient clinic (Hospitalisation) - Regular care (field [MED_ATD.MEDATD_TXT]="Inpatient clinic (Hospitalisation) - Regular care")
- Inpatient clinic (Hospitalisation) - Ventilation (field [MED_ATD.MEDATD_TXT]="Inpatient clinic (Hospitalisation) -Ventilation")
- Inpatient clinic (Hospitalisation) - nebulization (field [MED_ATD.MEDATD_TXT]="Inpatient clinic (Hospitalisation) -nebulization")

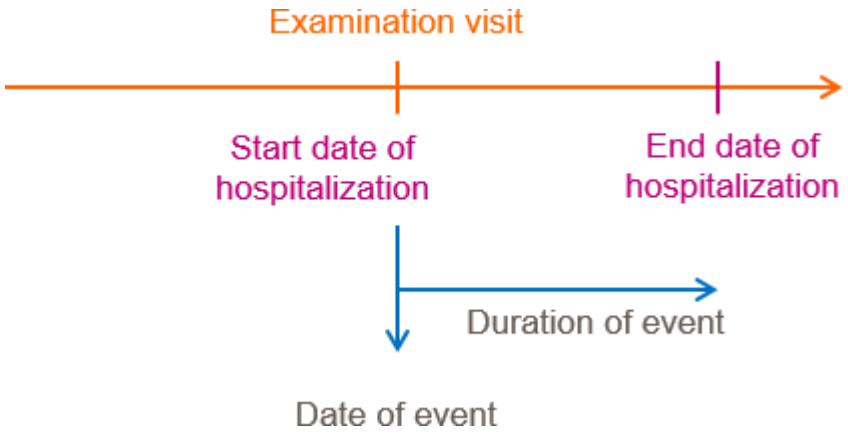
*Please note that if the subject has been admitted to*

- *Emergency Room* (field [MED_ATD.MEDATD_TXT]="*Emergency Room*")
- *General Practitioner* (field [MED_ATD.MEDATD_TXT]="*General Practitioner*")
- *Outpatient Clinic* (field [MED_ATD.MEDATD_TXT]="*Outpatient Clinic*")

*He will not be considered as hospitalized.*

The Figure 3 shows how is derived the start date of RSV-Hospitalization event and its duration.

**Figure 3 Derivation of RSV-Hospitalization events date and duration**

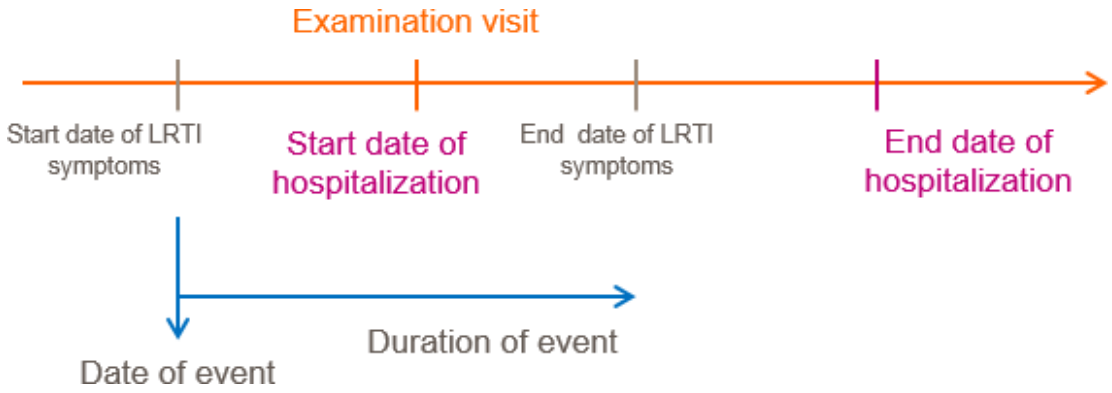


#### 11.2.1.9. RSV LRTI hospitalization

RSV LRTI hospitalization status will be defined positive when the subject is RSV hospitalization positive (see section 11.2.1.8) **AND** if he is positive for WHO LRTI (see section 11.2.1.4.1).

The Figure 4 shows how is derived the start date of RSV-LRTI Hospitalization event and its duration according to the corresponding LRTI event.

**Figure 4 Derivation of RSV-LRTI hospitalization events date and duration according to the corresponding LRTI event**

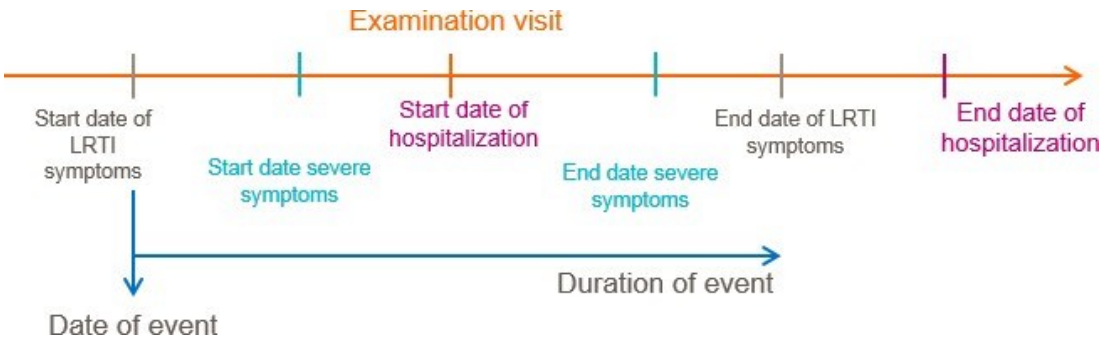



#### 11.2.1.10. RSV severe LRTI hospitalization

RSV LRTI hospitalization status will be defined positive when the subject is RSV hospitalization positive (see section 11.2.1.8) **AND** if he is positive for WHO Severe LRTI (see section 11.2.1.4.2).

The Figure 5 shows how is derived the start date of RSV-severe LRTI Hospitalization event and its duration according to the corresponding LRTI event.

**Figure 5 Derivation of RSV LRTI hospitalization events date and duration according to the corresponding LRTI event**



### 11.2.1.11. Visit for worsening of symptoms assessment

All symptoms collected from initial visits and during follow up of worsening of symptom visits are combined and counted as one episode with the most severe grade. The earliest date of reported symptom will be used as the start date of the episode. The latest date of reported symptom will be used as the end date of episode.

A worsening visit that is greater than 21 days after the initial visit will be count as a separate episode instead of worsening visit.

### 11.2.1.12. New episode rule

A new episode of an event is a single case of RTI, LRTI, severe LRTI, or hospitalization meeting the respective case definitions and severity scale with an interval of at least 7 symptom free days since the last episode that was diagnosed.

As mentioned in the section 11.2.1.11, any worsening visit that is greater or equal to 21 days after the initial visit will count as a new episode.

For example, Figure 6 and Figure 7 show how LRTI events are derived depending on the duration of symptoms free period.

**Figure 6 Derivation of 2 LRTI events date and duration with a symptom free period of at least 7 days**

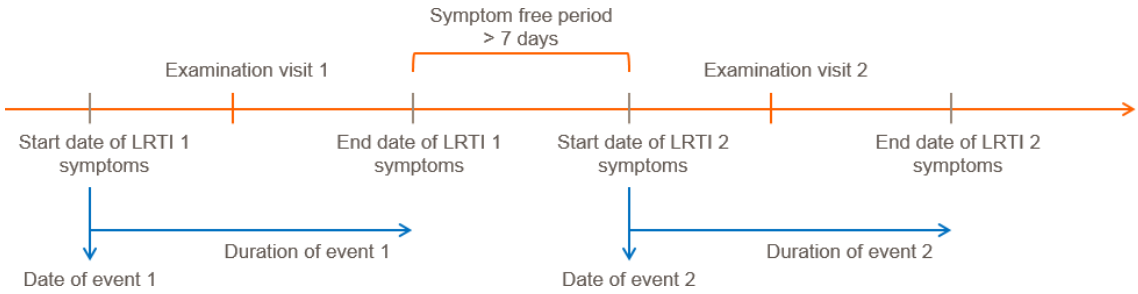
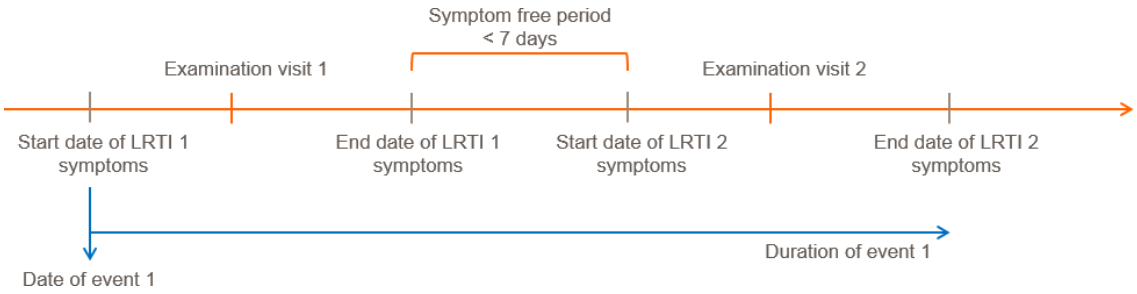



**Figure 7 Derivation of 2 LRTI events date and duration with a symptom free period below 7 days**



Please note that in this SAP, recurrent events are not persistent events, they are independent (new) events.

## 11.2.2. Symptoms

### 11.2.2.1. Difficulty breathing

The subject will be considered positive for difficulty breathing when one or several of the following items is reported in interview during the examination visit:

- Wheezing reported in interview during the examination visit or Dica (fields [CLN_SIGN.SIGN_CAT]=”Wheezing” and [CLN_SIGN.SYMP_REP]=”Y”)
- **And/or** Stridor reported in interview during the examination visit or Dica (fields [CLN_SIGN.SIGN_CAT]=”Stridor” and [CLN_SIGN.SYMP_REP]=”Y”)
- **And/or** Tachypnea reported in interview during the examination visit or Dica (fields [CLN_SIGN.SIGN_CAT]=”Tachypnea” and [CLN_SIGN.SYMP_REP]=”Y”)
- **And/or** Flaring the nostrils when breathing reported in interview during the examination visit or Dica (fields [CLN_SIGN.SIGN_CAT]=”Flaring Nostrils” and [CLN_SIGN.SYMP_REP]=”Y”)
- **And/or** any chest indrawing reported in interview during the examination visit or Dica (fields [CLN_SIGN.SIGN_CAT]=”Chest indrawing” and [CLN_SIGN.SYMP_REP]=”Y”)

*Please note that the symptoms taken into account are the ones reported by the parents and that such symptoms could be present or not at the time of examination visit.*

### 11.2.2.2. Increased respiratory rate

The subject will be considered to have increased respiratory rate if one of the following statement is reached:

- Respiratory rate (field [CLN_SGN2.RESPR_V])
- > 60/minute for subjects <2 months of age (fields [DEMOG.DOB_RAW] and [EXAM_VS2.ACTU_DT])
- > 50/minute for subjects 2-11 months of age(fields [DEMOG.DOB_RAW] and [EXAM_VS2.ACTU_DT])
- > 40/minute for subjects 12-24 months of age(fields [DEMOG.DOB_RAW] and [EXAM_VS2.ACTU_DT])

*Please note that respiratory rate is measured during the examination visit.*

## 11.2.3. Cord blood collection procedure

### 11.2.3.1. Duration between birth and cord blood collection

The duration between birth and cord blood collection expressed in hours will be computed using the birth date and time (fields [BIRTH_ST].[DOB_RAW] and [BIRTH_ST].[DOB_HH] and [BIRTH_ST].[DOB_MM]) and cord blood collection date and time (fields [LABSHEET].[SAMPRDAT] and [LABSHEET].[SAMP_HH] and [LABSHEET].[SAMP_MM]).

### 11.2.3.2. Duration between cord blood collection and centrifugation

The duration between cord blood collection and centrifugation expressed in hours will be computed using cord blood collection date and time (fields [LABSHEET].[SAMPRDAT] and [LABSHEET].[SAMP_HH] and [LABSHEET].[SAMP_MM]) and centrifugation date and time (fields [CORD_BL].[ CENTR_DT] and [CORD_BL].[ CENTR _HH] and [CORD_BL].[CENTR _MM]).

### 11.2.3.3. Duration between centrifugation and transfer of serum

The duration between cord blood collection and centrifugation expressed in hours will be computed using centrifugation date and time (fields [CORD_BL].[ CENTR_DT] and [CORD_BL].[ CENTR _HH] and [CORD_BL].[CENTR _MM]) and transfer of serum date and time (fields [CORD_BL].[SEPAR_DT] and [CORD_BL].[ SEPAR_HH] and [CORD_BL].[ SEPAR_MM]).

### 11.2.3.4. Duration between transfer of serum and storage

The duration between cord blood collection and centrifugation expressed in hours will be computed using birth date and time (fields [BIRTH_ST].[DOB_RAW] and [BIRTH_ST].[DOB_HH] and [BIRTH_ST].[DOB_MM]) and storage date and time (fields [CORD_BL].[TBFR_DT] and [CORD_BL].[ TBFR_HH] and [CORD_BL].[ TBFR_MM]).

### 11.2.3.5. Duration of overall process

The duration between cord blood collection and centrifugation expressed in hours will be computed using and storage date and time (fields [CORD_BL].[TBFR_DT] and [CORD_BL].[ TBFR_HH] and [CORD_BL].[ TBFR_MM]).

### 11.2.4. Medical attendance – Health care utilization

The following endpoint categories of healthcare utilization have been defined at each examination visit in MEDICALATTENDANCE screen:

- Outpatient visit: if [MED_ATD]. [MEDATD] = “General Practitioner” OR “Outpatient clinic”
- Emergency Room visit: IF [MED_ATD]. [MEDATD] =”Emergency Room”
- Inpatient Admission (non intensive care): IF [MED_ATD]. [MEDATD] = “Inpatient clinic (Hospitalisation) - Medium care” OR “Inpatient clinic (Hospitalisation) - Regular care” OR “Inpatient clinic (Hospitalisation) - nebulization”
- Inpatient Admission with intensive care: IF [MED_ATD]. [MEDATD] = “Inpatient clinic (Hospitalisation) - Intensive care” OR “Inpatient clinic (Hospitalisation) - Ventilation ”
- No consultation other than site clinic: IF [MED_ATD]. [MEDATD] = . (missing)
- Other

In case several medical attendances are reported for the same event, the worst event will be considered for the analyses.

# 12. ANNEX 3: STUDY SPECIFIC MOCK TFL

## 12.1. Descriptive analysis

### 12.1.1. Disposition of subjects

**Template 1 Number of subjects enrolled into the study and the number of subjects excluded from PPS analyses with reasons for exclusion – [overall] and [by country]**

| | Overall | | | AR | | | BD | | | CA | | | FI | | | HN | | | SA | | | TH | | | US | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Title** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** | **n** | **s** | **%** |
| Total screened subjects: subjects who signed the ICF | | | - | | | | | | | | | | | | | | | | | | | | | | | | |
| Screen failures | | | - | | | | | | | | | | | | | | | | | | | | | | | | |
| Subjects excluded from all stat analysis (code 900) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total cohort | | | 100 | | | | | | | | | | | | | | | | | | | | | | | | |
| Protocol violation (inclusion / exclusion) (code 2010) | | | - | | | | | | | | | | | | | | | | | | | | | | | | |
| PPS cohort | | | xx.x | | | | | | | | | | | | | | | | | | | | | | | | |
| Subjects not randomized to blood sampling visit (code 2500) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serological results were not available for subjects at visit 3 who had a BS as randomized from SBIR (code 2502) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total sub-cohort | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood sample taken but: non-compliance with blood sampling schedules (code 2501) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PPS sub-cohort | | | | | | | | | | | | | | | | | | | | | | | | | | | |

n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
%= percentage of subjects in the PPS relative to the Total cohort.
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## 12.1.2. Screening/study conclusion

### Template 2 Screening conclusion – overall and by country (Screened cohort)

| | **Total N =** | | **AR N =** | | **BD N =** | | **CA N =** | | **FI N =** | | **HN N =** | | **SA N =** | | **TH N =** | | **US N =** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Screening failure** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| **Reason of screening failure** | | | | | | | | | | | | | | | | | | |
| Eligibility criteria not fulfilled | | | | | | | | | | | | | | | | | | |
| Protocol violation | | | | | | | | | | | | | | | | | | |
| Consent withdrawal, not due to a Serious Adverse Event | | | | | | | | | | | | | | | | | | |
| Migrated / moved from the study area | | | | | | | | | | | | | | | | | | |
| Lost to follow-up | | | | | | | | | | | | | | | | | | |
| Non-serious AE | | | | | | | | | | | | | | | | | | |
| Serious Adverse Event related to study participation | | | | | | | | | | | | | | | | | | |
| Other | | | | | | | | | | | | | | | | | | |
| NA | | | | | | | | | | | | | | | | | | |

N = total number of subjects
n/% = number / percentage of subjects in a given category
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## Template 3 Number of subjects completing the primary study and number withdrawn with reasons for withdrawal – overall and by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Number of subjects completing the primary study** | | | | | | | | | | | | | | | | | | |
| Number of subjects withdrawn | | | | | | | | | | | | | | | | | | |
| **Reasons for withdrawal** | | | | | | | | | | | | | | | | | | |
| Consent withdraw al, not due to a Serious Adverse Event | | | | | | | | | | | | | | | | | | |
| Migrated/moved from the study area | | | | | | | | | | | | | | | | | | |
| Lost to follow-up | | | | | | | | | | | | | | | | | | |
| Non-Serious AE | | | | | | | | | | | | | | | | | | |
| Serious Adverse Event related to study participation | | | | | | | | | | | | | | | | | | |
| Other | | | | | | | | | | | | | | | | | | |

N = total number of subjects
n/% = number / percentage of subjects in a given category
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

# 12.2. Demographics/Birth status

## 12.2.1. Demographics at birth

### Template 4 Summary of demographic and baseline characteristics of subjects – overall and by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % |
| **Age of mother at delivery [years]** | | | | | | | | | | | | | | | | | | |
| 18-27 | | | | | | | | | | | | | | | | | | |
| 28-37 | | | | | | | | | | | | | | | | | | |
| >=38 | | | | | | | | | | | | | | | | | | |
| **Singleton or multiple pregnancy** | | | | | | | | | | | | | | | | | | |
| Singleton | | | | | | | | | | | | | | | | | | |
| Multiple | | | | | | | | | | | | | | | | | | |
| **Caesarian section** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| **Presence of meconium in the amniotic fluid** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | | |
| **Gestational age at birth (Weeks)** | | | | | | | | | | | | | | | | | | |
| ≤ 28 | | | | | | | | | | | | | | | | | | |
| 29-32 | | | | | | | | | | | | | | | | | | |
| 33-36 | | | | | | | | | | | | | | | | | | |
| ≥ 37 | | | | | | | | | | | | | | | | | | |
| **Gender of new born** | | | | | | | | | | | | | | | | | | |
| Male | | | | | | | | | | | | | | | | | | |
| Female | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Born in transmission season** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| **Predominant geographic ancestry** | | | | | | | | | | | | | | | | | | |
| African Heritage | | | | | | | | | | | | | | | | | | |

| | **Total N =** | | **AR N =** | | **BD N =** | | **CA N =** | | **FI N =** | | **HN N =** | | **SA N =** | | **TH N =** | | **US N =** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| / African American | | | | | | | | | | | | | | | | | | |
| American Indian or Alaskan Native | | | | | | | | | | | | | | | | | | |
| Asian – Central/South Asian Heritage | | | | | | | | | | | | | | | | | | |
| Asian – East Asian Heritage | | | | | | | | | | | | | | | | | | |
| Asian – Japanese Heritage | | | | | | | | | | | | | | | | | | |
| Asian – South East Asian Heritage | | | | | | | | | | | | | | | | | | |
| Native Hawaiian or Other Pacific Islander | | | | | | | | | | | | | | | | | | |
| White – Arabic /North African Heritage | | | | | | | | | | | | | | | | | | |
| White – Caucasian / European Heritage | | | | | | | | | | | | | | | | | | |
| Latino / Mestizo | | | | | | | | | | | | | | | | | | |
| Other | | | | | | | | | | | | | | | | | | |
| **Length [cm]** | | | | | | | | | | | | | | | | | | |
| Mean | | | | | | | | | | | | | | | | | | |
| SD | | | | | | | | | | | | | | | | | | |
| Median | | | | | | | | | | | | | | | | | | |
| Minimum | | | | | | | | | | | | | | | | | | |
| Maximum | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Weight [kg]** | | | | | | | | | | | | | | | | | | |
| <1 | | | | | | | | | | | | | | | | | | |
| 1-1.499 | | | | | | | | | | | | | | | | | | |
| 1.5-1.999 | | | | | | | | | | | | | | | | | | |
| 2-2.499 | | | | | | | | | | | | | | | | | | |
| ≥2.5 | | | | | | | | | | | | | | | | | | |
| **5 minutes Apgar score** | | | | | | | | | | | | | | | | | | |
| 0-3 | | | | | | | | | | | | | | | | | | |
| 4-6 | | | | | | | | | | | | | | | | | | |
| >=7 | | | | | | | | | | | | | | | | | | |
| **Breast feeding** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % |
| **Breastfeeding duration*** | | | | | | | | | | | | | | | | | | |
| Mean | | | | | | | | | | | | | | | | | | |
| SD | | | | | | | | | | | | | | | | | | |
| Median | | | | | | | | | | | | | | | | | | |
| Minimum | | | | | | | | | | | | | | | | | | |
| Maximum | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Highest education level of the mother: Higher / university education** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Highest education level of the father: Higher / university education** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Number of people living in the household at Month 3** | | | | | | | | | | | | | | | | | | |
| 1-3 | | | | | | | | | | | | | | | | | | |
| 4-6 | | | | | | | | | | | | | | | | | | |
| >=7 | | | | | | | | | | | | | | | | | | |
| Mean | | | | | | | | | | | | | | | | | | |
| SD | | | | | | | | | | | | | | | | | | |
| Median | | | | | | | | | | | | | | | | | | |
| Minimum | | | | | | | | | | | | | | | | | | |
| Maximum | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Number of other children ( <18 years old) living in the household at Month 3** | | | | | | | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | | | | | | | |
| 1-2 | | | | | | | | | | | | | | | | | | |
| >=3 | | | | | | | | | | | | | | | | | | |
| Mean | | | | | | | | | | | | | | | | | | |
| SD | | | | | | | | | | | | | | | | | | |
| Median | | | | | | | | | | | | | | | | | | |
| Minimum | | | | | | | | | | | | | | | | | | |

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % | Value or n | % |
| Maximum | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **Subject in regular close contact with toddlers at Month 3** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |
| **The child live in a surrounding where people smoke daily at Month 3** | | | | | | | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | | | | | | | |
| No | | | | | | | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | | | | | | | |

N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US
Transmission season:
October to March for Argentina, South Africa ;
April 2014 to September 2014 for Canada, Finland, United states;
All year long for Bangladesh, Honduras, Thailand
Note:
Gender information reported herein was collected during the ongoing extension study, causing some missing data
Breastfeeding duration was provided for subjects who breastfed

## Template 5 Summary of demographic characteristics of subjects with blood sample – overall and by time point (PPS sub cohort)

| | Month 2 N = | | Month 4 N = | | Month 6 N = | | Month 12 N = | | Month 18 N = | | Month 24 N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Country** | | | | | | | | | | | | |
| Argentina | | | | | | | | | | | | |
| Bangladesh | | | | | | | | | | | | |
| Canada | | | | | | | | | | | | |
| Finland | | | | | | | | | | | | |
| Honduras | | | | | | | | | | | | |
| South Africa | | | | | | | | | | | | |
| Thailand | | | | | | | | | | | | |
| US | | | | | | | | | | | | |
| **Gender of new born** | | | | | | | | | | | | |
| Male | | | | | | | | | | | | |
| Female | | | | | | | | | | | | |
| Missing | | | | | | | | | | | | |
| **Gestational age at birth (weeks)** | | | | | | | | | | | | |
| ≤ 28 | | | | | | | | | | | | |
| 29-32 | | | | | | | | | | | | |
| 33-36 | | | | | | | | | | | | |
| ≥ 37 | | | | | | | | | | | | |

N = total number of subjects at each timepoint
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
Note:
Gender information reported herein was collected during the ongoing extension study, causing some missing data

## Template 6 Number of subjects by center (Total enrolled cohort)

| Center | Total N = | |
|---|---|---|
| | n | % |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

N = number of subjects of total enrolled cohort
n = number of subjects enrolled for a given center
Center = GSK biologicals assigned center number
% = n/N

# 12.3. Incidence

## 12.3.1. Primary incidence analysis

### 12.3.1.1. (PO1) To determine the total health burden* of RSV-associated RTI with a suspicion of involvement of the lower respiratory tract

**Template 7 Incidence rate of first episode of [RSV RTI with suspicion of involvement of LRT, WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, WHO RSV LRTI hospitalization, WHO RSV severe LRTI hospitalization], by age interval – overall and by country (PPS)**

| | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects** | **Total number of first episode** | **Total number of person-years** | **Incidence rate (100 person-years)** | **LL** | **UL** |
| Overall | 0-5 | | | | | | |
| | 6-11 | | | | | | |
| | 0-11 | | | | | | |
| | 12-23 | | | | | | |
| | 0-23 | | | | | | |
| <each country > | … | | | | | | |

Incidence rate computed using the number of first episode as numerator and the total number of person-years over the entire follow-up as denominator

CI=confidence interval, LL, UL for incidence = Exact 95% Lower and Upper confidence limits

**Template 8 Incidence rate of first episode of WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, by age interval – by country (PPS)**

| | | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|---|
| **Country** | **Age interval** | **Episodes** | **Total number of subjects** | **Total number of first episode** | **Total number of person-years** | **Incidence rate (100 person-years)** | **LL** | **UL** |
| <each country > | 0-11 months | WHO RSV LRTI | | | | | | |
| | | WHO RSV severe LRTI | | | | | | |
| | | RSV hospitalization | | | | | | |
| | 12-23 months | WHO RSV LRTI | | | | | | |
| | | WHO RSV severe LRTI | | | | | | |
| | | RSV hospitalization | | | | | | |

Incidence rate computed using the number of first episode as numerator and the total number of person-years over the entire follow-up as denominator

CI=confidence interval, LL, UL for incidence = Exact 95% Lower and Upper confidence limits

## Template 9 Proportion affected by at least one episode of [RSV RTI with suspicion of involvement of LRT, WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, WHO RSV LRTI hospitalization, WHO RSV severe LRTI hospitalization] by age interval – overall and by country (PPS)

| | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects at birth** | **Total number of subjects affected** | **Proportion affected** | **LL** | **UL** |
| Overall | 0-5 | | | | | |
| | 6-11 | | | | | |
| | 0-11 | | | | | |
| | 12-23 | | | | | |
| | 0-23 | | | | | |
| <each country > | … | | | | | |

Proportion affected computed using the number of subjects experiencing at least one episode as numerator and the total number of subjects at start of the age interval as denominator.
CI=confidence interval, LL, UL for proportion affected = Exact 95% Lower and Upper confidence limits

## Template 10 Proportion affected by at least one episode of WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, by age interval – overall and by country (PPS)

| | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Episodes** | **Total number of subjects at birth** | **Total number of subjects affected** | **Proportion affected** | **LL** | **UL** |
| <each country > | 0-11 | WHO RSV LRTI | | | | | |
| | | WHO RSV severe LRTI | | | | | |
| | | RSV hospitalization | | | | | |
| | 12-23 | WHO RSV LRTI | | | | | |
| | | WHO RSV severe LRTI | | | | | |
| | | RSV hospitalization | | | | | |

Proportion affected computed using the number of subjects experiencing at least one episode as numerator and the total number of subjects at start of the age interval as denominator.
CI=confidence interval, LL, UL for proportion affected = Exact 95% Lower and Upper confidence limits

## Template 11 Incidence proportion of first episode of [RSV RTI with suspicion of involvement of LRT, WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, WHO RSV LRTI hospitalization, WHO RSV severe LRTI hospitalization] by monthly age interval in first six month of life– by country (PPS)

| | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects at risk** | **Total number Of first episode** | **Incidence proportion** | **LL** | **UL** |
| <each country > | Less than 1 | | | | | |
| | 1 | | | | | |
| | 2 | | | | | |
| | 3 | | | | | |
| | 4 | | | | | |
| | 5 | | | | | |

Incidence proportion computed using the number of first episode as numerator and the total number of subjects at risk as denominator.

Note that subjects who have presented a first episode in a previous category are not considered in the subsequent age categories.

CI=confidence interval, LL, UL for incidence proportion = Exact 95% Lower and Upper confidence limits

## Template 12 Incidence rate of first episode of [WHO RSV LRTI, WHO RSV severe LRTI and RSV hospitalization] in first 6 months of life with <=3 months or >3 months follow up in the transmission season – by country (PPS)

| | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|
| **Country** | **Follow up in transmission season** | **Total number of subjects** | **Total number of first episode** | **Total number of person-years** | **Incidence rate (100 person-years)** | **LL** | **UL** |
| <each country > | <=3 months | | | | | | |
| | >3 months | | | | | | |

Incidence rate computed using the number of first episode as numerator and the total number of person-years over the entire follow-up period as denominator

Transmission season:

October to March for Argentina, South Africa;

April 2014 to September 2014 for Canada, Finland, United states;

All year long for Bangladesh, Honduras, Thailand

CI=confidence interval, LL, UL for incidence = Exact 95% Lower and Upper confidence limits

### 12.3.1.2. Kaplan Meier analysis

**Template 13 Cumulative probability of observing first episode of [RSV-RTI with suspicion of involvement of LRTI, WHO RSV LRTI, WHO RSV severe LRTI, RSV hospitalization, WHO RSV LRTI hospitalization, WHO RSV severe LRTI hospitalization] at the end of 2 year follow-up period– overall and by country (PPS)**

| Country | Timepoint (Month of Age) | N | n | Cumulative probability of the first episode | LL | UL | median | Q1 | Q2 |
|---|---|---|---|---|---|---|---|---|---|
| Overall | 6 | | | | | | | | |
| | 12 | | | | | | | | |
| | 24 | | | | | | | | |
| <each country > | 6 | | | | | | | | |
| | 12 | | | | | | | | |
| | 24 | | | | | | | | |

Cumulative probability at the end of follow-up
N = total number of subjects
n = number of subjects with first episode reported
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Q1, Q3 = first and third quartiles

**Template 14 Cumulative probability of observing first episode of WHO RSV LRTI in subjects at the end of 2 year follow-up period– by country (PPS)**

NA

## 12.3.2. Secondary incidence analysis

### 12.3.2.1. (SO1) To determine the total health burden of non-RSV-associated RTI with a suspicion of involvement of the lower respiratory tract

### Template 15 Incidence rate of first episode of [RTI with suspicion of involvement of LRT (all cause), WHO LTRI (all cause), WHO severe LRTI (all cause)], by age interval – overall and by country (PPS)

| | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects** | **Total number of first episode (all cause)** | **Total number of person-years** | **Incidence rate (100 person-years)** | **LL** | **UL** |
| Overall | 0-5 | | | | | | |
| | 6-11 | | | | | | |
| | 0-11 | | | | | | |
| | 12-23 | | | | | | |
| | 0-23 | | | | | | |
| <each country> | … | | | | | | |

Incidence rate computed using the number of first episode (all cause) as numerator and the total number of person-years over the age interval as denominator
CI=confidence interval, LL, UL for incidence = Exact 95% Lower and Upper confidence limits
95% CI computed using exact method for first episode incidence

### Template 16 Monthly distribution of WHO RSV LRTI – by country (PPS)

| | **AR (N=)** | | **BD (N=)** | | **CA (N=)** | | **FI (N=)** | | **HN (N=)** | | **SA (N=)** | | **TH (N=)** | | **US (N=)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Calendar Month** | **n** | **%** | **N** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| January | | | | | | | | | | | | | | | | |
| February | | | | | | | | | | | | | | | | |
| March | | | | | | | | | | | | | | | | |
| April | | | | | | | | | | | | | | | | |
| May | | | | | | | | | | | | | | | | |
| June | | | | | | | | | | | | | | | | |
| July | | | | | | | | | | | | | | | | |
| August | | | | | | | | | | | | | | | | |
| September | | | | | | | | | | | | | | | | |
| October | | | | | | | | | | | | | | | | |
| November | | | | | | | | | | | | | | | | |
| December | | | | | | | | | | | | | | | | |

N=number of WHO RSV LRTI episode for each country
n (%) = total number and percent of WHO RSV LRTI episodes for each month
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## 12.3.3. Tertiary incidence analysis

### 12.3.3.1. (TO5) To assess the impact of potential RSV risk factors (e.g. complications at birth, family history of respiratory disease, living environment and household composition, breast feeding, passive smoking, day care attendance) on the incidence and severity of RSV-associated LRTI.

**Template 17 Potential risk factors for first [WHO RSV LRTI – WHO RSV severe LRTI] episode, evaluated in [Univariate – Multivariate] Cox model analysis for first [WHO RSV LRTI – WHO RSV severe LRTI] episode, over the 2 year follow-up period (PPS)**

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| RSV-A maternal antibodies levels in cord blood | Seronegative | | | | | |
| | Seropositive | | | | | |
| | Missing | | | | | |
| RSV-B maternal antibodies levels in cord blood | Seronegative | | | | | |
| | Seropositive | | | | | |
| | Missing | | | | | |
| RSV-A maternal antibodies levels in cord blood | Q1 (min - max) | | | | | |
| | Q2 (min - max) | | | | | |
| | Q3 (min - max) | | | | | |
| | Q4 (min - max) | | | | | |
| RSV-B maternal antibodies levels in cord blood | Q1 (min - max) | | | | | |
| | Q2 (min - max) | | | | | |
| | Q3 (min - max) | | | | | |
| | Q4 (min - max) | | | | | |
| RSV-A maternal antibodies levels in cord blood | Continuous | | | | | |
| RSV-B maternal antibodies levels in cord blood | Continuous | | | | | |
| Country | Argentina | | | | | |
| | ... | | | | | |
| | Missing | | | | | |
| Gender | Female | | | | | |
| | Male | | | | | |
| | Missing | | | | | |
| Time of birth | Within transmission season | | | | | |
| | Outside transmission season | | | | | |

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| Gestational age at birth | <= 36 weeks | | | | | |
| | >36 weeks | | | | | |
| Birth weight | < 2.5 kg | | | | | |
| | >= 2.5 kg | | | | | |
| Apgar at 5 mins of age | 0-3 | | | | | |
| | 4 – 6 | | | | | |
| | >= 7 | | | | | |
| | Missing | | | | | |
| First degree relative with FH of asthma | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the mother: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the father: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Number of people living in the household at Month 3 | 1-3 | | | | | |
| | 4-6 | | | | | |
| | >=7 | | | | | |
| Number of other children ( <18 years old) living in the household at Month 3 | 0 | | | | | |
| | 1-2 | | | | | |
| | >=3 | | | | | |
| Subject in regular close contact with toddlers at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| The child live in a surrounding where people smoke daily at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Breast feeding* | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |

Hazard ratio (95% CI) = Hazard ratio and 95% confidence intervals

RSV-A / RSV-B seronegative samples are defined as samples with RSV-A / RSV-B maternal antibodies levels in cord blood < LLOQ

RSV-A / RSV-B seropositive samples are defined as samples with RSV-A / RSV-B maternal antibodies levels in cord blood >= LLOQ

* Time-varying covariates :

- Number of observations used in the model = Number of observations which appeared at least once in the follow-up period. One observation can be counted in several modalities.
- Event = The number of events corresponds to the value recorded at the most recent visit before the endpoint.

## 12.4. Primary health care utilization analysis

### 12.4.1. (PO1) To determine the total health burden* of RSV-associated RTI with a suspicion of involvement of the lower respiratory tract

**Template 18 Number and percentage of healthcare utilization (supplementary to care provided by study sites) for all episodes of [WHO RSV LRTI, WHO RSV severe LRTI], by age interval [overall, in <each country>] (PPS)**

| Age interval (Months) | Characteristic | N | n | % |
|---|---|---|---|---|
| 0-5 | Outpatient visit | | | |
| | Emergency room visit | | | |
| | Inpatient Admission-Non-Intensive Care | | | |
| | Inpatient Admission-with intensive care | | | |
| | No consultation other than site clinic | | | |
| | Other | | | |
| 6-11 | … | | | |
| 0-11 | … | | | |
| 12-23 | … | | | |
| 0-23 | … | | | |

N = total number of episodes for the age interval considered
n/% = number / percentage of episodes in a given category with the most intense level of care utilized

**Template 19 Frequency of type of caregiver and number of days care utilized per caregiver for episodes of [WHO RSV LRTI, WHO RSV severe LRTI], all episodes considered, by age interval [overall, in <each country>] (PPS)**

| | | | | Number of days care per caregiver * | | | | |
|---|---|---|---|---|---|---|---|---|
| Age interval (Months) | Characteristics | N | n (%) | Mean | SD | Median | Min | Max |
| 0-5 | Usual care giver or another person took care of the child without missing work | | | | | | | |
| | A person had to stay home specifically because of the illness instead of going at work | | | | | | | |
| | A person was hired to care for the child specifically because of the illness | | | | | | | |
| 6-11 | … | | | | | | | |
| 0-11 | … | | | | | | | |
| 12-23 | | | | | | | | |
| 0-23 | | | | | | | | |

N = number of episodes for the age interval considered
n/% = number of episodes for which a caregiver of a given category is provided
SD = Standard deviation
*An event will be taken into account for the calculation of the duration only if type of utilization is reported for that event. The denominator is the n.

# 12.5. Performance of case definition

## 12.5.1. Primary performance of case definition analysis

### 12.5.1.1. (PO2) To assess the performance of the LRTI case definition and severity scale for RSV associated cases

**Template 20 Comparison between [WHO and GSK – WHO and Nokes – GSK and Nokes, WHO and exploratory] case definitions for RSV-LRTIs, all episodes considered (PPS)**

| | | WHO RSV LRTI case definition, all episodes | | Total |
|---|---|---|---|---|
| | | Case | Non Case | |
| **GSK RSV LRTI case definition, all episodes** | Case | | | |
| | Non Case | | | |
| Total | | | | |

**Template 21 Measures of agreement between [WHO and GSK – WHO and Nokes – GSK and Nokes, WHO and exploratory] case definitions for RSV-LRTIs, all episodes considered (PPS)**

| Measures of Agreement | Value | LL | UL |
|---|---|---|---|
| Sensitivity | | | |
| Specificity | | | |
| Positive predictive value | | | |
| Negative predictive value | | | |
| Proportion of overall agreement | | | |
| Cohen's kappa coefficient | | | |

Proportion of overall agreement = proportion of cases similarly classified
Cohen's kappa coefficient = the magnitude of the kappa coefficient represent the proportion of agreement greater than that expected by chance.
LL, UL = 95% Lower and Upper confidence limits
Note
The [first case definition in a pair] is considered as the classification of reference.

**Template 22 Comparison between [WHO and GSK – WHO and Nokes – GSK and Nokes – WHO and exploratory] case definitions for RSV severe-LRTIs, all episodes considered (PPS)**

| | | WHO RSV severe-LRTI case definition, all episodes | | Total |
|---|---|---|---|---|
| | | Case | Non Case | |
| GSK RSV severe-LRTI case definition, all episodes | Case | | | |
| | Non Case | | | |
| Total | | | | |

## Template 23 Measures of agreement between [WHO and GSK – WHO and Nokes – GSK and Nokes – WHO and exploratory] case definitions for RSV severe-LRTIs, all episodes considered (PPS)

| Measures of Agreement | Value | LL | UL |
|---|---|---|---|
| Sensitivity | | | |
| Specificity | | | |
| Positive predictive value | | | |
| Negative predictive value | | | |
| Proportion of overall agreement | | | |
| Cohen's kappa coefficient | | | |

Proportion of overall agreement = proportion of cases similarly classified

Cohen's kappa coefficient = the magnitude of the kappa coefficient represent the proportion of agreement greater than that expected by chance.

LL, UL = 95% Lower and Upper confidence limits

Note

The [first case definition in a pair] is considered as the classification of reference.

## Template 24 Number and percentages of RSV LRTI and RSV severe LRTIs by case definitions and hospitalization status, all episodes considered (PPS)

| | | Total episodes | Hospitalized | | | | Non-hospitalized | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Case definitions (all episodes)** | **Categories** | **N** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| RSV hospitalization | | | | | | | | | | |
| WHO | RSV LRTI | | | | | | | | | |
| | RSV severe-LRTI | | | | | | | | | |
| Nokes | RSVLRTI | | | | | | | | | |
| | RSV severe-LRTI | | | | | | | | | |
| GSK | RSV LRTI | | | | | | | | | |
| | RSV Severe LRTI | | | | | | | | | |
| Exploratory | RSV LRTI | | | | | | | | | |
| | RSV severe LRTI | | | | | | | | | |
| | RSV very severe LRTI | | | | | | | | | |

n= number of episodes by each hospitalization status in each category

N= total number of episodes

%=n/N

LL, UL = 95% Lower and Upper confidence limits

### Template 25 Comparison between RSV hospitalization and [WHO RSV LRTI hospitalization – Nokes RSV LRTI hospitalization, GSK RSV LRTI hospitalization, RSV LTRI hospitalization (exploratory)], all episodes considered (PPS)

| | | RSV hospitalization, all episodes | | Total |
|---|---|---|---|---|
| | | Case | Non Case | |
| **[WHO RSV LRTI hospitalization – Nokes RSV LRTI hospitalization, GSK RSV LRTI hospitalization], all episodes** | Case | | | |
| | Non Case | | | |
| Total | | | | |

Note:
RSV hospitalization is considered as the classification reference

### Template 26 Measures of agreement between RSV hospitalization and [WHO RSV LRTI hospitalization – Nokes RSV LRTI hospitalization, GSK RSV LRTI hospitalization, RSV LRTI hospitalization (exploratory)] all episodes considered (PPS)

| Measures of Agreement | Value | LL | UL |
|---|---|---|---|
| Sensitivity | | | |
| Specificity | | | |
| Positive predictive value | | | |
| Negative predictive value | | | |
| Proportion of overall agreement | | | |
| Cohen's kappa coefficient | | | |

Proportion of overall agreement = proportion of cases similarly classified
Cohen's kappa coefficient = the magnitude of the kappa coefficient represent the proportion of agreement greater than that expected by chance.
LL, UL = 95% Lower and Upper confidence limits
Note
RSV hospitalization is considered as the classification of reference.

### Template 27 Comparison between RSV hospitalization and [WHO RSV severe LRTI hospitalization – Nokes RSV severe LRTI hospitalization – GSK RSV severe LRTI hospitalization, RSV severe LRTI hospitalization (exploratory] all episodes considered (PPS)

| | | RSV hospitalization, all episodes | | Total |
|---|---|---|---|---|
| | | Case | Non Case | |
| **[WHO RSV severe LRTI hospitalization – Nokes RSV severe LRTI hospitalization – GSK RSV severe LRTI hospitalization], all episodes** | Case | | | |
| | Non Case | | | |
| Total | | | | |

## Template 28 Measures of agreement between RSV hospitalization and [WHO RSV severe LRTI hospitalization, Nokes RSV severe LRTI with hospitalization, GSK RSV severe LRTI hospitalization, RSV severe LRTI hospitalization (exploratory)] all episodes considered (PPS)

| Measures of Agreement | Value | LL | UL |
|---|---|---|---|
| Sensitivity | | | |
| Specificity | | | |
| Positive predictive value | | | |
| Negative predictive value | | | |
| Proportion of overall agreement | | | |
| Cohen's kappa coefficient | | | |

Proportion of overall agreement = proportion of cases similarly classified

Cohen's kappa coefficient = the magnitude of the kappa coefficient represent the proportion of agreement greater than that expected by chance.

LL, UL = 95% Lower and Upper confidence limits

Note

RSV hospitalization is considered as the classification of reference.

## Template 29 Clinical characteristics of WHO RSV LRTI and WHO RSV severe LRTI detected during the examination visit all cases and cases occurring under age of 6 months (PPS)

| | | Total N = | |
|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **n** | **%** |
| WHO RSV LRTI | RTI and SaO2 ≥ 95% and increased respiratory rate | | |
| | RTI and SaO2 < 95% and No increased respiratory rate | | |
| | RTI and SaO2 < 95% and increased respiratory rate | | |
| WHO RSV LRTI (< 6 months of age) | RTI and SaO2 ≥ 95% and increased respiratory rate | | |
| | RTI and SaO2 < 95% and No increased respiratory rate | | |
| | RTI and SaO2 < 95% and increased respiratory rate | | |
| WHO RSV Severe LRTI | RTI and SaO2 ≥ 95% and increased respiratory rate and at least one symptom induced by difficulty breathing[2] | | |
| | RTI and 93% ≤ SaO2 < 95% and No increased respiratory rate and at least one symptom induced by difficulty breathing | | |
| | RTI and 93% ≤ SaO2 < 95% and increased respiratory rate and at least one symptom induced by difficulty breathing[2] | | |
| | RTI and SaO2 < 93% and no increased respiratory rate and no symptoms induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and increased respiratory rate and no symptoms induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and No increased respiratory rate and at least one symptom induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and increased respiratory rate and at least one symptom induced by difficulty breathing | | |
| | RTI and SaO2 ≥ 95% and increased respiratory rate and at least one symptom induced by difficulty breathing[2] | | |
| WHO RSV Severe LRTI (< 6 months of age) | RTI and 93% ≤ SaO2 < 95% and No increased respiratory rate and at least one symptom induced by difficulty breathing | | |
| | RTI and 93% ≤ SaO2 < 95% and increased respiratory rate and at least one symptom induced by difficulty breathing[2] | | |
| | RTI and SaO2 < 93% and no increased respiratory rate and no symptoms induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and increased respiratory rate and no symptoms induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and No increased respiratory rate and at least one symptom induced by difficulty breathing | | |
| | RTI and SaO2 < 93% and increased respiratory rate and at least one symptom induced by difficulty breathing | | |

RTI = respiratory tract infection
SaO2 = Blood Oxygen Saturation
LRTI= Lower respiratory tract infection
N = total number of episodes
n/% = number / percentage of episodes in a given category
Increase respiratory rate: ≥ 60/minute (< 2m of age); ≥ 50/minute (2-11m of age); ≥ 40/minute (12-24m of age)
Symptoms induced by difficulty breathing: Irritability/agitation, Lethargy/sleepiness, Severe chest in drawing, Reduced/no vocalization, Apnoea > 20 sec, Cyanosis, Stop feeding well/dehydration

## 12.5.2. Tertiary performance of case definition analysis

### 12.5.2.1. (TO3) To explore the association of RSV viral load with the incidence of RSV-associated RTI, LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale).

**Template 30 Descriptive statistics of total RSV viral load during all RSV episodes classified according to WHO severity scale occurring during the [first year of life - second year of life-2 year follow-up period] by non overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| RSV asymptomatic (Excluding RSV-RTI, WHO RSV-LRTI,WHO RSV-severe LRTI) | | | | | | | | |
| RSV RTI (Excluding WHO RSV-LRTI, WHO RSV-severe LRTI) | | | | | | | | |
| WHO RSV LRTI (Excluding WHO RSV-severe LRTI) | | | | | | | | |
| WHO RSV-severe LRTI | | | | | | | | |

n= Number of RSV episodes meeting the case definitions (an episode is assigned to a single category based on the highest severity of the symptom experienced).
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

**Template 31 Descriptive statistics of total RSV viral load during all RSV episodes classified according to WHO severity scale occurring during the [first year of life - second year of life-2 year follow-up period] by overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| RSV asymptomatic | | | | | | | | |
| RSV RTI | | | | | | | | |
| WHO RSV LRTI | | | | | | | | |
| WHO RSV-severe LRTI | | | | | | | | |

n= Number of RSV episodes meeting the case definitions.
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

**Template 32 Descriptive statistics of total RSV viral load during all RSV hospitalization episodes classified according to WHO severity scale occurring during the [first year of life - second year of life- 2 year follow-up period] by non overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| RSV hospitalization (Excluding WHO RSV LRTI hospitalization, WHO RSV severe LRTI hospitalization) | | | | | | | | |
| WHO RSV LRTI hospitalization (Excluding WHO RSV severe LRTI hospitalization) | | | | | | | | |
| WHO RSV Severe LRTI hospitalization | | | | | | | | |

n= Number of RSV hospitalization episodes meeting the case definitions (an episode is assigned to a single category based on the highest severity of the symptom experienced).
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

**Template 33 Descriptive statistics of *total* RSV viral load during all *RSV hospitalization episodes classified according to WHO severity scale occurring during the [first year of life - second year of life- 2 year follow-up period]* by overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| RSV hospitalization | | | | | | | | |
| WHO RSV LRTI hospitalization | | | | | | | | |
| WHO RSV Severe LRTI hospitalization | | | | | | | | |

n= Number of RSV hospitalization episodes meeting the case definitions
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

## Template 34 Incidence rate of first episode of [RSV LRTI (exploratory), RSV severe LRTI (exploratory)], by age interval – overall and by country (PPS)

| | | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects** | **Total number of first episode** | **Total number of person-years** | **Incidence rate (100 person-years)** | **LL** | **UL** |
| Overall | 0-5 | | | | | | |
| | 6-11 | | | | | | |
| | 0-11 | | | | | | |
| | 12-23 | | | | | | |
| | 0-23 | | | | | | |
| <each country > | … | | | | | | |

Incidence rate computed using the number of first episode as numerator and the total number of person-years over the entire follow-up as denominator

CI=confidence interval, LL, UL for incidence = Exact 95% Lower and Upper confidence limits

## Template 35 Proportion affected by at least one episode of [RSV LRTI (exploratory), RSV severe LRTI (exploratory)] by age interval – overall and by country (PPS)

| | | | | | 95% exact CI | |
|---|---|---|---|---|---|---|
| **Country** | **Age interval (Months)** | **Total number of subjects at birth** | **Total number of subjects affected** | **Proportion affected** | **LL** | **UL** |
| Overall | 0-5 | | | | | |
| | 6-11 | | | | | |
| | 0-11 | | | | | |
| | 12-23 | | | | | |
| | 0-23 | | | | | |
| <each country > | … | | | | | |

Proportion affected computed using the number of subjects experiencing at least one episode as numerator and the total number of subjects at birth as denominator.

CI=confidence interval, LL, UL for proportion affected = Exact 95% Lower and Upper confidence limits

## Template 36 Descriptive statistics of total RSV viral load during all RSV episodes classified according to exploratory severity scale occurring during the [first year of life - second year of life-2 year follow-up period] by non overlapping disease severity (PPS)

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| Exploratory RSV LRTI (Excluding exploratory RSV-severe LRTI, exploratory RSV very severe LRTI) | | | | | | | | |
| Exploratory RSV-severe LRTI (excluding exploratory RSV very severe LRTI) | | | | | | | | |
| Exploratory RSV very severe LRTI | | | | | | | | |

n= Number of RSV episodes meeting the case definitions (an episode is assigned to a single category based on the highest severity of the symptom experienced).
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

## Template 37 Descriptive statistics of total RSV viral load during all RSV episodes classified according to exploratory severity scale occurring during the [first year of life - second year of life-2 year follow-up period] by overlapping disease severity (PPS)

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| Exploratory RSV LRTI | | | | | | | | |
| Exploratory RSV-severe LRTI | | | | | | | | |
| Exploratory RSV very severe LRTI | | | | | | | | |

n= Number of RSV episodes meeting the case definitions.
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

**Template 38 Descriptive statistics of total RSV viral load during all RSV hospitalization episodes classified as according to exploratory severity scale occurring during the [first year of life - second year of life- 2 year follow-up period] by non overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| Exploratory RSV LRTI hospitalization (Excluding exploratory RSV-severe LRTI hospitalization, exploratory RSV very severe LRTI hospitalization) | | | | | | | | |
| Exploratory RSV-severe LRTI hospitalization (excluding exploratory RSV very severe LRTI hospitalization) | | | | | | | | |
| Exploratory RSV very severe LRTI hospitalization | | | | | | | | |

n= Number of RSV hospitalization episodes meeting the case definitions (an episode is assigned to a single category based on the highest severity of the symptom experienced).
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

**Template 39 Descriptive statistics of *total* RSV viral load during all *RSV hospitalization episodes classified according to exploratory severity scale occurring during the [first year of life - second year of life- 2 year follow-up period]* by overlapping disease severity (PPS)**

| Category | n | Mean | 95% CI | SD | Q1 | Median | Q3 | Min/Max |
|---|---|---|---|---|---|---|---|---|
| Exploratory RSV LRTI hospitalization | | | | | | | | |
| Exploratory RSV-severe LRTI hospitalization | | | | | | | | |
| Exploratory RSV very severe LRTI hospitalization | | | | | | | | |

n= Number of RSV hospitalization episodes meeting the case definitions
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

# 12.6. Serology

## 12.6.1. Secondary serology analysis

### 12.6.1.1. (SO2) To evaluate the association between RSV-associated LRTI, RSV-associated severe LRTI and RSV neutralizing antibodies in the baseline cord blood samples collected from subjects, at birth.

**Template 40 Seropositivity rate and geometric mean titres of [RSV-A – RSV-B] neutralising antibodies in the cord blood, Overall and by country (PPS)**

| | | ≥[8 – 6] | | | | GMT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | 95% CI | | | |
| **Country** | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** |
| Overall | | | | | | | | | | |
| Each Country | | | | | | | | | | |

GMT = geometric mean antibody titer calculated on PPS subjects
N = Total number of subjects with available results
n/% = number/percentage of subjects with titer equal to or above [8 - 6]
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum

**Template 41 Seropositivity rate and geometric mean titres of [RSV-A – RSV-B] neutralising antibodies by subjects classified according to non-overlapping disease severity categories, in the first 3 months and 6 months of life, [Overall and by country] (PPS)**

| | | | | [8 – 6] | | | GMT | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | | | | |
| **Country** | **Age interval** | | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** | **Q1** | **Q3** |
| [Overall – by Country] | 0-2 months | Non Case | | | | | | | | | | | | |
| | | WHO RSV LRTI (excluding WHO RSV severe LRTI) | | | | | | | | | | | | |
| | | WHO RSV severe LRTI | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | 0-5 months | … | | | | | | | | | | | | |

GMT = geometric mean antibody titer calculated on PPS subjects
N = Total number of subjects in the given category with available result (a subject is assigned to a single category based on the highest severity of the symptom experienced)
n/% = number/percentage of subjects with titer equal to or above [8 – 6]
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Q1/Q3 = Quartile 1/Quartile 3
Note :
Non case is defined as subject not experiencing WHO RS V LRTI or WHO RSV severe LRTI in the given time interval
An episode is confirmed as RSV positive using swab sample by qRT-PCR
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

## Template 42 Seropositivity rate and geometric mean titres of [RSV-A – RSV-B] neutralising antibodies by subjects classified according to overlapping disease severity categories, in the first 3 months and 6 months of life, [Overall and by country] *(*PPS)

| | | | | [8 – 6] | | | | | GMT | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | | | |
| **Country** | **Age interval** | | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** | **Q1** | **Q3** |
| [Overall – by Country] | 0-2 months | Non Case | | | | | | | | | | | | |
| | | WHO RSV LRTI | | | | | | | | | | | | |
| | | WHO RSV severe LRTI | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | 0-5 months | … | | | | | | | | | | | | |

GMT = geometric mean antibody titer calculated on PPS subjects
N = Total number of subjects in the given catoegory with available results
n/% = number/percentage of subjects with titer equal to or above [8 – 6]
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Q1/Q3 = Quartile 1/Quartile 3
Note :
Non case is defined as subject not experiencing WHO RS V LRTI or WHO RSV severe LRTI in the given time interval
An episode is confirmed as RSV positive using swab sample by qRT-PCR
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

## Template 43 [Univariate – Multivariate] estimated coefficients for Cox models with RSV-A and RSV-B by seropostivity status, for first WHO [RSV-LRTI – RSV Severe LRTI ] episode, over the follow-up period from [0-2 months – 0-5 months] (PPS)

| **Characteristics** | **Category** | **Number of Observations Used in the model** | **Event** | **Hazard ratio (95% CI)** | **p-value** | **Global p-value** |
|---|---|---|---|---|---|---|
| RSV-A maternal antibodies levels in cord blood | Seronegative | | | | | |
| | Seropositive | | | | | |
| RSV-B maternal antibodies levels in cord blood | Seronegative | | | | | |
| | Seropositive | | | | | |
| Country | Argentina | | | | | |
| | … | | | | | |
| | Missing | | | | | |
| Gender | Female | | | | | |
| | Male | | | | | |
| | Missing | | | | | |
| Time of birth | Within transmission season | | | | | |
| | Outside transmission season | | | | | |

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| Gestational age at birth | <= 36 weeks | | | | | |
| | >36 weeks | | | | | |
| Birth weight | < 2.5 kg | | | | | |
| | >= 2.5 kg | | | | | |
| Apgar at 5 mins of age | 0-3 | | | | | |
| | 4 – 6 | | | | | |
| | >= 7 | | | | | |
| | Missing | | | | | |
| First degree relative with FH of asthma | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the mother: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the father: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Number of people living in the household at Month 3 | 1-3 | | | | | |
| | 4-6 | | | | | |
| | >=7 | | | | | |
| Number of other children ( <18 years old) living in the household at Month 3 | 0 | | | | | |
| | 1-2 | | | | | |
| | >=3 | | | | | |
| Subject in regular close contact with toddlers at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| The child live in a surrounding where people smoke daily at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Breast feeding* | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |

Hazard ratio (95% CI) = Hazard ratio and 95% confidence intervals
RSV-A seronegative samples are defined as samples with RSV-A maternal antibodies levels in cord blood < 8
RSV-B seronegative samples are defined as samples with RSV-B maternal antibodies levels in cord blood < 6
RSV-A seropositive samples are defined as samples with RSV-A maternal antibodies levels in cord blood >= 8
RSV-B seropositive samples are defined as samples with RSV-B maternal antibodies levels in cord blood >= 6
Subjects with missing cord blood value for RSV-A or RSV-B were excluded from this analysis
* Time-varying covariates :

- Number of observations used in the model = Number of observations which appeared at least once in the follow-up period. One observation can be counted in several modalities.
- Event = The number of events corresponds to the value recorded at the most recent visit before the endpoint.
- Event = The number of events corresponds to the value recorded at the most recent visit before the endpoint.

**Template 44 [Univariate – Multivariate] estimated coefficients for Cox models with RSV-A and RSV-B as semi-quantitative variable by quartiles, for first WHO [RSV-LRTI – RSV Severe LRTI ] episodes, over the follow-up period from [0-2 months – 0-5 months] (PPS)**

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| RSV-A maternal antibodies levels in cord blood | Q1 (min - max) | | | | | |
| | Q2 (min - max) | | | | | |
| | Q3 (min - max) | | | | | |
| | Q4 (min - max) | | | | | |
| RSV-B maternal antibodies levels in cord blood | Q1 (min - max) | | | | | |
| | Q2 (min - max) | | | | | |
| | Q3 (min - max) | | | | | |
| | Q4 (min - max) | | | | | |
| Country | Argentina | | | | | |
| | … | | | | | |
| | Missing | | | | | |
| Gender | Female | | | | | |
| | Male | | | | | |
| | Missing | | | | | |
| Time of birth | Within transmission season | | | | | |
| | Outside transmission season | | | | | |
| Gestational age at birth | <= 36 weeks | | | | | |
| | >36 weeks | | | | | |
| Birth weight | < 2.5 kg | | | | | |
| | >= 2.5 kg | | | | | |
| Apgar at 5 mins of age | 0-3 | | | | | |
| | 4 – 6 | | | | | |
| | >= 7 | | | | | |
| | Missing | | | | | |
| First degree relative with FH of asthma | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the mother: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the father: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Number of people living in the household at Month 3 | 1-3 | | | | | |
| | 4-6 | | | | | |
| | >=7 | | | | | |
| Number of other children ( <18 years old) living in the household at Month 3 | 0 | | | | | |
| | 1-2 | | | | | |
| | >=3 | | | | | |

| **Characteristics** | **Category** | **Number of Observations Used in the model** | **Event** | **Hazard ratio (95% CI)** | **p-value** | **Global p-value** |
|---|---|---|---|---|---|---|
| Subject in regular close contact with toddlers at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| The child live in a surrounding where people smoke daily at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Breast feeding* | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |

Hazard ratio (95% CI) = Hazard ratio and 95% confidence intervals
Subjects with missing cord blood value for RSV-A or RSV-B were excluded from this analysis
* Time-varying covariates :
- Number of observations used in the model = Number of observations which appeared at least once in the follow-up period. One observation can be counted in several modalities.
- Event = The number of events corresponds to the value recorded at the most recent visit before the endpoint.

## Template 45 [Univariate – Multivariate] estimated coefficients for Cox models with RSV-A and RSV-B as continuous variable, for first WHO [RSV-LRTI – RSV Severe LRTI ] episodes, over the follow-up period from [0-2 months – 0-5 months] (PPS)

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| RSV-A maternal antibodies levels in cord blood | Continuous | | | | | |
| RSV-B maternal antibodies levels in cord blood | Continuous | | | | | |
| Country | Argentina | | | | | |
| | … | | | | | |
| | Missing | | | | | |
| Gender | Female | | | | | |
| | Male | | | | | |
| | Missing | | | | | |
| Time of birth | Within transmission season | | | | | |
| | Outside transmission season | | | | | |
| Gestational age at birth | <= 36 weeks | | | | | |
| | >36 weeks | | | | | |
| Birth weight | < 2.5 kg | | | | | |
| | >= 2.5 kg | | | | | |
| Apgar at 5 mins of age | 0-3 | | | | | |
| | 4 – 6 | | | | | |
| | >= 7 | | | | | |
| | Missing | | | | | |

| Characteristics | Category | Number of Observations Used in the model | Event | Hazard ratio (95% CI) | p-value | Global p-value |
|---|---|---|---|---|---|---|
| First degree relative with FH of asthma | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the mother: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Highest education level of the father: Higher education / university | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Number of people living in the household at Month 3 | 1-3 | | | | | |
| | 4-6 | | | | | |
| | >=7 | | | | | |
| Number of other children ( <18 years old) living in the household at Month 3 | 0 | | | | | |
| | 1-2 | | | | | |
| | >=3 | | | | | |
| Subject in regular close contact with toddlers at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| The child live in a surrounding where people smoke daily at Month 3 | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |
| Breast feeding* | Yes | | | | | |
| | No | | | | | |
| | Missing | | | | | |

Hazard ratio (95% CI) = Hazard ratio and 95% confidence intervals
Subjects with missing cord blood value for RSV-A or RSV-B were excluded from this analysis
* Time-varying covariates :

- Number of observations used in the model = Number of observations which appeared at least once in the follow-up period. One observation can be counted in several modalities.
- Event = The number of events corresponds to the value recorded at the most recent visit before the endpoint.

### Template 46 Descriptive statistics of total RSV viral load during first episode of WHO RSV LRTI episode by quartiles of [RSV A – RSV B] neutralizing antibody titres in cord blood in first 6 months of life, (PPS)

| | Total Viral Load | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Quartiles of neutralizing antibody titers** | **n** | **Mean** | **95% CI** | **SD** | **Q1** | **Median** | **Q3** | **Min/Max** |
| Q1 | | | | | | | | |
| Q2 | | | | | | | | |
| Q3 | | | | | | | | |
| Q4 | | | | | | | | |

n= Number of 1st episode within the quartile
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd Quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
An episode is confirmed as RSV positive using swab sample by qRT-PCR
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis

## 12.6.1.2. (SO3) To determine the level of RSV antibody at 2, 4, 6, 12, 18 and 24 months in a randomly selected sub-cohort of subjects.

### Template 47 Seropositivity rate and geometric mean titres of [RSV-A – RSV-B] neutralising antibodies by timepoint, Overall (PPS – sub cohorts)

| | | ≥[8 – 6] | | | | GMT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | 95% CI | | | |
| Time point (Month) | N | n | % | LL | UL | value | LL | UL | Min | Max |
| 0 | | | | | | | | | | |
| 2 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| 18 | | | | | | | | | | |
| 24 | | | | | | | | | | |

GMT = geometric mean antibody titer calculated on PPS sub-cohorts subjects
N = Number of subjects with available results at both baseline and sampling timepoint
n/% = number/percentage of subjects with titer equal to or above [8 – 6]
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Note: Blood draw at month 0 is from cord blood sample
Note: Subjects that have no available result for randomized timepoints are not included in analysis of timepoint 0

## 12.6.2. Tertiary serology analysis

### 12.6.2.1. (TO7) To assess the natural decay of maternal antibody levels using a single follow-up blood sample collected from a randomly selected sub-cohort of subjects at 2, 4, 6, 12, 18 and 24 months.

**Template 48 Seropositivity rate and geometric mean titres of [RSV-A – RSV-B] neutralising antibodies of cord blood sample by subjects randomized to a timepoint for sampling(PPS sub cohort)**

| | | | [8 – 6] | | | | GMT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | | |
| **Antibody** | | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** |
| Anti-[RSV-A – RSV-B] Neutralizing Antibody in cord blood | Subjects sampled at month 2 | | | | | | | | | | |
| | Subjects sampled at month 4 | | | | | | | | | | |
| | Subjects sampled at month 6 | | | | | | | | | | |
| | Subjects sampled at month 12 | | | | | | | | | | |
| | Subjects sampled at month 18 | | | | | | | | | | |
| | Subjects sampled at month 24 | | | | | | | | | | |
| | Overall | | | | | | | | | | |

GMT = geometric mean antibody titer calculated on PPS sub-cohorts subjects
N = Number of subjects with available results at both baseline and sampling timepoint
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above [8 – 6]
MIN/MAX = Minimum/Maximum

**Template 49 Number and percentage of subjects with an [RSV-A – RSV-B] positive *nasal swab* during the study before time of blood sampling (PPS sub-cohort)**

| | Total | | |
|---|---|---|---|
| **Blood sampling timepoint (month)** | **N** | **N** | **%** |
| 2 | | | |
| 4 | | | |
| 6 | | | |
| 12 | | | |
| 18 | | | |
| 24 | | | |

N = Number of subject by time point
n/% = number / percentage of episodes in a given category

## Template 50 Summary of sequential models of the natural decay of maternal antibody levels (Total sub-cohort)

| | | | 95% CI | | |
|---|---|---|---|---|---|
| **Sequential models** | **N** | **Natural decay rate** | **LL** | **UL** | **Half-life** |
| 1: Model with all subjects except subjects with an RSV positive nasal swab during the study before time of sampling | | | | | |
| 2 | | | | | |
| … | | | | | |
| Final: Most accurate model | | | | | |

Note:

Natural decay rate is defined using a using linear regression between the log of antibody level and time in months with subject as a random effect.

Each step/model is used to reduce the sample to uninfected subjects only. Subjects with an antibody titer at the sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected, eliminated and the decay curve refined. The expected value of antibody titer of each subject is computed using based on their baseline (cord blood) value and the established decay curve defined using the natural decay rate at the previous step.

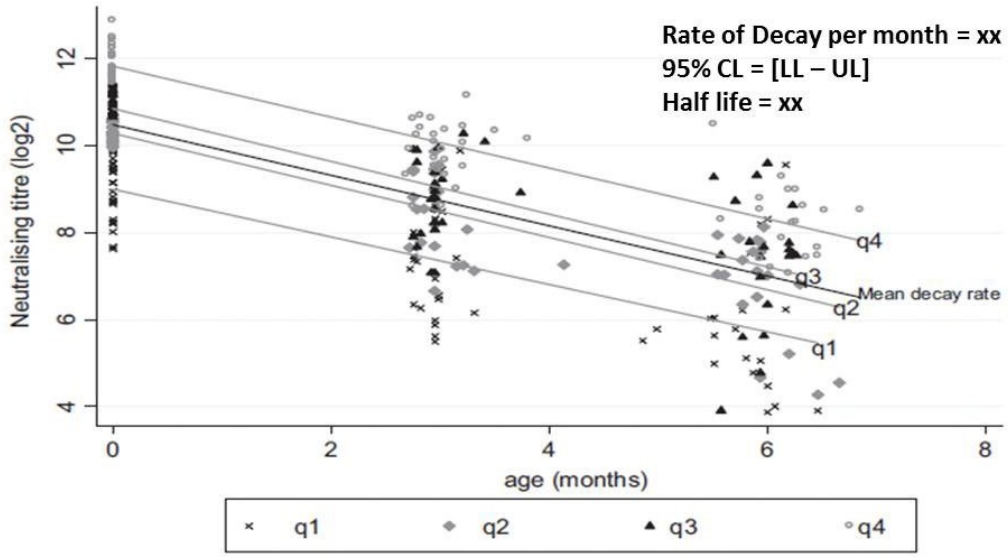
The decay model is fitted only using subject with blood sample at 2, 4, 6, and 12 month

The sequential analysis is repeated up to 5 times until the most accurate decay curve is established

N = Number of subjects used in the model

LL, UL for percentage = Lower and Upper confidence limits

## Template 51 Decay rate of [RSV-A – RSV-B] maternal antibody levels assuming a fixed rate of decay Neutralizing antibodies per months) (PPS sub-cohort)




q1-q4: quartile of [RSV-A – RSV-B] cord blood antibodies

## Template 52 Prevalence of [RSV A – RSV B – RSV] infection, at 2, 4, 6, 12, 18 and 24 months in a randomly selected sub-cohort of subjects by assessing antibodies in serum [Overall – by country] (PPS sub-cohort)

| | | | | | 95% CI | |
|---|---|---|---|---|---|---|
| **Country** | **Time point (Month)** | **N** | **n** | **Proportion (in %)** | **LL** | **UL** |
| [Overall – by country] | 2 | | | | | |
| | 4 | | | | | |
| | 6 | | | | | |
| | 12 | | | | | |
| | 18 | | | | | |
| | 24 | | | | | |

N = total number of subject at time of sampling

n = number of subjects with an antibody titer at the sampling time that is more than 2-fold above the expected value for month 2, 4, 6, and 12 month subject, and number of subject with antibodies in serum above [8 – 6] for month 18 and 24 subjects

LL, UL for percentage = Exact 95% Lower and Upper confidence limits

# 12.7. Other viruses and RSV infection

## 12.7.1. Tertiary other viruses and RSV infection analysis

### 12.7.1.1. (TO) To explore the association of RSV and other respiratory viruses with the incidence of LRTI and/or severe LRTI (as determined by the LRTI case definition and severity scale) using xTAG™ RVP Fast assay.

**Template 53 The occurrence of respiratory viral infections, by cause, identified in cases [WHO LRTI – WHO severe LRTI – WHO RSV LRTI, WHO RSV severe LRTI] in the first two year of life, overall and by country (PPS)**

| | | Age Group | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 2 month | 3 – 5 month | 6 – 11 moth | 12 - 23 month | Total |
| | | N = xx | N = xx | N = xx | N = xx | N = xx |
| Country | Respiratory virus identified | | | | | |
| Overall | Influenza A/H1, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Influenza A/H3, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Influenza B, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Influenza, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Parainfluenza virus type 1, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Parainfluenza virus type 2, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Parainfluenza virus type 3, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Parainfluenza virus type 4, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Any Parainfluenza virus, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Rhinovirus, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Adenovirus, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Bocavirus, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Coronavirus 229E, n(%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| | Coronavirus OC43, n(%) | | | | | |
| | Coronavirus NL63, n(%) | | | | | |
| | Coronavirus HKU1, n(%) | | | | | |
| | Any Coronavirus, n(%) | | | | | |
| | [RSVA (RT-qPCR), n(%)] | | | | | |
| | [RSVB (RT-qPCR), n(%)] | | | | | |
| <Each country> | … | | | | | |
| | … | | | | | |
| | … | | | | | |
| | | | | | | |

N = Total number of [all – RSV positive] cases with [WHO LRTI – WHO severe LRTI] at given age interval
n = number of [WHO LRTI – WHO severe LRTI] cases positive for a given viral infection
% = n/N
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note:
Infection with other respiratory viruses is determined using xTAG™ RVP Fast assay

## Template 54 Frequency of respiratory viral co-infections identified in WHO [LRTI - severe LRTI – RSV LRTI – RSV severe LRTI] the first two years of life, overall and by country (PPS)

| | | Age Group | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 2 month | 3 – 5 month | 6 – 11 moth | 12 - 23 month | Total |
| | | N = xx | N = xx | N = xx | N = xx | N = xx |
| Country | Co-infection | | | | | |
| Overall | No co-infection | n (%) | n (%) | n (%) | n (%) | n (%) |
| | 1 other virus | n (%) | n (%) | n (%) | n (%) | n (%) |
| | 2 other viruses | n (%) | n (%) | n (%) | n (%) | n (%) |
| | >2 other virus | n (%) | n (%) | n (%) | n (%) | n (%) |
| By country | | | | | | |

N = Total number of WHO [LRTI – severe LRTI] cases at given age interval
n = number of WHO [LRTI - severe LRTI] cases for a category of other viral infection
% = n/N
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note:
Infection with other respiratory viruses is determined using xTAG™ RVP Fast assay

## Template 55 Viral single and co-infections among all WHO [LRTI – severe LRTI ] cases, (PPS)

| | ALL | Single infection | Co – infection |
|---|---|---|---|
| | N = | N = | N = |
| Respiratory virus identified | | | |
| Influenza A/H1, n(%) | n(%) | n(%) | n(%) |
| Influenza A/H3, n(%) | n(%) | n(%) | n(%) |
| Influenza B, n(%) | n(%) | n(%) | n(%) |
| influenza, n(%) | n(%) | n(%) | n(%) |
| Parainfluenza virus type 1, n(%) | n(%) | n(%) | n(%) |
| Parainfluenza virus type 2, n(%) | n(%) | n(%) | n(%) |
| Parainfluenza virus type 3, n(%) | n(%) | n(%) | n(%) |
| Parainfluenza virus type 4, n(%) | n(%) | n(%) | n(%) |
| Any Parainfluenza virus, n(%) | n(%) | n(%) | n(%) |
| Rhinovirus, n(%) | n(%) | n(%) | n(%) |
| Adenovirus, n(%) | n(%) | n(%) | n(%) |
| Bocavirus, n(%) | n(%) | n(%) | n(%) |
| Coronavirus 229E, n(%) | n(%) | n(%) | n(%) |
| Coronavirus OC43, n(%) | n(%) | n(%) | n(%) |
| Coronavirus NL63, n(%) | n(%) | n(%) | n(%) |
| Coronavirus HKU1, n(%) | n(%) | n(%) | n(%) |
| Any Coronavirus, n(%) | n(%) | n(%) | n(%) |
| RSVA (RT-qPCR) , n(%) | n(%) | n(%) | n(%) |
| RSVB (RT-qPCR) , n(%) | n(%) | n(%) | n(%) |

N = number of [WHO LRTI, WHO severe LRTI] cases in single infection, co-infection, and overall categories
n = number of WHO [LRTI - severe LRTI] cases for respiratory virus identified
% = n/N
Note:
RSV infection is determined using RT-qPCR
Infection with other respiratory viruses is determined using xTAG™ RVP Fast assay

# 12.8. Practical implementation of protocol

## 12.8.1. Cord blood collection, storage, and processing

### Template 56 Number and percentage of subjects according to the storage process of the cord blood sample, Overall and by country (PPS)

| | | | Total N= | |
|---|---|---|---|---|
| **Country** | **Characteristics** | **Categories** | **n** | **%** |
| Overall | Cord storage condition until blood collection | Refrigerated | | |
| | | Wet ice | | |
| | | Room temperature | | |
| | | Processed immediately | | |
| | Type of tube used to collect cord blood | Quest tube | | |
| | | Plain tube | | |
| | | Tube with gel separator | | |
| | | Other | | |
| | Storage of the cord blood sample | Refrigerated | | |
| | | Wet ice | | |
| | | Room temperature | | |
| | | Processed immediately | | |
| | Storage of the serum sample | Refrigerated | | |
| | | Wet ice | | |
| | | Room temperature | | |
| | | Processed immediately | | |
| <*each country*> | | | | |

N = total number of subjects
n/% = number / percentage of subjects in a given category

### Template 57 Duration between collections and completion of processing of cord blood sample (PPS)

| | | Total | | | | | |
|---|---|---|---|---|---|---|---|
| **Country** | **Process duration** | **n** | **Mean** | **SD** | **Median** | **Minimum** | **Maximum** |
| Overall | Duration of overall process (hours) | | | | | | |
| | Duration of process between collection and centrifugation (hours) | | | | | | |
| | Duration of process between centrifugation and transfer of serum (hours) | | | | | | |
| | Duration of process between transfer of serum and storage (hours) | | | | | | |
| Each country | … | | | | | | |

Overall process duration: Duration of process between collection and storage of cord blood sample
n= Number of subjects with cord blood sample in each country considered
SD=Standard Deviation

## Template 58 Descriptive statistics of [RSV-A - RSV-B] maternal antibody levels in cord blood according to [Storage condition until blood collection - Storage condition until centrifugation - Storage condition until tube was frozen] (PPS)

| | [RSV-A –RSV-B] maternal antibodies N= | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Storage condition until blood collection** | **n** | **GMT** | **95% CI** | **SD** | **Q1** | **Median** | **Q3** | **Min/Max** |
| Refrigerated | | | | | | | | |
| Wet ice | | | | | | | | |
| Room temperature | | | | | | | | |
| Processed immediately | | | | | | | | |

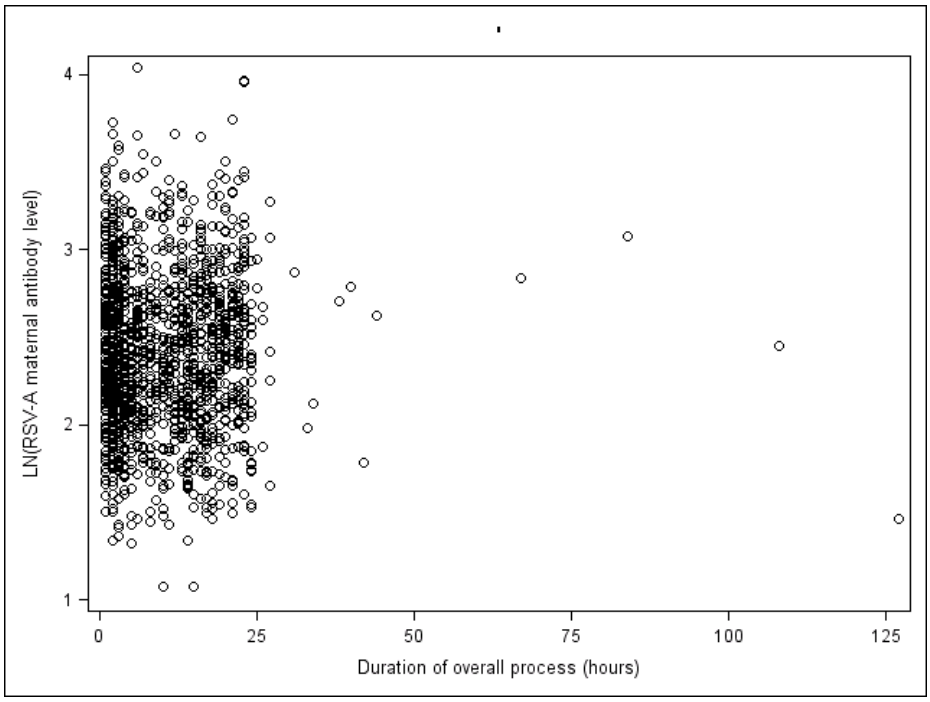
N = total number of subjects
n= Number of events in each category
GM = Geometric mean
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quantiles
Min/Max = Minimum/Maximum

## Template 59 Descriptive statistics of [RSV-A - RSV-B] maternal antibody levels in cord blood according to tube type (PPS)

| | [RSV-A –RSV-B] maternal antibodies N= | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Storage condition until blood collection** | **n** | **GMT** | **95% CI** | **SD** | **Q1** | **Median** | **Q3** | **Min/Max** |
| Primary tube | | | | | | | | |
| Plain tube | | | | | | | | |
| Tube with gel separator | | | | | | | | |
| Other | | | | | | | | |

N = total number of subjects
n= Number of events in each category
GM = Geometric mean
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quantiles
Min/Max = Minimum/Maximum

**Template 60 Plot of log10 [RSV-A - RSV-B] antibody level in cord blood according to the [overall process duration - process between collection and centrifugation - process between centrifugation and transfer of serum - process between transfer of serum and storage] (PPS)**




## 12.8.2. Evaluation of surveillance and protocol procedure

**Template 61 Number and percent of outcome of the surveillance contact, overall and by country (PPS)**

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Exam visit indicated | | | | | | | | | | | | | | | | | | |
| Exam visit not indicated | | | | | | | | | | | | | | | | | | |
| Exam visit already existed | | | | | | | | | | | | | | | | | | |

N = total number of surveillance visit in a given country
n = number of visits under each outcome
% = n/N
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## Template 62 Number and percent of examination visit by number of days between surveillance contact and next recorded examination visit, overall by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Duration (days)** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Same day as surveillance contact | | | | | | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | | | |
| 4 – 6 | | | | | | | | | | | | | | | | | | |
| >6, or never | | | | | | | | | | | | | | | | | | |

N = Total number of surveillance contact indicating an exam visit in a given country
n = number of surveillance contacts indicating a visit where an examination visit occured for a given duration
% = n/N
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## Template 63 Number and percent of examination visit associated with previous surveillance contact, overall and by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Examination visit with a surveillance contact preceding 72 hours indicating an examination visit | | | | | | | | | | | | | | | | | | |
| Examination visit with a surveillance contact preceding 72 hours not indicating an examination visit or already existing | | | | | | | | | | | | | | | | | | |
| Examination with no surveillance contact preceding 72 hours | | | | | | | | | | | | | | | | | | |

N = total number of examination visit in a given country
n = number of examination visits under each catgory
% = n/N
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## Template 64 Number and percent of examination visit by nasal swab collection status, overall and by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nasal swabs** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Yes | | | | | | | | | | | | | | | | | | |
| Not done, refused | | | | | | | | | | | | | | | | | | |
| Not done, other | | | | | | | | | | | | | | | | | | |

N = Total number of examination visit in given country
n = number of visits with swab collection in the given category
% = n/N
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

## Template 65 Number and percent of examination visit by number of days between onset of [cough or difficulty breathing – cough – difficulty breathing] and follow up examination visit, overall and by country (PPS)

| | Total N = | | AR N = | | BD N = | | CA N = | | FI N = | | HN N = | | SA N = | | TH N = | | US N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| If yes, time between onset of symptom and examination visit (days) | | | | | | | | | | | | | | | | | | |
| Same day as exam visit | | | | | | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | | | |
| 4 – 6 | | | | | | | | | | | | | | | | | | |
| >6 | | | | | | | | | | | | | | | | | | |

N = Total number of examination visit in a given country with onset of [cough or difficulty breathing – cough – difficulty breathing] reported
n = number of examination visits for which onset of [cough or difficulty – cough – difficulty breathing] occurred for a given category
% = n/N
AR = Argentina
BD = Bangladesh
CA = Canada
FI = Finland
HN = Honduras
SA = South Africa
TH = Thailand
US = US

**Template 66 Descriptive statistics of total RSV viral load by number of days between any symptom apparition and nasal swab collection calculated for first [WHO RSV-LRTI – WHO RSV Severe LRTI] episodes (PPS)**

| | Number first episode N= | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of days from onset of any symptom until swab collection** | **n** | **Mean** | **95% CI** | **SD** | **Q1** | **Median** | **Q3** | **Min/Max** |
| Same day as onset of symptom | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 – 6 | | | | | | | | |
| >6 | | | | | | | | |

N = Total number of [WHO RSV-LRTI – RSV Severe LRTI] episodes
n= Number of first episodes swabbed for a given category
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs or examination visits for an episode. In such cases, the swab with highest viral load was considered for this analysis
The date of nasal swab collection is the date of examination

**Template 67 Descriptive statistics of total RSV viral load by number of days between onset of [cough or difficulty – cough – difficulty breathing] and nasal swab collection calculated for first WHO [RSV-LRTI – RSV Severe LRTI] episode (PPS)**

| | Total N= | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of days between onset of [cough or difficulty – cough – difficulty breathing] breathing until swab collection** | **n** | **Mean** | **95% CI** | **SD** | **Q1** | **Median** | **Q3** | **Min/Max** |
| Same day as onset of cough or difficulty breathing | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 – 6 | | | | | | | | |
| >6 | | | | | | | | |

N = Total number of [RSV-RTI – RSV-LRTI – RSV Severe LRTI] episodes
n= Number of events in each category
SD=Standard Deviation
Q1 and Q3 = 1st and 3rd quartiles
Min/Max = Minimum/Maximum
Total RSV viral load computed as RSV A Viral load + RSV B Viral load
Note:
There may have been multiple swabs for an episode. In such cases, the swab with highest viral load was considered for this analysis
The date of nasal swab collection is the date of examination