Retrospective surveillance and enhanced case-finding of congenital rubella syndrome cases
This protocol was prepared as part of a collaboration between the ECDC Vaccine-preventable Disease programme and the European Programme for Intervention Epidemiology Training.

Authors: Alastair Donachie and David Hendrickx - EPIET fellows

Coordination and supervision: Tarik Derrough and Emmanouela Sdona - ECDC Vaccine-preventable Disease programme

Acknowledgments:

This protocol was prepared and developed in consultation with Dr. Guenter Pfaff who provided expertise from the verification process of measles and rubella elimination in the European Region.

We would like to acknowledge the review provided by Gianfranco Spiteri (ECDC), Alicia Barrassa (Instituto de Salud Carlos III, Spain) and Kostas Danis (Santé Publique France, France), EPIET coordinators.

We would like to acknowledge the comments and suggestions on the technical content of this document by experts from the Vaccine-preventable Diseases and Immunization Unit of the WHO Regional Office for Europe and Global Immunization Division of the US Centers for Disease Control and Prevention.
Contents

Abbreviations ............................................................................................................................................... iv
Introduction .................................................................................................................................................. 1
  Rationale ................................................................................................................................................. 1
  Aim ......................................................................................................................................................... 1
  Objectives ................................................................................................................................................ 1
Methods ....................................................................................................................................................... 3
  Overall study design.................................................................................................................................. 3
  Methods study phase 1 ................................................................................................................................ 3
  Methods study phase 2 ................................................................................................................................ 3
  Description ............................................................................................................................................. 4
  Study population ...................................................................................................................................... 4
  Study period .......................................................................................................................................... 4
  Study setting .......................................................................................................................................... 4
  Case definitions & classifications ............................................................................................................ 4
  Case identification and data sources ....................................................................................................... 6
  Limitations ............................................................................................................................................. 8
  Ethical considerations and approval ......................................................................................................... 9
  Procedures for the management and follow-up of suspected CRS cases .................................................... 9
  Roles and responsibilities ....................................................................................................................... 9
  Budget ................................................................................................................................................ 9
  Communication of results and expected outputs ...................................................................................... 9
References .................................................................................................................................................. 10
Annexes ..................................................................................................................................................... 12

Tables

Table 1. EU and WHO case definitions for CRS and CRI (WHO definition only) .................................................. 5
Table 2. Review of available data sources for the estimation of CRS burden in an EU countryr .............................................. 6
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>congenital rubella syndrome</td>
</tr>
<tr>
<td>CRI</td>
<td>congenital rubella infection</td>
</tr>
<tr>
<td>EPIET</td>
<td>EPIET (Field Epidemiology path) of ECDC's Fellowship Programme</td>
</tr>
<tr>
<td>EU/EEA</td>
<td>European Union/European Economic Area</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>RVC</td>
<td>Regional Verification Commission</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
</tbody>
</table>
Introduction

On a global scale, reported rubella cases declined 97% between 2000 (670,894 cases in 102 countries) and 2016 (22,361 cases in 165 countries) [1]. In 2015, the WHO Region of the Americas declared that rubella and congenital rubella syndrome (CRS) had been eliminated. In 2012, the WHO Regional Office for Europe recommended measures to be undertaken by the WHO European Region countries to eliminate measles and rubella, and to support the prevention of CRS [2–4]. In 2014, the WHO Regional Office for Europe published the framework for the verification process and the steps needed to document measles and rubella elimination [5]. ECDC is supporting European Union (EU) and European Economic Area (EEA) Member States in their efforts to achieve the elimination goal. In 2016, 33 (62%) of the 53 WHO European Region countries were declared free of endemic rubella virus transmission [8]. Rubella and congenital rubella, including CRS, are included in the list of communicable diseases notifiable at EU level. An official EU case definition exists for rubella and CRS [6]. Although substantial progress has been made in reducing the transmission of rubella in the WHO European Region, challenges to achieving its elimination goals remain.

Rationale

Strengthening CRS surveillance is included as one of the four strategies to achieve elimination. In line with the WHO surveillance guidelines and the framework for documenting rubella elimination, all WHO Regional Office for Europe Member States should develop a CRS surveillance system to capture the majority of infants with suspected CRS within the country [2,5]. If there is no surveillance in place, countries may first opt to establish CRS surveillance at a few sentinel sites and then broaden the surveillance, including additional sites later.

According to a cross-sectional survey conducted by ECDC between June and November 2012 among 29 EU/EEA countries, 28 had national surveillance for CRS, mostly mandatory (26/28), comprehensive (27/28) and case-based (27/28) [7]. Eight countries had active surveillance and six countries required zero-reporting for CRS surveillance. Twenty-seven countries collected laboratory data and 24 had adopted the EU case definition for CRS. All countries had a reference laboratory for confirmation of suspected congenital rubella cases. However, at a meeting of the WHO European Regional Verification Commission for Measles and Rubella Elimination in October 2015, several European countries still could not provide evidence for the existence of sensitive nationwide or effective sentinel surveillance for CRS [8].

Other alternative approaches may also be used to identify CRS cases (e.g. registries for rubella in pregnancy and retrospective searches for CRS.) Supplementary information, such as surveillance sensitivity and population immunity involving serosurvey studies on rubella, CRS and measles may form part of the annual status update provided by countries to the National Verification Committee for measles and rubella elimination and to the Regional Verification Commission for measles and rubella elimination (RVC). This supplementary information can be useful for the triangulation of data and for the RVC to evaluate the disease status of a country.

As several EU/EEA countries still cannot provide sufficient evidence for the existence of sensitive surveillance systems for detecting CRS cases, additional studies measuring surveillance sensitivity would be useful to evaluate the disease status of a country.

The generic protocol presented in this document was developed for ECDC by fellows of the EPIET programme to provide EU/EEA Member States with an adaptable tool to estimate the incidence of CRS cases in their countries. This study protocol describes a process that any EU/EEA country can use to retrospectively identify probable CRS cases in infants in the three years preceding the study’s implementation and to evaluate the completeness of their current CRS surveillance system.

Aim

The overall aim of the study is to estimate national infant1 CRS incidence and allow the identification of additional CRS cases not documented by routine CRS surveillance activities.

Objectives

Primary objective

- To estimate the incidence of CRS in infants in an EU/EEA country for the three-year period preceding the study’s implementation.

1 For the purpose of this protocol, we define infants as all children in their first year of life.
Specific objectives

- To describe the CRS surveillance arrangements in place in the country.
- To identify the data sources to be used to retrieve CRS cases among infants and rubella cases among pregnant women for whom records in relevant data sources are available.
- To estimate CRS incidence based on reported cases by the country’s surveillance system, and to compare this to CRS incidence calculated on the basis of the retrospective review of data sources.
- To estimate the positive predictive value (PPV) of the existing national CRS surveillance system, and that accomplished through the retrospective review of data sources.
- To formulate recommendations to improve the sensitivity of the country’s CRS surveillance system.
Methods

Overall study design

The methodology proposed in this protocol is a catalogue of best practices used in previous studies where retrospective case finding of CRS cases was implemented (Annex 2).

To retrieve peer-reviewed scientific articles discussing methodologies and approaches documenting the burden of CRS at the local, regional and national level, an extensive literature review was performed in PubMed using keywords (Annex 1). Following this review, a number of best practice methods were identified for retrospective case finding of CRS cases (Annex 2).

Since available data sources will vary between countries, the precise study methods will differ depending on the setting in which the protocol is implemented. The extent of data collection activities will therefore also vary accordingly. This requires the development of a country-specific study protocol based on the generic study design and methods described in this document.

Therefore, the proposed generic study design consists of two sequential phases:

Study phase 1: A review and description of CRS surveillance arrangements and other relevant data sources by country.

Study phase 2: A review of health facility patient records and other data sources for the retrospective identification of CRS cases in the three years preceding the study's implementation. The specific methods used in study phase 2 will be informed by the outcomes of study phase 1.

Methods study phase 1

Description

The aim of study phase 1 is to provide a comprehensive review and description of the following aspects of the CRS surveillance system in the country under study:

- The CRS surveillance arrangements and other relevant public health indicators for the preceding three years, including any changes that might have occurred during that time. These include:
  - Notification data for rubella infection and CRS, if available for the study period
  - Availability of surveillance data variables for analysis;
  - Date of rubella vaccination introduction including any changes over time. A description of the vaccination schedule and doses, and, if available, vaccination coverage data for the indicated doses for children and pregnant women;
  - Any rubella outbreaks during the study period;
  - Literature review of rubella and CRS surveillance activities in the country (if available).

- Health facilities where infants with CRS are likely to be treated, and a description of the availability of relevant data sources, such as hospital admission databases. These facilities include:
  - birth and neonatal facilities of general hospitals;
  - secondary or tertiary healthcare facilities with specialised doctors such as ophthalmologists, cardiologists, audiologists and neonatologists;
  - specialist care centres such as children hospitals, care centres for hearing disabilities and blindness.

- Health facilities where pregnant women are likely to be screened for rubella, and a description of the availability of relevant data sources. These facilities include:
  - general hospitals and private clinics that provide maternal and neonatal care;
  - obstetric centres.

- The availability of other data sources that may be used to document CRS cases, for example:
  - rubella laboratory registries;
  - birth records;
  - birth defect registries;
  - infant death registries;
  - pregnancy termination registries.

2 Certain countries may have national- and/or state-level hospital admission databases that can be used for the purpose of this study. In countries where this is not the case, investigators should evaluate the feasibility of including all relevant health facilities in their setting, and if necessary consider a sampling approach.
• Other factors to facilitate study implementation:
  – population denominator for study population;
  – Ethical/consent requirements.

Data collection
Annex 3 provides a structured data collection form for the purpose of this description.

CRS incidence calculation (estimated)
Based on CRS cases reported by the surveillance system, annual estimated CRS cumulative incidences (incidence proportions) can be calculated for each of the three years of the study's timeframe using the following numerator and denominator:

- Numerator: number of reported CRS cases among infants born between 1 January and 31 December in a given year.
- Denominator: number of live births in a given year (reported per 1 000 live births)

An overall estimated CRS incidence for all cases reported in the study period can be performed by calculating the average of the three annual incidences.

Methods study phase 2
Description
The aim of study phase 2 is to use the relevant data sources identified in study phase 1 to perform a retrospective review of documented CRS cases in the three years preceding the study's implementation.

Based on this review, an observed CRS incidence can be calculated for comparison with the estimated CRS incidence determined in study phase 1. Similarly, the PPV of the CRS surveillance system described in study phase 1 can also be compared to that of the retrospective review performed in study phase 2. As the specific methods that will be used in study phase 2 will vary between countries, here we list relevant methods that can be used depending on data source availability.

Study population
The study population will consist of infants born in the three-year study period (1 January Year 1 to 31 December Year 3), and their mothers for whom records in relevant data sources are available (see 'case identification and data sources').

Study period
The study will cover the three full years preceding the study's year of implementation.

Study setting
The study will primarily take place in the hospital setting and may include specialty departments and wards such as maternity, cardiology, ophthalmology, otorhinolaryngology and neurology.

Case definitions and classifications
The study will use the case definitions already implemented by EU/EEA countries for the notification of CRS and, if applicable, congenital rubella infection (CRI) cases. For most EU/EEA countries this will mean applying the EU case definition, but the decision of which case definition to use for the study should be taken by the country themselves. WHO case definitions for CRS and CRI are also available and could be considered in this study. Draft data collection sheets and analysis tables included in the annexes are based on the EU case definitions for CRS, but can be adapted as required [9].

EU and WHO case definitions for CRS and CRI (WHO definition only) which can be used in the study are detailed below (Table 1).

---

3 In this protocol, congenital rubella infection refers to infants infected with rubella before birth, but who have no signs or symptoms associated with CRS.
### Table 1. EU and WHO case definitions for CRS and CRI (WHO definition only)

<table>
<thead>
<tr>
<th></th>
<th>EU</th>
<th>WHO</th>
</tr>
</thead>
</table>
| **Clinical complications**| Group A: cataracts, congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy Group B: purpura, splenomegaly, microcephaly, developmental delay, meningo-encephalitis, radiolucent bone disease, jaundice that begins within 24 hours of birth | Any infant < 1 year of age or any stillborn* with:  
≥ 1 Group A conditions  
Or 1 Group A condition and 1 Group B condition |
| **Clinical criteria**      | ≥ 1 of the following:  
- Isolation of rubella virus from a clinical specimen  
- Detection of rubella virus nucleic acid  
- Rubella virus specific antibody response (IgM)  
- Persistence of rubella IgG between 6 and 12 months of age | - Positive blood test for rubella specific IgM^  
- Detection of rubella virus in specimens from pharynx or urine† |
| **Laboratory criteria**    | Any infant or stillborn born to a woman with a laboratory confirmed rubella infection during pregnancy | N/A |
| **Epidemiological criteria** | Any infant or stillborn born to a woman with a laboratory confirmed rubella infection during pregnancy | N/A |
| **CRS case classifications** | Probable case  
Any stillborn or infant either not tested or with negative laboratory results with ≥ 1 of the following:  
- An epidemiological link and ≥ 1 Group A condition(s)  
- Meeting the clinical criteria for CRS Confirmed case  
Any stillborn meeting the laboratory criteria Or  
Any infant meeting the laboratory criteria and one of the following two:  
- An epidemiological link  
- ≥ 1 Group A conditions | Suspected CRS case  
Any infant in whom a health worker suspects CRS based on the following signs: heart disease and/or suspicion of deafness and/or ≥ 1 eye sign#  
Or  
Any infant with mother with history of suspected or confirmed rubella during pregnancy |
|                           | Clinically confirmed CRS case  
Any infant who fulfils clinical criteria according to a qualified physician | Laboratory confirmed CRS case  
Any clinically confirmed CRS case that also fulfils the laboratory criteria |
|                           | Congenital rubella infection  
Any infant without clinical signs of CRS but who has a positive rubella-specific IgM test | |

* EU case definition only.

^ Not clinically confirmed

† For suspected CRS cases

# Cataract, diminished vision, nystagmus, squint, microphthalmus, congenital glaucoma
Case identification and data sources

CRS cases can be identified from routine notification data collected on rubella infection and CRS (if countries already have a system in place), and from the review of data sources identified in study phase 1.

Depending on available data sources by country, ICD codes, laboratory diagnoses or free text searches will be used to identify CRS cases. Country study protocols should therefore include a brief evaluation of the data sources available in their setting and indicate whether they are included in the study (Table 2). This table will be based on the data sources identified in study phase 1.

Table 2. Review of available data sources for the estimation of CRS burden in an EU country

<table>
<thead>
<tr>
<th>Data source</th>
<th>Available? (y/n)</th>
<th>Included in study? (y/n)</th>
<th>If available but not included, reason?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of rubella infection and CRS notified through the national surveillance system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital records*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella laboratory registries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth records</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defect registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant death registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy termination registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella in pregnancy registries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please indicate)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Principal data method; this is a minimum data source requirement for the study

The retrospective review of hospital records is the principal data collection method of this study and should therefore be performed by all countries choosing to implement the protocol. If available, it is recommended that additional data sources are included. Where ethical, logistical or other considerations preclude the inclusion of any such additional data sources, these should be clarified in the data source audit table.

A. Retrospective review of maternity and tertiary hospital records

CRS cases can be identified based on a review of maternity and tertiary hospital admissions for pregnant women and infants admitted in the three-year study timeframe. If the implementing country maintains a national hospital admission database, this data source could be used for purpose of this study. If a country does not have a national registry for hospital admissions, other available health facility admission registries at a state or regional level should be considered. If only individual hospital records are available, study investigators should contact individual hospital data managers and request them to extract all data for CRS cases based on the relevant ICD codes.

If an exhaustive review of health facility patient records is deemed unrealistic in the setting of the implementing country, a purposive sampling strategy could be considered to identify and select health facilities where CRS cases are most likely to be diagnosed for inclusion, such as paediatric hospitals. Furthermore, a random, representative sampling strategy is not advised, given that CRS remains a rare diagnosis in EU/EEA countries and incidence may vary greatly across hospitals, hospital wards and regions.

All patient records concerning eligible hospital admissions will be screened for the following:

In infants:

- ICD codes consistent with a CRS diagnosis (Annex 4)
- ICD codes consistent with clinical signs associated with CRS (Annex 4)

The review of infant hospitalisation records could focus on specific hospital departments or specialised care units, such as cardiology, ophthalmology, otorhinolaryngology and neurology.

In pregnant women:

- ICD codes consistent with a rubella diagnosis

For all infants for whom relevant ICD codes were documented, a more in-depth review of hospital and data records should be performed to evaluate whether the infant fulfils the criteria for a probable or confirmed CRS case in accordance with the relevant case definitions.

For all pregnant women with relevant documented ICD codes pregnancy outcomes should be reviewed, screened for diagnosis of CRS and assigned to a case classification if the relevant criteria are fulfilled.
B. Retrospective review of rubella laboratory registers

CRS cases can be identified based on a review of confirmed rubella infections in infants and pregnant women from a country’s national\(^4\) or sub-national reference laboratory for rubella in the three-year study timeframe.

All cases of laboratory-confirmed rubella in pregnant women or CRS in infants should be investigated and classified in accordance with the relevant CRS case definition.

C. Retrospective review of birth records

CRS cases can be identified by reviewing all birth records documented in the three-year study timeframe.

A birth record showing a mention of CRS diagnosis, any birth defect associated with CRS, or rubella infection in the mother should prompt a review of available medical and laboratory records in consideration of possible CRS classification in accordance with the relevant CRS case definition.

D. Retrospective review of birth defect registries

CRS cases can be identified by reviewing birth defect registry entries documented in infants in the three-year study timeframe.

A birth defect record showing a mention of CRS diagnosis, any birth defect associated with CRS, or of rubella infection in the mother should prompt a review of available medical and laboratory records in consideration of possible CRS classification in accordance with the relevant CRS case definition.

E. Retrospective review of infant death records

CRS cases can be identified based on a review of infant death registries for entries documented in the three-year study timeframe.

An infant death record showing a mention of CRS diagnosis or any birth defect associated with CRS should prompt a review of available medical and laboratory records with a view to possible CRS classification in accordance with the relevant CRS case definition.

F. Retrospective review of pregnancy termination records

Rubella in pregnancy cases can be identified based on a review of pregnancy termination records, including all pregnancy terminations documented in the three-year study timeframe.

A pregnancy termination record showing a mention of CRS diagnosis or any birth defect associated with CRS should prompt a review of available medical and laboratory records with a view to possible CRS classification in accordance with the relevant CRS case definition.

CRS case data collection

For every unique probable or confirmed CRS case documented by means of data collection methods A to F, a CRS case data collection form should be completed using available data sources.

A generic data collection form and accompanying data library are available in Annexes 5 and 6 respectively. The data collection form provided in this study protocol uses the EU case definition. If the case definition already implemented in a country is different to the EU case definition and/or countries would prefer to use the WHO case definition, this template can be adapted accordingly.

Redundancy checks should be performed to ensure that probable and confirmed CRS cases are not duplicates of CRS cases already identified by other data collection methods. For example, two separately documented CRS cases that share the same date of birth should be closely examined to ensure that they are in fact two unique cases.

---

\(^4\) According to the ECDC Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU/EEA countries in 2013, 27 countries have a national reference laboratory for CRS.
**Statistical analysis**

The data should be compiled and entered into a study database that can be used for the descriptive analysis, calculation of CRS incidence and PPV comparison. The choice of the statistical software lies with the investigational site.

A sample data analysis plan is included in Annex 7.

**CRS incidence calculation (observed)**

Based on CRS cases documented in the retrospective review of available data sources, annual observed CRS cumulative incidences (incidence proportions) can be calculated using as:

- **Numerator**: number of documented CRS cases identified in study phase 2 amongst infants born between 1 January and 31 December in a given year during the three-year study timeframe.
- **Denominator**: number of live births in a given year during the three-year study timeframe (report per 1,000 live births).

An overall observed CRS incidence for all cases reported in the study period can be calculated by finding the average of the three annual incidences.

See Table 2 in Annex 7 for an example of how annual and overall CRS cumulative incidences can be summarised for comparison purposes between estimated and observed incidence calculations.

Depending on the data sources available in countries, one additional option for assessing CRS incidence could be to use a pooled incidence calculation (estimating the population incidence on the basis of previously published incidence data, weighted by variance) [10]. A similar method has been applied in previous studies to estimate disease burden [11]. The pooled incidence can serve as an additional point of comparison for the estimated CRS incidence calculated in study phase 1.

**Tabulating CRS cases and calculating PPV**

Table 2 in Annex 7 illustrates how counts of documented CRS cases and corresponding PPV values can be presented, allowing for comparison of these indicators between the existing CRS surveillance system and the retrospective review carried out in study phase 2.

The PPV calculates the proportion of true, laboratory-confirmed CRS cases among all documented CRS cases, whether they are laboratory-confirmed or not.

The PPV of the existing CRS surveillance system (PPV$_{\text{surv}}$) can be calculated as follows, using the surveillance system's CRS case definitions:

\[
\text{PPV}_{\text{surv}} = \frac{\text{Number of CRS cases confirmed by laboratory testing}}{\text{Total number of all CRS cases documented by the CRS surveillance system}}
\]

The PPV of the retrospective review of hospital records and other available data sources performed in study phase 2 (PPV$_{\text{retro}}$) can be calculated as follows, using the same CRS case definitions:

\[
\text{PPV}_{\text{retro}} = \frac{\text{Number of confirmed CRS cases}}{\text{Number of probable CRS cases} + \text{number of confirmed CRS cases}}
\]

**Limitations**

**Case identification - ICD or other codes used for case identification**

There are limitations linked to the use of ICD codes for outcome determination. Previous studies for other diseases have found that ICD codes can have a low sensitivity and lead to underestimation of the burden of disease.

**Laboratory definitions**

The potential limitations arising from laboratory diagnostic tests should be mentioned: sensitivity and specificity of laboratory tests.

**Information bias**

The ICD classification may be influenced by the knowledge of rubella vaccination status.
**Reporting variability**
It is possible that the reporting of CRS related outcomes using ICD codes may not be consistent over time and the completeness of reporting may vary. In order to account for this discrepancy in hospital-related CRS outcomes, another ICD disease class could be described to see whether there is a difference in reporting over time.

**Data source representativeness**
The data sources used by each country in this study may not be representative and give an accurate reflection of the true burden of CRS.

**Country-specific limitations, e.g. duplicate cases**
Each country should describe the potential limitations applying to their own setting. One possible limitation for each country could be the inability to identify duplicate cases, especially in situations where no unique identifier is used in the national surveillance systems. In this case, specific algorithms using a key variable, such as date of birth, need to be used.

**Ethical considerations and approval**
Depending on the nature and national regulations of each country, ethical approval may be needed. Each country is to investigate and specify the ethics committee requirements that may apply for the study.

**Procedures for the management and follow-up of suspected CRS cases**
Depending on available data sources used for retrospective case-finding in this study, each country will need to adapt their own standard operating procedures (SOPs) for the investigation and management of suspected CRS cases accordingly.

**Roles and responsibilities**
The roles and responsibilities of the study team members at each study site should be well defined (e.g. principal investigator, assistant, etc.)

Each country should describe the team member’s roles and responsibilities.

**Budget**
The main budget line should be specified:
- Payment of study site members
- Payment for data extraction (if applicable)
- Application fee to ethical committee (if applicable)
- Others.

Each country is to define the budget lines.

**Communication of results and expected outputs**
The generic study protocol will be adapted and implemented in specific EU/EEA countries. A report or scientific article may be written to summarise how the generic study protocol was developed and/or to present the main findings following implementation.
References


Annex 1. Keywords used in literature search to retrieve peer-reviewed scientific abstracts documenting CRS burden assessment methodologies

**Date:** 4 April 2017  
**Purpose of the search:** To retrieve peer-reviewed scientific paper that discussed methodologies and approaches to document the burden of CRS at local, regional and national level.

**Keywords**

<table>
<thead>
<tr>
<th>POPULATION: Pregnant women</th>
<th>OUTCOME: CRS</th>
<th>INTERVENTION: Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Pregnancy&quot;[Mesh]</td>
<td>CRS</td>
<td>Rubella</td>
</tr>
<tr>
<td>Pregnan*</td>
<td>congenital rubella syndrome</td>
<td>German measles</td>
</tr>
<tr>
<td>Gestat*</td>
<td>congenital malformation</td>
<td></td>
</tr>
<tr>
<td>Childbearing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of articles retrieved: 771.
## Annex 2. Literature review of CRS burden assessment methodology for retrospective case finding

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Country</th>
<th>Assessment method</th>
<th>Study population</th>
<th>Data sources</th>
</tr>
</thead>
</table>
| Cozza et al., 2015 (12) | Italy          | Retrospective case-finding by scanning hospital discharge registries to identify hospitalisations for rubella in pregnancy and CRS. In addition, searched clinical history of CRS mothers in the delivery assistance certificate registry. | Mothers/new-borns with discharge ICD codes of rubella in pregnancy or congenital rubella. | -Hospital Discharge Registry  
-Delivery Assistance Certificate Registry  
-Individual Hospital Record |
| Jiménez et al., 2007 (13) | Costa Rica     | Determined national CRS burden by i) observed: retrospective review of cases seen in the national paediatric referral hospital (patient files + laboratory reports); ii) calculation of the expected number of CRS cases based on rubella cases in women of childbearing age reported to the compulsory surveillance system; and iii) the estimation of the number of CRS cases based on analytical models. | All patients registered in the admissions database with CRS associated ICD codes (listed in article) or patients under three months of age for who a positive IgM test was recorded in laboratory records. | -Hospital clinical files  
-Hospital laboratory reports |
| Toda et al., 2015 (14) | Vietnam        | Developed a CRS sentinel surveillance system in three national paediatric hospitals. Six months of cases were retrospectively enrolled into the surveillance data, followed by 18 months of prospective data collection. Suspected cases were identified based on indications of congenital heart disease, cataracts, hearing impairment, and/or infants from mothers with a history of suspected or confirmed rubella infection in pregnancy. Suspected cases were investigated and blood specimens taken for IgM. | Infants with suspected CRS: at least one condition of congenital heart disease, cataracts or hearing impairment and/or those with mothers with a history of suspected or confirmed rubella infection in pregnancy. | -Case investigation form  
-Hospital records  
-Laboratory records |
| Upreti et al., 2011 (15) | Nepal          | Surveillance used the existing measles surveillance system to introduce rubella surveillance in two steps: i) IgM negative cases for measles were tested for rubella, ii) IgM testing for both measles and rubella were done for all suspected cases. 2) Sentinel surveillance: enrolled all women of childbearing age who attended outpatient departments of 10 hospitals. Questionnaires were administered and blood samples taken for rubella IGG testing; 3) Cross sectional study performed in cohort of hearing-impaired school children school, children were examined for ocular morbidity indications and audiometric testing. | All children enrolled at a school for the deaf. | -Questionnaire: sociodemographic and medical history |
| Hyde et al., 2015 (18) | Brazil         | CRS cases were identified through medical records of regional health departments, paediatric specialty services (cardiology, otolaryngology, ophthalmology, and fetal medicine) at six referral hospitals, and two centres providing services to deaf children. | Children with birth defects clinically compatible with CRS. | -Medical records  
-Study questionnaire (demographic data, History of RUBV infection and related clinical information, rubella vaccination status) |
| Zimmerman et al., 2001 (17) | United States | Review of computerised discharge data of infants at an El Paso hospital. Cases were selected on the basis of charts that contained ICD-9 codes for conditions associated with CRS. Article suggests that a good way to monitor for CRS at the hospital level is to perform rubella-specific IgM tests on infants who fail hearing, in particular in higher risk groups. | Infants with hospital discharge ICD codes associated with CRS (list provided in article). | -Hospital discharge data |
| Durski et al., 2013 (18) | Solomon Islands | Prospective CRS surveillance was conducted at the neonatal nursery, paediatric and post-natal wards, and the paediatric cardiology and ophthalmology clinics of the study hospital. Retrospective case finding was performed by reviewing medical records. | Infants fulfilling the WHO case definitions (suspected, clinically confirmed and laboratory confirmed). | -Medical records |
### Authors, Year | Country | Assessment method | Study population | Data sources |
--- | --- | --- | --- | --- |
Giambi et al, 2015 (19) | Italy | Descriptive analysis of CRS cases reported to the national surveillance system using EU case definitions. Calculated CRS incidence based on confirmed and probable cases. To assess under-reporting, an evaluation of the completeness of the surveillance system compared to CRS diagnoses documented in hospital discharge records was performed. Other possible sources mentioned in the article includes 'delivery-assistance certificate registers', which includes clinical histories of mothers or babies with CRS, laboratory data, and whether reporting can be integrated. | All CRS cases notified to the CRS and rubella in pregnancy surveillance system. | -Surveillance system database |
Sugishita et al, 2015 (20) | Japan | Analysis based on cases extracted from the national surveillance system. All physicians are required to report all laboratory confirmed CRS cases. | All CRS cases notified to the CRS surveillance system. | -Surveillance system database |
Khandaker et al, 2014 (21) | Australia | Describes a sentinel surveillance system for reporting confirmed and suspected CRS cases. Implemented a surveillance protocol with standardized case definitions and instruments in selected sentinel sites. Surveillance sites consisted of referral health facilities with resources to perform adequate neonatal and infant clinical/laboratory diagnosis and management. | All CRS cases notified to one of the two CRS surveillance systems. | -Surveillance system database |
Whittembury et al, 2011(22) | Peru | Describes a surveillance system for CRS cases: 1) National Notifiable Diseases Surveillance System which relies on passive case reporting by clinicians or by reporting positive laboratory findings 2) Australian Paediatric Surveillance Unit undertakes active surveillance via child health clinicians and sends them monthly report cards about the conditions under surveillance. | All CRS cases notified to the CRS surveillance system. | -Surveillance system database |
Choe et al, 2010 (23) | Republic of Korea | Reviews CRS surveillance system and suggests improvements. Used health insurance data for comparison. | All CRS cases notified to the CRS surveillance system. | -Surveillance system database -Korean Health Insurance Review Agency -Laboratory surveillance system |
Lanzieri et al, 2007 (24) | Brazil | Analysis based on notification data. | All CRS cases notified to the surveillance system. | -CRS surveillance system database |
Lanzieri et al, 2004 (25) | Brazil | Authors performed an analysis of rubella notification data and a retrospective review for CRS in seven hospitals. They searched for conditions compatible with CRS or with a maternal rubella history (ICD10). Standardized questionnaires were administered to all suspected cases. CRS incidence estimates were calculated. Cost of CRS disease to the national health system was also estimated. Also compared the number of compatible CRS cases notified through the surveillance system to the number identified in the hospital record review. | Infants with conditions compatible with CRS or a maternal rubella history + households of cases (although article does not seem to report on these findings) | -Hospital admission/discharge records -Study questionnaire (demographics, clinical signs and symptoms, birth weight, laboratory results, maternal data) - Costing data from the National Health System |
Katow et al, 2004 (26) | Japan | Describes the use of a questionnaire sent out to hospitals as a tool to document the number of CRS cases. Around 1000 hospitals were sent the questionnaire. The authors also describe sourcing data from publications and meeting presentations. | All suspected CRS cases reported by questionnaire or notified to the infectious disease surveillance system. | -Completed questionnaires sent out to hospitals and authors of relevant journals and conference presentations -National infectious disease surveillance system database -National Institute of Infectious Diseases registry |
Lanzieri et al, 2003 (27) | Brazil | Describes a rubella outbreak investigation and the CRS surveillance implemented afterwards. Enhanced CRS surveillance was done by i) follow up of pregnant case patients; ii) active CRS case finding at health facilities in the region, where hospital admission/discharge registers and medical, nursery and laboratory registry books were reviewed retrospectively. Prospective active surveillance was implemented through weekly visits to the health facilities. | Pregnant woman who tested positive for rubella during the outbreak All suspected CRS cases identified as part of the prospective surveillance activities. | -Hospital admission/discharge registries -Medical, nursery, laboratory registry -Books -Patient medical charts -Standardized case investigation questionnaires |
<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Country</th>
<th>Assessment method</th>
<th>Study population</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venerosi et al, 2001</td>
<td>Australia</td>
<td>Describes the use of a birth defect registry in Western Australia and the various information sources that it uses. It evaluates the benefit of supplementing the data collected by the registry with pregnancy termination data recorded in the state's Hospital Morbidity Data System.</td>
<td>All cases coded as terminations of pregnancy for fetal abnormality (the study does not focus solely on CRVCRS, but also other causes of early termination).</td>
<td>-Birth defect registry -Hospital Morbidity Data System</td>
</tr>
<tr>
<td>Lawn et al, 2000</td>
<td>Ghana</td>
<td>Congenital rubella syndrome cases were identified through prospective surveillance and retrospective surveys of hospital records. A rubella serosurvey of pregnant urban and rural women was performed.</td>
<td>Not specified</td>
<td>-Hospital records</td>
</tr>
<tr>
<td>Cutts et al, 1999</td>
<td>NA</td>
<td>Reviewed the literature to identify studies of rubella antibody prevalence in developing countries that were conducted on populations with no major selection bias, prior to wide-scale rubella vaccination in the country. Used a simple catalytic model to describe age-specific prevalence of susceptibility to rubella virus infection in given populations. Estimates of the incidence of infection among pregnant women were calculated.</td>
<td>Literature review: papers on seroprevalence of rubella in developing countries.</td>
<td>NA</td>
</tr>
<tr>
<td>Panagiotopoulos et al</td>
<td>Greece</td>
<td>Performed a literature review to document the events leading to a rubella epidemic in Greece in 80s-90s. Performed a retrospective survey to document CRS cases that ensued. As assessment of the burden of CRS was made based on available (Greek) literature, including peer-reviewed articles, government reports and databases. No formal CRS surveillance system was in place during the timeframe covered in the article.</td>
<td>Literature review: all available information on immunisation policies and practices, vaccination coverage, serologically detected immunity, occurrence of rubella and CRS in Greece.</td>
<td>-Greek medical literature for publications on rubella and CRS, conference proceedings, government documents.</td>
</tr>
<tr>
<td>Sullivan et al, 1999</td>
<td>Australia</td>
<td>The epidemiology of rubella and CRS was documented using two surveillance systems: (i) National Notifiable Diseases Surveillance System was used to document rubella cases; (ii) The Australian Paediatric Surveillance Unit was used to document CRS cases.</td>
<td>All cases of CRS documented in any of the two described surveillance systems.</td>
<td>-National Notifiable Diseases Surveillance System -Australian Paediatric Surveillance Unit</td>
</tr>
<tr>
<td>Cheffins et al, 1998</td>
<td>Australia</td>
<td>A population-based descriptive study using data from South Australian notiﬁcations of disease, births and terminations of pregnancy, the rubella immunisation programme, antenatal rubella antibody screening and paediatric hospital case records.</td>
<td>All cases of CRS notiﬁed to the South Australian disease notification registry, documented rubella-related terminations of pregnancy</td>
<td>-South Australian disease notification registry -Births and terminations of pregnancy registry -Rubella immunisation programme -Antenatal rubella antibody screening data -Paediatric hospital case records</td>
</tr>
<tr>
<td>Schluter et al, 1996</td>
<td>United States</td>
<td>Described clinical presentation and epidemiology of US infants with CRS and identiﬁed missed opportunities for maternal vaccination. Data from CRS cases reported to the National Congenital Rubella Syndrome Registry (NCRSR) from 1985-1996 was analysed.</td>
<td>CRS cases reported to the National Congenital Rubella Syndrome Registry.</td>
<td>-National Congenital Rubella Syndrome Registry</td>
</tr>
<tr>
<td>Condon et al, 1993</td>
<td>Australia</td>
<td>Review of records of the Birth Defects Registry for cases of CRS; surveys of obstetricians for terminations of pregnancy for maternal rubella infection, schoolgirls eligible for the 1991 annual rubella vaccination campaign and immunisation records.</td>
<td>All cases of CRS reported in the WA Birth Defects Registry.</td>
<td>-Western Australian Birth Defects Registry -Survey of pregnancy terminations for MRI -Survey of annual rubella vaccination campaign Immunisation records</td>
</tr>
<tr>
<td>Ueda et al, 1986</td>
<td>Japan</td>
<td>A nationwide survey of deaf children with a history of maternal rubella in special schools for the deaf in Japan.</td>
<td>Deaf children with a history of maternal rubella in special schools for the deaf.</td>
<td>-Study questionnaire</td>
</tr>
</tbody>
</table>
Annex 3. Data collection form for phase

### Section 1: CRS surveillance and context

**Documenting the CRS surveillance system and other public health indicators relevant to the context of the study setting.**

#### A. Current CRS surveillance system

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a CRS surveillance system in your setting?</td>
<td>(y/n)</td>
</tr>
<tr>
<td>What type of data is available?</td>
<td></td>
</tr>
<tr>
<td>If case-based, which data are collected?</td>
<td>(list variables)</td>
</tr>
<tr>
<td>What is the legal basis of reporting?</td>
<td></td>
</tr>
<tr>
<td>What type of surveillance system exists?</td>
<td></td>
</tr>
<tr>
<td>Comprehensive, sentinel, indicate whether active, passive or both</td>
<td></td>
</tr>
<tr>
<td>What is the source of reporting?</td>
<td></td>
</tr>
<tr>
<td>Physicians, hospitals, laboratories, other</td>
<td></td>
</tr>
<tr>
<td>Is there a case definition used?</td>
<td></td>
</tr>
<tr>
<td>(y/n; if yes, specify whether compatible with EU or WHO case definition)</td>
<td></td>
</tr>
<tr>
<td>What type of cases are reported?</td>
<td></td>
</tr>
<tr>
<td>Probable, confirmed, discarded, other</td>
<td></td>
</tr>
<tr>
<td>Is zero-reporting required?</td>
<td>(y/n)</td>
</tr>
<tr>
<td>Does your country have a CRS reference laboratory?</td>
<td>(y/n)</td>
</tr>
</tbody>
</table>

**Is underreporting of CRS monitored in your setting? If so, how?**

#### B. Rubella vaccination

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>When was rubella vaccination introduced in your setting?</td>
<td>(year)</td>
</tr>
<tr>
<td>Have rubella vaccination strategies changed since the introduction?</td>
<td>(y/n; if yes, clarify)</td>
</tr>
<tr>
<td>Is vaccination coverage data available for the study period?</td>
<td>(y/n; if yes, clarify)</td>
</tr>
</tbody>
</table>

#### C. Rubella outbreaks

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did any rubella outbreaks occur during the study period?</td>
<td>(y/n; if yes, clarify)</td>
</tr>
</tbody>
</table>

### Section 2: Healthcare institutes for pediatric care

**Identification of healthcare institutes where infants with CRS are likely to be diagnosed or where they receive care for symptoms associated with CRS.**

Which of the following healthcare facilities are present in the study setting? Are patient records stored in this facility? Can these records be accessed by the study team?

#### Facility present? records stored? records accessible?

<table>
<thead>
<tr>
<th>Facility present?</th>
<th>records stored?</th>
<th>records accessible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Section 3: Healthcare institutes for maternal care where rubella in pregnancy might be diagnosed

**Identification of healthcare institutes where pregnant women are likely to be assessed for CRS.**

Which of the following healthcare facilities are present in the study setting? Are patient records stored in this facility? Can these records be accessed by the study team?

#### Facility present? records stored? records accessible?

<table>
<thead>
<tr>
<th>Facility present?</th>
<th>records stored?</th>
<th>records accessible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics and gynaecology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetric centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwifery centre</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section 4: The availability of other data sources that may be used to document CRS cases
Details on the availability of additional data sources for the identification of CRS cases, besides those provided by health facility records.

Which of the following healthcare facilities are present in the study setting? Are patient records stored in this facility? Can these records be accessed by the study team?

<table>
<thead>
<tr>
<th>Other relevant data sources</th>
<th>Records stored?</th>
<th>Records accessible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella laboratory registries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defect registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant death registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy termination registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella in pregnancy registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Section 5: Other factors to facilitate study implementation
Details on the availability of denominator data for incidence calculations, and information on ethical requirements for study implementation

A. Availability of a suitable study population denominator for incidence calculations

<table>
<thead>
<tr>
<th>Number of live births per year available?</th>
<th>Other suitable denominators?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(y/n)</td>
<td>(y/n; if yes, clarify)</td>
</tr>
</tbody>
</table>

B. Ethical considerations relevant to study implementation

<table>
<thead>
<tr>
<th>Ethics committee review required?</th>
<th>Other ethical considerations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(y/n; if yes, specify name and expected turnaround time)</td>
<td>(y/n; if yes, clarify)</td>
</tr>
</tbody>
</table>
Annex 4. International Classification of Disease (ICD)-9 or ICD-10 discharge codes consistent with one or more manifestations of CRS to be used in the study

1. Congenital rubella syndrome (771.0/P35)
2. Cataracts (743.3/Q12)
3. Congenital glaucoma (743.2/Q15-H40)
4. Deafness and hearing impairment (389.1/H90)
5. Congenital heart disease (745, 747/Q20-Q26)
6. Dermal erythropoiesis (759.89/P83.8)
7. Microcephaly (742.1/Q02)

  (http://apps.who.int/classifications/icd10/browse/2016/en)
Annex 5. CRS data collection form (phase 2)

A. General
1. Study site.
2. Name of the healthcare institution/hospital.
3. Source of report(s):
   - Death register
   - Laboratory
   - Hospital register
   - Birth register
   - Birth defect register
   - Rubella in pregnancy register
   - Other (please specify)

B. Demographics
4. Name of patient.
5. Name of parent/guardian.
6. Date of Birth (MM/DD/YY)
7. Sex: Male, Female
8. Country of residence:
9. Were you born in your country of residence: Yes, No
10. Country of birth:

C. Present illness/ outcome
9. Date of detection of signs and symptoms of CRS (MM/DD/YY)
10. Date of hospital admission.
11. Date of hospital discharge.
12. First two ICD codes available for same individual in same hospitalisation episode (if more than one diagnosis)
13. Outcome of the event
   - Still under treatment
   - Died
   - Transferred
   - Discharged
14. Date of discharge, transfer or death (where relevant) (MM/DD/YY)
15. If transferred, name of hospital
16. Was the patient transferred from another hospital: Yes, No
17. If “yes” where was the patient transferred from?
D. Clinical

(Please circle the appropriate responses) 1=Yes; 2=No; 9=Unknown

18. Was the patient diagnosed with CRS? Yes (1) No (2) Unknown (9)

If yes (Y), complete the CRS clinical and laboratory information below.

19. Did the patient present with any of the following symptoms/signs?

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Y</th>
<th>N</th>
<th>Unk</th>
<th>Clinical Characteristics</th>
<th>Y</th>
<th>N</th>
<th>Unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataracts</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Mental Retardation</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Pigmentary Retinopathy</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Microcephaly</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Congenital Glaucoma</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Meningoencephalitis</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Hearing Impairment</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Hepatosplenomegaly</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Heart Defect (Congenital)</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Jaundice</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Patent Ductus Arteriosis</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Purpura</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>Radiolucent bone disease</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary Stenosis</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Septal Defect</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

E. Laboratory Diagnosis

20. Was the diagnosis of CRS confirmed by a laboratory? Y(1) N(2) Unk(9)

21. If yes, what type of laboratory testing was done? (Circle all that apply)
   a) Serology (IgM) (date) ___/__/__
   b) Sustained IgG (date) ___/__/__
   c) Virus isolated (from clinical specimens – throat swab, urine) (date) ___/__/__
   d) PCR (from clinical specimens – throat swab, urine) (date) ___/__/__
   e) Other (specify) _____________________ (date) ___/__/__

F. Maternal history

22. Age of mother at time of delivery (years)……………………

23. Country of birth……………………

24. Gravidity……….. Parity……………..

25. Did the mother have a rubella-like illness during pregnancy Y(1) N(2) Unk(9)

26. If yes, period of gestation at the time of illness (in weeks)……………………

27. Which of the following signs and symptoms were present:

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
<th>Unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Other (specify)…………….</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

28. Was rubella infection diagnosed during pregnancy? Yes (1) No (2) Unknown (9)

If yes, when (date) ____/__/__
**G. Mother’s immunisation history**

29. Was the mother vaccinated against rubella?  Yes (1) No (2) Unknown (9)

30. If yes, how many doses
   1
   2

31. Vaccination status is documented by:
   Card  
   History

32. Date of vaccination (MM/DD/YY) __/__/__

**H. Contact history**

31. Was the mother in contact with a known or suspected case of rubella during the index pregnancy?  
   Yes (1) No (2) Unknown (9)

32. If yes, period of gestation in weeks………………

Other comments:
………………………………………………………………………………………………………………………………………………………………………………………………………………………………
………………………………………………………………………………………………………………………………………………………………………………………………………………………………
………………………………………………………………………………………………………………………………………………………………………………………………………………………………
………………………………………………………………………………………………………………………………………………………………………………………………………………………………

**Final classification based on EU case definitions**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable case</td>
<td></td>
</tr>
<tr>
<td>Confirmed case</td>
<td></td>
</tr>
</tbody>
</table>

Date Completed ___/___/___  Person Completing (initials) ______

**EU Case definitions**

**Probable case**
Any stillborn or infant either not tested OR with negative laboratory results with at least one of the following two:
- An epidemiological link AND at least one of the conditions listed in the category ‘A’ CRS clinical criteria
- Meeting the clinical criteria for CRS

**Confirmed case**
Any stillborn meeting the laboratory criteria
OR
Any infant meeting the laboratory criteria AND at least one of the following two: —
- An epidemiological link
- At least one of the conditions listed in the category ‘A’ CRS clinical criteria.
### Variable name | Type | Values and coding | Description
--- | --- | --- | ---
**dateofbirth** | Date | DD/MM/YYYY | Date of birth
sex | Numeric (binary) | 0=Male 1=Female | Sex
**sourcereport** | Numeric (categorical) | 1=Death register 2= Laboratory 3=Hospital register 4=Birth register 5=Birth defect register 6= Rubella in pregnancy register | Source of report/register
Country_residence | Numeric (categorical) | Categorize all countries with a specific number | Specific country of residence from the selective list
Birthcountry_residence | Numeric (categorical) | | Birthplace the same as country of residence
datedetected | Date | DD/MM/YYYY | Date of detection of signs and symptoms of CRS
outcome_patient | Numeric (categorical) | 1=Still under treatment 2= Died 3=Transferred 4= Discharged | Outcome of CRS
dateadm | Date | DD/MM/YYYY | Date of hospital admission
datedisch | Date | DD/MM/YYYY | Date of hospital discharge
date_disch_trans_death | Date | DD/MM/YYYY | Date of discharge, transfer or death
hostrans | Numeric (binary) | 0= No 1=Yes | Patient transferred from another hospital
patientdiagnos | Numeric (categorical) | 0=Yes 1= No 9=Unk | Patient diagnosed with CRS
clinical_signs_symptoms | Numeric (categorical) | 0=Yes 1= No 9=Unk | Clinical characteristics of patient
lab_diagnos | Numeric (categorical) | 0=No 1= Yes 9=Unk | Laboratory diagnosis of CRS
lab_test | Numeric (categorical) | 1=SEROLOGY (IgM), 2= Sustained IgG, 3=Virus isolated from clinical specimen(blood, urine, throat swab), 4= PCR, 5=Other | Laboratory test used to confirm diagnosis
lab_testingdate | Date | DD/MM/YYYY | Date laboratory testing was performed
lab_sampletype | Numeric (categorical) | 1= Blood, 2= urine, 3= throat swab, 4=Other | Type of sample analysed
motherage_delivery | Numeric | XX | Age of mother at time of delivery
Mother_birthcountry | Numeric (categorical) | Categorize all countries with a specific number | Country of birth of the mother
rubella_illnesspregnancy | Numeric (categorical) | 0=No 1= Yes 9=Unk | Mother had rubella-like illness during pregnancy
rubella_illness_gestweek | Numeric | 1-XX | Gestation period in weeks mother was ill with rubella-like illness
mother_signsandsymptoms | Numeric (categorical) | 0=No 1= Yes 9=Unk | Signs and symptoms of mother
rubelladiagnos_pregnancy | Numeric (categorical) | 0=No 1= Yes 9=Unk | Rubella diagnosis during pregnancy
mother_vaccinated | Numeric (binary) | 0= No 1=Yes | Mother vaccinated against rubella
mother_dateofvacc | Date | DD/MM/YYYY | Date of vaccination of mother
mother_contact | Numeric (categorical) | 0=No 1= Yes 9=Unk | Mother in contact with a suspected or confirmed rubella case during pregnancy
rubella_contact_gestweek | Numeric | 1-XX | Gestation period in weeks mother was in contact with a suspected or confirmed rubella case
## Annex 7. Data analysis plan

### Table 1. Description of CRS cases identified in the retrospective review study

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>n</th>
<th>%</th>
<th>Clinical characteristics patient</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td>Patient diagnosed with CRS?</td>
<td>yes</td>
<td>-</td>
</tr>
<tr>
<td>prepartum</td>
<td>-</td>
<td>-</td>
<td>no</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0-3 months</td>
<td>-</td>
<td>-</td>
<td>unknown</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4-8 months</td>
<td>-</td>
<td>-</td>
<td>documented signs/symptoms</td>
<td>cataracts</td>
<td>-</td>
</tr>
<tr>
<td>9-12 months</td>
<td>-</td>
<td>-</td>
<td>congenital glaucoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td>hearing impairment</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>aortic stenosis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>male</td>
<td>-</td>
<td>-</td>
<td>unknown</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>female</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Nationality of mother</strong></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>country a</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>country b</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>country c</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>...</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Source of CRS reports</strong></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Data source</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>hospital register</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>laboratory</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>death register</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>birth register</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>...</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CRS EU case definition type</strong></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case type</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>probable</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>confirmed</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rubella status mother</strong></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRI diagnosed during pregnancy?</td>
<td>yes</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated before pregnancy?</td>
<td>yes</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Number and incidence of suspected and confirmed CRS cases by year; routine surveillance vs retrospective review

<table>
<thead>
<tr>
<th></th>
<th>Routine CRS surveillance</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>CRS Retrospective Review</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n prob</td>
<td>n conf</td>
<td>n total</td>
<td>i conf</td>
<td>PPV</td>
<td>n prob</td>
<td>n conf</td>
<td>n total</td>
</tr>
<tr>
<td><strong>Year 1</strong></td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>...</td>
<td>0.33</td>
<td>24</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td><strong>Year 2</strong></td>
<td>21</td>
<td>14</td>
<td>35</td>
<td>...</td>
<td>0.40</td>
<td>26</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td><strong>Year 3</strong></td>
<td>24</td>
<td>17</td>
<td>41</td>
<td>...</td>
<td>0.41</td>
<td>25</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>65</td>
<td>41</td>
<td>106</td>
<td>...</td>
<td>0.39</td>
<td>75</td>
<td>52</td>
<td>127</td>
</tr>
</tbody>
</table>

n = number of cases
i = cumulative incidence per 1000 live births in the indicated year
prob = probable cases
conf = confirmed cases
total = suspected + confirmed cases
PPV = positive predictive value

Note: mock data used for illustrative purposes
ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.


HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);

- more than one copy or posters/maps:
  from the European Union’s representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications: