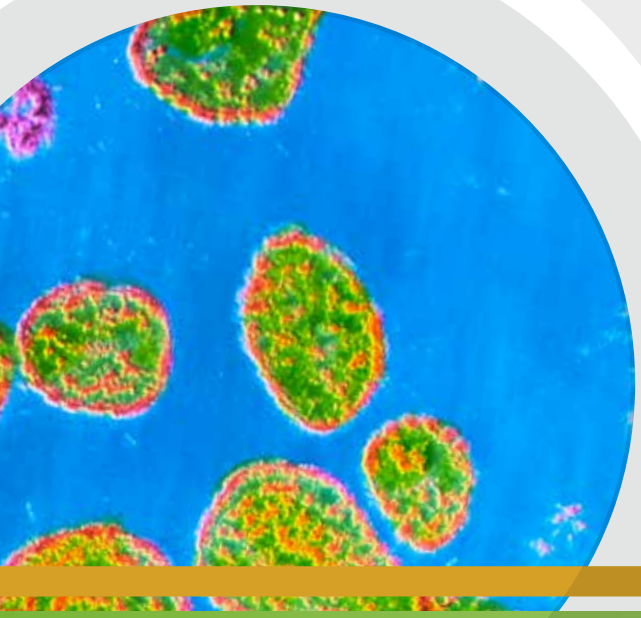
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL



TECHNICAL REPORT

Retrospective surveillance and enhanced case-finding of congenital rubella syndrome cases

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

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.

Suggested citation: European Centre for Disease Prevention and Control. Retrospective surveillance and enhanced case-finding of congenital rubella syndrome cases. Stockholm: ECDC; 2018

Stockholm, September 2018

ISBN 978-92-9498-281-0
doi: 10.2900/887027
Catalogue number TQ-05-18-064-EN-N

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 4
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

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

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 captures 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 infant[1] 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[2]. 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[2]. 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[3] (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)

	EU	WHO
Clinical complications associated with CRS	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	
Clinical criteria	Any infant < 1 year of age or any stillborn* with: ≥ Group A conditions Or 1 Group A condition and 1 Group B condition	
Laboratory 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†
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 - ≥ 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 signs# **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

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

* 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_{surv}) can be calculated as follows, using the surveillance system's CRS case definitions:

$$PPV_{surv} = \frac{\text{Number of CRS cases confirmed by laboratory testing}}{\text{Total number of all CRS cases documented by the CRS surveillance system}}$$

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

$$PPV_{retro} = \frac{\text{Number of confirmed CRS cases}}{\text{Number of probable CRS cases + number of confirmed CRS cases}}$$

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

1. Grant G, Reef S, Patel M, Knapp J, Dabbagh A. Progress in Rubella and Congenital Rubella Syndrome Control and Elimination — Worldwide, 2000–2016. (MMWR), Morb Mortal Wkly Rep. 2017;66(45):1256–1260.
2. World Health Organization Regional Office for Europe: Surveillance guidelines for Measles, Rubella and Congenital Rubella Syndrome in the WHO European Region-updated December 2012. 2009;24–33. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/measles-and-rubella/publications/2012/surveillance-guidelines-for-measles,-rubella-and-congenital-rubella-syndrome-in-the-who-european-region,-update-december-2012
3. World Health Organization Regional Office for Europe. Renewed commitment to measles and rubella elimination and prevention of congenital rubella syndrome in the WHO European Region by 2015 - Regional Committee for Europe. 2010. p. 1–4.
4. World Health Organization Regional Office for Europe. Eliminating measles and rubella and preventing congenital rubella infection - WHO European Region Strategic Plan. 2005. Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/79028/E87772.pdf
5. World Health Organization Regional Office for Europe: Eliminating measles and rubella - Framework for the verification process in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2012. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/158304/EURO_MR_Elimin_Verification_Processv2.pdf
6. European Commission. Commission Implementing Decision 2012/506/EU of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Counci. Off J Eur Union [Internet]. 2012;55(3):1–263. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:262:0001:0057:EN:PDF
7. European Centre for Disease Prevention and Control. Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU / EEA countries [Internet]. ECDC Technical report. 2013. 1-44 p. Available from: http://ecdc.europa.eu/en/publications/Publications/survey-rubella-pregnancy-congenital-surveillance-systems-may-2013.pdf
8. World Health Organization Regional Office for Europe. Fourth meeting of the European Regional Verification Commission for Measles and Rubella Elimination. Copenhagen: WHO; 26-29 October 2015. Available at: http://www.euro.who.int/__data/assets/pdf_file/0011/304958/4th-RVC-meeting-report.pdf?ua
9. World Health Organization. Introducing rubella vaccine into national immunization programmes- A step-by-step guide. Geneva: WHO. 2015. p. 1–76. Available at: http://www.who.int/immunization/documents/who_ivb_15.07/en/
10. Woodward M. Meta-analysis. In Epidemiology: Study Design and Data Analysis. Third Edition. US; 2014. Chapman and Hall/CRC, pp. 565-603.
11. Ling ML, Apisarnthanarak A, Madriaga G. The burden of healthcare-associated infections in south-east Asia: A systematic literature review and meta-analysis. Clin Infect Dis. 2015;60(11):1690–9.
12. Cozza V, Martinelli D, Cappelli MG, Tafuri S, Fortunato F, Prato R. Further efforts in the achievement of congenital rubella syndrome/rubella elimination: Alternative sources of information for retrospective case finding, Puglia Region, Italy, 2003-2011. Hum Vaccines Immunother. 2015;11(1):220–4.
13. Jiménez G, Avila-Aguero ML, Morice A, Gutiérrez H, Soriano A, Badilla X, et al. Estimating the burden of congenital rubella syndrome in Costa Rica, 1996-2001. Pediatr Infect Dis J [Internet]. 2007;26(5):382–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17468646
14. Toda K, Reef S, Tsuruoka M, Iijima M, Dang TH, Duong TH, et al. Congenital rubella syndrome (CRS) in Vietnam 2011-2012-CRS epidemic after rubella epidemic in 2010-2011. Vaccine. 2015;33(31):3673–7. Available from: http://dx.doi.org/10.1016/j.vaccine.2015.06.035
15. Upreti SR, Thapa K, Pradhan YV, Shakya G, Sapkota YD, Anand A, et al. Developing rubella vaccination policy in Nepal - Results from rubella surveillance and seroprevalence and congenital rubella syndrome studies. J Infect Dis. 2011;204(SUPPL. 1):433–8.
16. Hyde TB, Sato HK, Hao L, Flannery B, Zheng Q, Wannemuehler K, et al. Identification of serologic markers for school-aged children with congenital rubella syndrome. J Infect Dis. 2015;212(1):57–66.
17. Zimmerman L, Reef SE. Incidence of congenital rubella syndrome at a hospital serving a predominantly Hispanic population, El Paso, Texas. Pediatrics. 2001;107(3):E40.
18. Durski KN, Tituli C, Ogaoga D, Musto J, Joshua C, Dofai A, et al. An outbreak investigation of congenital rubella syndrome in Solomon Islands, 2013. World Heal Organiztion West Pacific Reg. 2016;7(1):10–3. Available from: http://ojs.wpro.who.int/ojs/index.php/wpsar/article/view/406/648
19. Giambi C, Filia A, Rota M, Del Manso Di Giacomo M, Declich S, Nacca G, et al. Congenital rubella still a public health problem in Italy: analysis of national surveillance data from 2005 to 2013. Eurosurveillance. 2015;20(16):1–10. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=25953272%5Cnhttp://www.eurosurveillance.org/images/dynamic/EE/V20N16/art21103.pdf%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015995229
20. Sugishita Y, Shimatani N, Katow S, Takahashi T, Hori N. Epidemiological characteristics of rubella and congenital rubella syndrome in the 2012–2013 epidemics in Tokyo, Japan. Jpn J Infect Dis. 2015;68(2):159–65.
21. Khandaker G, Zurynski Y, Jones C. Surveillance for congenital rubella in Australia since 1993: Cases reported between 2004 and 2013. Vaccine. 2014;32(50):6746–51. Available from: http://dx.doi.org/10.1016/j.vaccine.2014.10.021
22. Whittembury A, Galdos J, Lugo M, Suárez-Ognio L, Ortiz A, Cabezudo E, et al. Congenital rubella syndrome surveillance as a platform for surveillance of other congenital infections, Peru, 2004-2007. J Infect Dis. 2011;204(SUPPL. 2):2004–7.

23. Choe YJ, Lee ST, Song KM, Cho H, Bae GR, Lee JK. Surveillance and Control of Rubella in the Republic of Korea From 2001 to 2009: The Necessity for Enhanced Surveillance to Monitor Congenital Rubella Syndrome. Osong Public Heal Res Perspect. 2010;1(1):23–8. Available from: http://dx.doi.org/10.1016/j.phrp.2010.12.007
24. Lanzieri TM, Pinto D, Prevots DR. Impact of rubella vaccination strategy on the occurrence of congenital rubella syndrome. J Pediatr (Rio J). 2007;83(5):415–21. Available from: http://www.scielo.br/pdf/jped/v83n5/v83n5a04.pdf
25. Lanzieri TM, Parise MS, Siqueira MM, Fortaleza BM, Segatto TC, Prevots DR. Incidence, clinical features and estimated costs of congenital rubella syndrome after a large rubella outbreak in Recife, Brazil, 1999-2000. Pediatr Infect Dis J. 2004;23(12):1116–22.
26. Katow S. Surveillance of congenital rubella syndrome in Japan, 1978-2002: Effect of revision of the immunization law. Vaccine. 2004;22(29–30):4084–91.
27. Lanzieri TM, Segatto TC, Siqueira MM, de Oliviera Santos EC, Jin L, Prevots DR. Burden of congenital rubella syndrome after a community-wide rubella outbreak, Rio Branco, Acre, Brazil, 2000 to 2001. Pediatr Infect Dis J. 2003;22(4):323–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12690271
28. Venerosi A, Valanzano A, Alleva E, Calamandrei G. Ascertainment of pregnancies terminated because of birth defects: Effect on completeness of adding a new source of data. Vol. 63, Teratology. 2001. p. 23–5.
29. Lawn JE, Reef S, Baffoe-Bonnie B, Adadevoh S, Caul EO, Griffin GE. Unseen blindness, unheard deafness, and unrecorded death and disability: Congenital rubella in Kumasi, Ghana. Am J Public Health. 2000;90(10):1555–61.
30. Cutts F, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. Int J Epidemiol. 1999;28(6):1176–84. Available from: http://ije.oxfordjournals.org/content/28/6/1176.abstract
31. Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. BMJ. 1999;319(7223):1462–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=28289&tool=pmcentrez&rendertype=abstract
32. Sullivan EM, Burgess MA, Forrest JM. The epidemiology of rubella and congenital rubella in Australia, 1992 to 1997. Commun Dis Intell. 1999;23(8):209–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10497832
33. Cheffins T, Chan A, Keane RJ, Haan EA, Hall R. The impact of rubella immunisation on the incidence of rubella, congenital rubella syndrome and rubella-related terminations of pregnancy in South Australia. Br J Obstet Gynaecol. 1998 Sep;105(9):998–1004. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9763052
34. Schluter WW, Reef SE, Redd SC, Dykewicz CA. Changing epidemiology of congenital rubella syndrome in the United States. J Infect Dis. 1998;178(3):636–41.
35. Condon RJ, Bower C. Rubella vaccination and congenital rubella syndrome in Western Australia. Med J Aust. 1993 Mar 15;158(6):379–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8479351
36. Ueda K, Tokugawa K, Yukiaki N, Mikio K. Incidence of Congenital Rubella Syndrome in Japan (1965–1985): A nationwide survey of the number of deaf children with history of maternal rubella attending special schools for the deaf in Japan. Am J Epidemiol. 1986;124(5):807–15.

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

Date: 4 April 2017

Source: PubMed (https://www.ncbi.nlm.nih.gov/pubmed)

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

POPULATION: Pregnant women	OUTCOME: CRS	INTERVENTION: Rubella
"Pregnant Women"[Mesh] "Pregnancy"[Mesh] Pregnan* Gestat* Childbearing Gravidity Mother* Maternal Antenatal Perinatal Prenatal	**"Rubella Syndrome, Congenital"[Mesh]** CRS congenital rubella syndrome congenital malformation	**"Rubella"[Mesh]** Rubella German measles

Number of articles retrieved: 771.

Annex 2. Literature review of CRS burden assessment methodology for retrospective case finding

Authors, Year	Country	Assessment method	Study population	Data sources
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) Seroprevalence: 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 (16)	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 new-born 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 registries', 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	Two surveillance systems 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 one of the two CRS surveillance systems.	-Surveillance system database
Whittembury et al, 2011(22)	Peru	Describes a sentinel surveillance system for reporting confirmed and suspected CRS cases. Implemented a surveillance protocol with standardised 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 the CRS surveillance system (population at risk = infants born to mothers with rubella exposure during pregnancy.	-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 registries 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

Authors, Year	Country	Assessment method	Study population	Data sources
Venerosi et al, 2001 (28)	Australia	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.	All cases coded as terminations of pregnancy for fetal abnormality (the study does not focus solely on CRI/CRS, but also other causes of early termination).	-Birth defect registry -Hospital Morbidity Data System
Lawn et al, 2000 (29)	Ghana	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.	Not specified	-Hospital records
Cutts et al, 1999 (30)	NA	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.	Literature review: papers on seroprevalence of rubella in developing countries.	NA
Panagiotopoulos et al, 1999 (31)	Greece	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.	Literature review: all available information on immunisation policies and practices, vaccination coverage, serologically detected immunity, occurrence of rubella and CRS in Greece.	-Greek medical literature for publications on rubella and CRS, conference proceedings, government documents.
Sullivan et al, 1999 (32)	Australia	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.	All cases of CRS documented in any of the two described surveillance systems.	-National Notifiable Diseases Surveillance System -Australian Paediatric Surveillance Unit
Cheffins et al, 1998 (33)	Australia	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.	All cases of CRS notified to the South Australian disease notification registry, documented rubella-related terminations of pregnancy	-South Australian disease notification registry -Births and terminations of pregnancy registry -Rubella immunisation programme -Antenatal rubella antibody screening data -Paediatric hospital case records
Schluter et al, 1998 (34)	United States	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.	CRS cases reported to the National Congenital Rubella Syndrome Registry.	-National Congenital Rubella Syndrome Registry
Condon et al, 1993 (35)	Australia	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.	All cases of CRS reported in the WA Birth Defects Registry.	-Western Australian Birth Defects Registry -Survey of pregnancy terminations for MRI -Survey of annual rubella vaccination campaign Immunisation records
Ueda et al, 1986 (36)	Japan	A nationwide survey of deaf children with a history of maternal rubella in special schools for the deaf in Japan.	Deaf children with a history of maternal rubella in special schools for the deaf.	-Study questionnaire

Annex 3. Data collection form for phase

Section 1: CRS surveillance and context

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

A. Current CRS surveillance system	
Is there a CRS surveillance system in your setting? *(y/n)*	
What type of data is available? *(no data, case-based, aggregated)*	
If case-based, which data are collected? *(list variables)*	
What is the legal basis of reporting? *(mandatory, voluntary)*	
What type of surveillance system exists? *(comprehensive, sentinel; indicate whether active, passive or both)*	
What is the source of reporting? *(physicians, hospitals, laboratories, other)*	
Is there a case definition used? *(y/n; if yes, specify whether compatible with EU or WHO case definition)*	
What type of cases are reported? *(probable, confirmed, discarded, other)*	
Is zero-reporting required? *(y/n)*	
Does your country have a CRS reference laboratory? *(y/n)*	
Is underreporting of CRS monitored in your setting? If so, how? *(y/n; if yes, clarify)*	

B. Rubella vaccination	
When was rubella vaccination introduced in your setting? *(year)*	
Have rubella vaccination strategies changed since the introduction? How? *(y/n; if yes, clarify)*	
Is vaccination coverage data available for the study period? *(y/n; if yes, clarify)*	

C. Rubella outbreaks	
Did any rubella outbreaks occur during the study period? *(y/n; clarify)*	

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?
secondary or tertiary care facilities			
maternity			
neonatology			
pediatrics			
opthalmology			
cardiology			
audiology			
other?			
other birth facilities			
midwifery unit			
birth centre			
other?			
specialist care centres			
hearing disability centre			
sight disability centre			
other?			

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

Identification of healthcare institutes where pregant women are likely to be screened for CRI

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?
secondary or tertiary care facilities			
maternity			
neonatology			
obstetrics and gynaecology			
other?			
other maternal health facilities			
obstetric centre			
midwifery centre			
other?			

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?

	records stored?	records accessible?
other relevant data sources		
rubella laboratory registries		
birth records		
birth defect registry		
infant death registry		
pregnancy termination registry		
rubella in pregnancy registries		
other?		

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	
number of live births per year available? *(y/n)*	
other suitable denominators? *(y/n; if yes, clarify)*	

B. Ethical considerations relevant to study implementation	
ethics committee review required? *(y/n; if yes, specify name and expected turnaround time)*	
other ethical considerations? *(y/n; if yes, clarify)*	

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)

- ICD-9. International Statistical Classification of Diseases and Related Health Problems 9th Revision. Geneva: World Health Organization; 1978 (http://www.who.int/iris/handle/10665/39473).

-ICD-10. International Statistical Classification of Diseases and Related Health Problems 10th Revision. Geneva: World Health Organization; 2016

(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?

Clinical Characteristics	Y	N	Unk	**Clinical Characteristics**	Y	N	Unk
Cataracts	1	2	9	Mental Retardation	1	2	9
Pigmentary Retinopathy	1	2	9	Microcephaly	1	2	9
Congenital Glaucoma	1	2	9	Meningoencephalitis	1	2	9
Hearing Impairment	1	2	9	Hepatosplenomegaly	1	2	9
Heart Defect (Congenital)	1	2	9	Jaundice	1	2	9
Patent Ductus Arteriosis	1	2	9	Purpura	1	2	9
Aortic Stenosis	1	2	9	Radiolucent bone disease	1	2	9
Pulmonary Stenosis	1	2	9				
Atrial Septal Defect	1	2	9				
Other	_____						

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:

	Y	N	Unk
Fever	1	2	9
Rash	1	2	9
Lymphadenopathy	1	2	9
Arthritis/arthralgia	1	2	9

Other (specify).....

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

Probable case ☐

Confirmed case ☐

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.

Annex 6. Data variables to collect for analysis

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)	0= No, 1=Yes	Birthplace the same as country of residence
dateofsignssymptoms	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
hosptrans	Numeric (binary)	0= No 1=Yes	Patient transferred from another hospital
patientdiagnos	Numeric (categorical)	0=No 1= Yes 9=Unk	Patient diagnosed with CRS
clinical_signs_symptoms	Numeric (categorical)	0=No 1= Yes 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 pegnancy
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

	n	%
patient demographics		
age		
prepartum	-	-
0-3 months	-	-
4-8 months	-	-
9-12 months	-	-
unknown	-	-
gender		
male	-	-
female	-	-
unknown	-	-
nationality of mother		
country a	-	-
country b	-	-
country c	-	-
…	-	-
unknown	-	-
source of CRS reports		
data source		
hospital register	-	-
laboratory	-	-
death register	-	-
birth register	-	-
…	-	-
unknown	-	-
CRS EU case definition type		
case type		
probable	-	-
confirmed	-	-
unknown		

	n	%
clinical characteristics patient		
patient diagnosed with CRS?		
yes	-	-
no	-	-
unknown	-	-
documented signs/symptoms		
cataracts	-	-
congenital glaucoma	-	-
hearing impairment	-	-
aortic stenosis	-	-
…	-	-
unknown	-	-
hospitalisation status		
admitted to hospital		
yes	-	-
no	-	-
unknown	-	-
hospitalisation duration		
< 1 month	-	-
1-3 months	-	-
>3 months	-	-
unknown	-	-
hospitalisation outcome		
remains under treatment	-	-
died	-	-
transferred	-	-
discharged	-	-
unknown	-	-
rubella status mother		
CRI diagnosed during pregnancy?		
yes	-	-
no	-	-
unknown	-	-
vaccinated before pregancy?		
yes	-	-
no	-	-
unknown	-	-

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

	routine CRS surveillance					CRS retrospective review				
	n prob	n conf	n total	i conf	PPV	n prob	n conf	n total	i conf	PPV
year 1	20	10	30	…	0,33	24	16	40	…	0,40
year 2	21	14	35	…	0,40	26	18	44	…	0,41
year 3	24	17	41	…	0,41	25	18	43	…	0,42
Overall	65	41	106	…	0,39	75	52	127	…	0,41

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

European Centre for Disease Prevention and Control (ECDC)

Address:
Gustav III:s boulevard 40, SE-169 73 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

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.
www.ecdc.europa.eu/en/aboutus/transparency

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:

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

Publications Office