

# Guidelines for surveillance of congenital rubella syndrome and rubella

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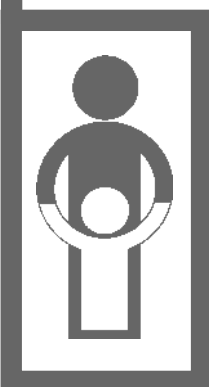
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# Preface

In 1995-1996, the Steering Committee on Epidemiology and Field Research of the WHO Global Programme for Vaccines and Immunization (now the Department of Vaccines and Other Biologicals) sponsored a global review on congenital rubella syndrome (CRS) and the use of rubella vaccine. The review found that approximately 50 developing countries had conducted substantial studies to assess their CRS burden; other countries asked for guidance on methods suitable for surveillance of CRS (Cutts et al. 1997). By mid-1996, 78 countries (including 28% of all developing countries) had introduced rubella vaccine into their national immunization programmes; however, not all these countries had implemented CRS and rubella surveillance (Robertson et al. 1997).

Since the mid-1990s, interest of immunization programmes in measles has flourished. As of 1999, some 113 countries have set measles elimination targets and a global network of measles laboratories is under development. Many countries involved in measles elimination will also be thinking about whether to include rubella vaccine in their national immunization programmes, if this has not already occurred, and whether rubella elimination would be an appropriate additional target. In 1998, the English-speaking Caribbean countries were the first to set a rubella elimination target (Hinman et al. 1998, Irons et al. 1998, Plotkin et al. 1999).

This document has been developed for countries using rubella vaccine and for countries considering whether to add rubella vaccine to their national immunization programme. These guidelines provide a framework for planning a surveillance system for CRS and, in the rubella elimination phase, rubella itself. Countries will need to adapt the guidelines to their local situation. Some countries with more financial and technical resources (including collaborating research institutions) may wish to build more sophisticated surveillance systems, incorporating a greater number of laboratory tests and/or more complex screening of newborns for birth defects.

This is the field test version of a document under development by WHO. Comments from users of the document are welcome, as are recommendations for improving it. These should be forwarded to Dr S. Robertson, Department of Vaccines and Other Biologicals, World Health Organization, 1211 Geneva 27, Switzerland.

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# 1. Introduction

**Surveillance of congenital rubella syndrome (CRS)** requires a comprehensive system to detect suspected CRS cases in infants who present to a range of different health services. Suspected cases must be investigated, with full clinical and laboratory investigation. CRS incidence should be reported as number of CRS cases per 1000 live births per year. Most industrialized countries have established surveillance of CRS with national disease notification programmes and/or birth defects monitoring programmes (*Cheffins et al. 1998, Orenstein et al. 1985, Rebiere & Jacob 1998, Schluter et al. 1998, Tookey & Peckham 1999*). However, in developing countries (as for neonatal tetanus) CRS cases are likely to be under-reported in areas and among populations where a high proportion of births occur at home and where neonatal and childhood deaths are often unreported. In such settings, outbreak investigations can help to identify CRS cases.

Rubella outbreak investigations have documented the occurrence of CRS in developing countries in different regions of the world (**Table 1**, *Cutts et al. 1997*). These rates are higher than those reported from many industrialized countries in the pre-vaccination period (*Banatvala 1998*).

**Table 1: Rates of congenital rubella syndrome (CRS) per 1000 live births in seven developing countries prior to the introduction of rubella vaccine**

Country	Year (s)	Rate of CRS per 1000 live births	Reference
Israel	1972	1.7	<i>Swartz et al. 1975</i>
Jamaica	1972-81	0.4	<i>Baxter 1986</i>
Oman	1988 1993	0.5 0.7	<i>Juma 1989</i> <i>EPI 1994</i>
Panama	1986	2.2	<i>Owens &amp; Espino 1989</i>
Singapore	1969	1.5	<i>Dorasingam &amp; Goh 1981</i>
Sri Lanka	1994-95	0.9	<i>Gunasekera &amp; Gunasekera 1996</i>
Trinidad and Tobago	1982-83	0.6	<i>Ali et al. 1986</i>

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**Surveillance of rubella** is likely to be most practical when countries have reached the stage of measles/rubella elimination, when rash illness surveillance and investigation (including laboratory tests) will be used to detect the circulation of measles and rubella viruses. Therefore, case-based rubella surveillance is only recommended in countries that have established a rubella elimination goal (*Hinman et al. 1998, Irons 1998, Plotkin et al. 1999*). In countries that have not reached the rubella elimination phase, rubella outbreak investigation can be used to activate CRS surveillance.

**Rubella immunization coverage** should be monitored in all groups targeted to receive rubella vaccine. This will depend on the rubella immunization strategy adopted (*Robertson et al. 1997*).

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## 2. The diseases

The International Classification of Diseases classifies rubella as two diseases: rubella (ICD-9 056; ICD-10 B06) and congenital rubella syndrome (ICD-9 771.0; ICD-10 P35.0) (*WHO 1993, Benenson 1995*).

### 2.1 Rubella

Rubella is a common cause of maculopapular rash illness with fever. The disease has few complications unless it is contracted by a pregnant woman. Rubella infection in pregnancy can lead to miscarriage, stillbirth, or an infant born with congenital rubella infection.

The clinical diagnosis of rubella is unreliable, as it is one of many diseases causing maculopapular rash with fever (Table 2). The differential diagnoses include measles, dengue, parvovirus B19, human herpesvirus 6, Coxsackie, Echo, Ross River, Chikungunya, entero, and adenoviruses, and *Streptococcus* group A (beta haemolytic) (*Bell et al. 1975, Cubel et al. 1997, Davidkin et al. 1998, Dietz et al. 1992, Frieden & Resnick 1991, Rodriguez et al. 1998, Shirley et al. 1987*). Measles is most frequently associated with cough, coryza, and conjunctivitis, though these are relatively nonspecific symptoms common to a number of viral infections. Joint symptoms are seen in up to 60% of adult women with rubella (*Banatvala & Best 1998*), but joint symptoms are also frequent with parovirus B19 infection and with dengue and other arbovirus diseases (Table 2). Post-auricular adenopathy is associated with rubella and roseola infantum (usually seen in children <four years); thus, the differential diagnosis of these diseases remains difficult in young children (*Tait et al. 1996*). For these reasons, confirmation of rubella is not possible without laboratory testing.

#### *Immune response in rubella*

The humoral immune response to rubella infection has been well studied. Rubella-specific IgM is diagnostic of acute infection; IgM usually appears within four days after onset of the rash and can persist up to 4-12 weeks. Rubella-specific IgG is a long-term marker of previous rubella infection; IgG begins to rise after the onset of the rash, peaks about four weeks later, and generally lasts for life (*Best & O'Shea 1995*).

**Table 2: Features of some of the diseases causing febrile illness with generalized rash**  
(Benenson 1995, Frieden & Resnick 1991, Remington & Klein 1995)

Disease	Rubella	Measles	Dengue fever	Erythema infectiosum <sup>1</sup>	Roseola infantum <sup>2</sup>
<b>Causative agent</b>	rubella virus	measles virus	dengue virus	parvo-virus B19	human herpes virus 6
<b>Incubation period (days)</b>	14-23	7-18	2-12	4-20	10
<b>Fever</b>	yes	yes	yes	yes	yes
<b>Rash</b>	yes	yes	yes	yes	yes
<b>Conjunctivitis</b>	yes	yes	yes	yes	no
<b>Coryza</b>	yes	yes	yes	yes	no
<b>Joint symptoms</b>	yes (especially adult women)	no	yes	yes (especially adults)	no
<b>Postauricular adenopathy</b>	yes	no	no	no	yes
<b>Diagnostic test</b>	IgM	IgM	IgM	IgM	IgM
<b>Result of infection during pregnancy stillbirth</b>	yes	yes	yes <sup>3</sup>	yes	no
<b>birth defects</b>	yes	no	no	no	no
<b>Vaccine-preventable</b>	yes	yes	no	no	no

<sup>1</sup> Also known as fifth disease.

<sup>2</sup> Also known as sixth disease, or exanthem subitum.

<sup>3</sup> Three fetal deaths reported following onset of dengue fever in mothers between weeks 17 and 24 of pregnancy (Carles et al. 1999).

## 2.2 Congenital rubella syndrome (CRS)

A rubella-infected fetus carried to term may be born with congenital rubella syndrome (CRS). Some defects associated with CRS may be recognizable at birth, while others are detected months or even years later. CRS manifestations may be transient (e.g. purpura), permanent structural manifestations (e.g. deafness, central nervous system defects, congenital heart disease, cataract), or late-emerging conditions (e.g. diabetes mellitus). Table 3 lists the major clinical manifestations of congenital rubella.

**Hearing loss.** The WHO definition of hearing loss in children is permanent unaided hearing threshold level for the better ear of 26 dB or greater (Smith 1999). Hearing loss occurs in 70-90% of CRS cases, and in 50% of these children it is the only sign of CRS, although it is often not detected initially. There is evidence that the amount of hearing loss due to CRS has been underestimated, and mild to moderate hearing impairment due to CRS may be as frequent as severe to profound hearing impairment (Upfold 1984). Where there is no rubella vaccination programme, CRS is the most

important cause of non-genetic congenital hearing loss (*Smith 1999*). If congenital heart disease is also present, treatment with certain drugs (loop diuretics and aminoglycosides) may add to the hearing damage. Congenital hearing loss interferes with normal development of speech and language; hearing and vision loss make socialization much more difficult.

Testing for hearing impairment in infants and young children is difficult: audiometry in this age group has poor validity and reliability; distraction testing (head turn to novel sound) has poor sensitivity and specificity where testers are not well trained (*McCormick 1991*). In industrialized countries the average age when hearing loss is identified is about two years (*Ekel et al. 1998*).

Two newer objective methods used to test infant hearing in industrialized countries are otoacoustic emissions (OAE) and auditory brainstem response (ABR) (*Mehl & Thompson 1998*). There are no studies reported using these tests in developing countries. OAE has been shown to have 90% sensitivity and 91% specificity for hospital screening of neonates (*Plinkert et al. 1990*). The cost of OAE equipment is approximately US\$ 3000 to US\$ 5000; some OAE equipment is portable but robustness in the field setting is not known; use of OAE equipment is easily learned (*Smith 1999*). ABR has been shown to have 100% sensitivity and 91% specificity for hospital screening of neonates (*Hyde et al. 1990*). The cost of ABR equipment is approximately US\$ 11 000 - US\$ 23 000; ABR equipment is not portable; ABR tests are usually conducted at a referral centre (*Smith 1999*).

**Table 3: Main clinical manifestations of congenital rubella**  
(adapted from *Dudgeon 1975 and Cooper 1985*)

Category	Specific manifestation
General	Fetal loss (spontaneous abortion and stillbirth) Low birthweight Mental retardation
Auditory system	Sensorineural deafness: unilateral or bilateral Central auditory deafness Speech defects
Cardiovascular system	Patent ductus arteriosus Pulmonary stenosis Ventricular septal defects Complex congenital heart disease
Ocular system	Pigmented retinopathy Cataracts: pearly, dense, nuclear 50% bilateral, very often with retinopathy Microphthalmos
Transient neonatal manifestations (extensive infection; high mortality)	Thrombocytopenia with or without purpura Hepatosplenomegaly Meningoencephalitis Bony radiolucencies Adenopathies
Late-emerging or developmental	Late-onset interstitial pneumonitis (age 3-12 months) Insulin-dependent diabetes mellitus

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**Eye signs.** In contrast to CRS-associated deafness, most of the CRS eye signs are readily recognized by parents and health care personnel (*Pararajasegaram 1999*). Health care workers should suspect CRS in an infant under one year of age (a) where there is a maternal history of rubella in pregnancy or (b) when the mother gives a history of one or more of the following: infant not visually fixing on the mother, eyes smaller than normal, rapid oscillation of the baby's eyes, squint, and/or suspicion of hearing difficulty.

Referral to a secondary or tertiary eye centre (*WHO 1996a*) is recommended if any of the following eye signs are detected:

- white pupil (cataract),
- diminished vision,
- pendular movement of the eyes (nystagmus),
- squint,
- smaller eye ball (microphthalmos),
- larger eye ball (congenital glaucoma).

### ***Immune response in infants with CRS***

The serum immune response in CRS differs from that seen in rubella (and from many other viral diseases). At birth, the serum of an infant with CRS contains maternally derived rubella-specific IgG antibodies as well as IgG and IgM antibodies synthesized by the fetus. Maternal rubella-specific IgG is also found in normal infants born to women who are immune to rubella. Therefore, rubella-specific IgM is used to diagnose congenital rubella infection in infants. In infants with CRS, rubella-specific IgM can be detected in nearly 100% at age 0-5 months; about 60% at age 6-12 months; and 40% at age 12-18 months; IgM is rarely detected after age 18 months (*Chantler et al. 1982*).

Infants with CRS shed rubella virus for long periods. Rubella virus can be found in the nasopharyngeal secretions of more than 80% of infants with CRS during the first month of life, 62% at age 1-4 months, 33% at age 5-8 months, 11% at age 9-12 months, and only 3% during the second year of life (*Cooper 1967*). Infants with CRS who are shedding rubella virus are infectious and appropriate infection control measures should be instituted (*Benenson 1995*). It is particularly important to prevent exposure of nonimmune pregnant women to these infants. A general requirement for rubella immunization of hospital personnel at risk of exposure (e.g., obstetrics, paediatrics, and ophthalmology staff) against rubella will help in preventing nosocomial spread of rubella.

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## 3. Proposed stages of rubella control

These guidelines propose three stages of rubella control. Recommended CRS/rubella surveillance activities will depend on the stage the country has reached (Table 4).

### Stage 1: Planning for rubella vaccine

- **For countries that wish to assess whether to add rubella vaccine to their national immunization programme, baseline information on the disease burden due to CRS may be helpful.**

There are several options for assessing the disease burden due to CRS:

1. Carry out CRS surveillance for at least two years, either nationwide or in selected urban and rural populations where there are at least 200 000 births per year.
2. When a rubella outbreak is detected, conduct investigations, including laboratory tests, of a small number of suspected rubella cases per month (perhaps 5 to 10 investigations per month). All febrile rash illnesses in pregnancy should be investigated. If rubella cases are reported in individuals > 15 years of age, active surveillance should be conducted until nine months after the end of the outbreak to identify suspected CRS cases in infants 0-11 months of age.
3. Conduct antenatal serosurveys to assess the proportion of women at risk for rubella infection in pregnancy.
4. Where resources permit, conduct a community-based serological survey to estimate the potential CRS disease burden and the potential impact of different rubella vaccination strategies.

### Stage 2: CRS prevention

- **For countries where rubella vaccine has been incorporated into the national immunization programme, but a rubella elimination target has not been set:**
  1. Monitor rubella vaccine coverage in the public and private sectors in all groups targeted to receive vaccine, by year, and by geographic area.
  2. Conduct case-based CRS surveillance, with investigation and laboratory testing of every suspected case in areas where this is feasible and appropriate laboratory support is available.
  3. Report aggregated data on suspected rubella cases monthly, by district.
  4. When a rubella outbreak is detected, conduct investigations as in Stage 1.
  5. Some countries may wish to conduct antenatal serosurveillance at selected sites to monitor rubella susceptibility of women of childbearing age.

### Stage 3: Rubella elimination

- For countries where a rubella elimination target has been set (usually linked to a measles elimination target):
  1. Monitor rubella vaccine coverage as in Stage 2.
  2. Conduct case-based CRS surveillance, with investigation and laboratory testing of every suspected case.
  3. Conduct case-based surveillance for all febrile rash illnesses, with laboratory assessment of each case for measles and, if negative, for rubella. Most countries at this stage will have established a system for reporting febrile rash illness within 48 hours.
  4. Investigate outbreaks of febrile rash illnesses and all febrile rash illnesses in pregnancy. When a rubella outbreak is detected, conduct investigations as in Stage 1.
  5. Some countries may conduct antenatal serosurveillance as in stage 2.

**Table 4: Recommended surveillance activities, by stage of rubella immunization programme**

	Stage of rubella immunization programme		
	Stage 1	Stage 2	Stage 3
<b>Surveillance activities</b>	<b>Not using rubella vaccine but want to assess CRS disease burden</b>	<b>CRS prevention rubella vaccine used in national immunization programme</b>	<b>Rubella elimination</b>
<b>CRS surveillance</b>	<ul style="list-style-type: none"> <li>• Conduct case-based CRS surveillance in infants 0-11 months.</li> <li>• Report total number of CRS cases per year.</li> <li>• Report number of CRS cases per 1000 live births per year.</li> </ul>		
<b>Rubella surveillance</b>		<ul style="list-style-type: none"> <li>• Report number of suspected rubella cases each month, by district.</li> </ul>	<ul style="list-style-type: none"> <li>• Conduct case-based surveillance for febrile rash illness; investigate every case including laboratory tests.</li> </ul>
<b>Outbreak investigation</b>	<ul style="list-style-type: none"> <li>• During outbreak, investigate 5 to 10 rash illness cases per month (with laboratory tests) to confirm rubella as cause of outbreak.</li> <li>• During outbreak, investigate all rash illnesses in pregnancy.</li> <li>• During outbreak (and nine months after) conduct active surveillance to detect suspected CRS cases in infants 0-11 months.</li> </ul>		
<b>Serosurveillance</b>		<ul style="list-style-type: none"> <li>• If resources permit, establish serosurveillance at selected antenatal clinics to monitor susceptibility in women of childbearing age.</li> </ul>	
<b>Rubella vaccine coverage</b>		<ul style="list-style-type: none"> <li>• Monitor rubella vaccine coverage in target groups.</li> <li>• Conduct coverage surveys, if needed.</li> <li>• Conduct missed opportunity surveys.</li> </ul>	

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## 4. Role of CRS/rubella surveillance coordinator(s)

Once a country decides to carry out the appropriate surveillance activities for one of the stages of rubella control, it will be helpful to identify a CRS/rubella surveillance coordinator. Larger countries may need to consider involving several CRS/rubella coordinators: an epidemiologist, a laboratory coordinator, and an immunization coordinator.

For countries in Stage 1, the surveillance coordinator(s) needs to focus on establishing case-based CRS surveillance. This will require identification of paediatricians and/or neonatologists who will conduct clinical examinations for suspected CRS patients, complete the case investigation forms, send serum samples for rubella-specific IgM testing, and refer infants to an ophthalmologist, otologist, or cardiologist, as needed. It may be practical to identify one such qualified physician for each province or region; it is likely that this specialist would be located at the provincial or regional referral hospital.

For countries in Stage 2, an additional responsibility of the surveillance coordinator(s) will be to ensure that rubella vaccine coverage is monitored in all target groups. Some countries may wish to consider establishing antenatal serosurveillance at selected sentinel sites as a long-term method for monitoring the rubella susceptibility of pregnant women.

For countries in Stage 3, an additional responsibility of the CRS/rubella surveillance coordinator(s) will be to collaborate with epidemiologists and laboratories involved in measles elimination activities in order to establish a practical system for surveillance of febrile rash illnesses (*EPI 1996*).

Responsibilities of the CRS/rubella surveillance coordinator(s) may also include:

- developing appropriate training materials consistent with the national surveillance system already in place,
- developing appropriate case investigation forms and laboratory investigation forms (examples are provided in this document),
- identifying qualified physicians who will be available to examine infants with suspected CRS,
- coordinating with the national rubella laboratory to verify that adequate IgM test kits are supplied; to ensure specimens are sent on time to the laboratory; to check that reports from the laboratory are reported,
- conducting training on the CRS/rubella surveillance system,

- 
- maintaining a linelist of suspected CRS cases,
  - coordinating outbreak investigations,
  - coordinating rubella vaccine coverage monitoring consistent with other vaccine coverage monitoring systems,
  - analysing surveillance data and providing feedback.

Health workers participating in routine surveillance or in serosurveys must be trained and closely supervised. Financial support will be needed to train the staff participating in each province or region. They need to be provided with detailed information on case definitions, data collection and recording, and blood specimen collection and handling.

Regular communication is needed between each reporting site and the central surveillance coordinator(s). The surveillance coordinator(s) should identify a contact person in each reporting site who will be responsible for completing case report forms, ensuring that appropriate blood specimens are collected and transported to the laboratory, and delivering case report forms. Case report forms should be reviewed for completeness and accuracy as they are submitted. Laboratory registers need to be cross-checked against registers of suspected cases and clinical reports to determine whether potential cases have been missed.

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## 5. Surveillance of CRS

In these guidelines, we recommend that routine CRS surveillance focuses on identifying infants 0-11 months of age with CRS, although some defects associated with CRS may not be detectable until older ages (see section 2.2). In children older than one year it is very difficult to confirm rubella as the specific etiology of congenital malformations or birth defects. When an outbreak of rubella is reported, surveillance for CRS should be enhanced (see section 7).

The annual number of CRS cases should be reported. The annual rate of CRS cases per 1000 live births should also be reported. To calculate the rate, it will be necessary to define the catchment area for cases (district, province, entire country) and the annual number of live births in that catchment area.

Staff at sites currently participating in the routine communicable disease surveillance system will need to receive guidelines and training on CRS surveillance. It is also important to recognize that infants with CRS may be seen by medical specialists at facilities that do not normally participate in the routine disease surveillance system; these may include eye hospitals (*WHO 1996a*) and hospitals specializing in cardiac surgery. In implementing CRS surveillance, it may be particularly helpful to obtain the support of the National Programme for Prevention of Blindness and Deafness (*WHO 1996c*); the National Pediatrics Society, the National Society of Obstetricians, the National Society of Cardiologists, etc. To be meaningfully involved in CRS surveillance, such groups will need information on the standard case definitions; procedures for investigating and reporting suspected CRS cases; copies of CRS case investigation forms; and information on handling specimens and shipping them to the appropriate laboratory.

The following sites and specialists should be provided with written guidelines and, if necessary, training:

- Sites that routinely participate in surveillance for EPI diseases (including epidemiologists, nurses, and community health workers),
- Neonatal wards and neonatal intensive care units,
- Obstetrics services, including obstetricians and midwives,
- General hospitals, including the paediatric ward,
- Referral hospitals,
- Ophthalmologists, optometrists, and primary eye care workers,
- Otologists and audiologists,
- Cardiologists and cardiac surgeons.

See Appendix A for a flow chart of CRS surveillance activities.

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## 5.1 Case definitions

The following provisional case definitions are recommended for the field test version of this document.

### ***Suspected CRS case***

A suspected case is any infant less than one year of age in whom a health worker suspects CRS.

A health worker should suspect CRS where there is a maternal history of suspected or confirmed rubella during pregnancy.

A health worker should suspect CRS when the infant presents with heart disease, and/or suspicion of deafness, and/or one or more of the following eye signs: white pupil (cataract); diminished vision; pendular movement of the eyes (nystagmus); squint; smaller eye ball (microphthalmos); larger eye ball (congenital glaucoma).

Health workers should refer all suspected CRS cases to a qualified physician.

### ***Clinically-confirmed CRS case***

A clinically-confirmed case is one in which a qualified physician detects two of the complications in section (a) OR one from group (a) and one from group (b):

- (a) Cataract(s) and/or congenital glaucoma; congenital heart disease; loss of hearing; pigmentary retinopathy.
- (b) Purpura; splenomegaly; microcephaly; mental retardation; meningoencephalitis; radiolucent bone disease; jaundice with onset within 24 hours after birth.

### ***Laboratory-confirmed CRS case***

A laboratory-confirmed CRS case is an infant with a positive blood test for rubella IgM who has clinically-confirmed CRS.

### ***Congenital rubella infection (CRI)***

An infant with a positive blood test for rubella IgM who does not have clinically-confirmed CRS is classified as having congenital rubella infection (CRI).

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## 5.2 Case reports

A standard reporting form should be completed for each case of suspected CRS (see example in Appendix B). The following information is important:

- Infant's clinical signs and symptoms,
- Infant's date of birth,
- Date of notification,
- Date of case investigation,
- Date of blood specimen collection from the infant,
- Results of IgM test,
- Mother's history of a febrile rash illness or exposure to a febrile rash illness during this pregnancy,
- Mother's address or addresses during this pregnancy,
- Mother's history of travel during this pregnancy,
- Mother's history of rubella immunization.

## 5.3 Laboratory testing

A blood sample (1 ml) should be collected from every infant with suspected CRS as soon after birth as possible. Almost all infants with CRS will have a positive rubella-specific IgM test in the first six months of life, and 60% will be positive during the second six months of life. For surveillance purposes, a single blood specimen is generally considered adequate to either confirm or discard CRS. If, however, the first specimen is negative for rubella IgM and there exists a compelling clinical and/or epidemiological suspicion of CRS, a second blood specimen should be requested. Further information on laboratory aspects is provided in section 9 of this document.

Some countries with more extensive resources and/or access to a research laboratory may wish to add more complex laboratory procedures for diagnosis of CRS (*Banatvala & Best 1998, Diaz Ortega 1999*).

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# 6. Surveillance of rubella

Surveillance of rubella becomes a priority in Stage 3, when the country has set a rubella elimination target. Usually, this occurs at the time that the country establishes a measles elimination target. In this situation, combined measles/rubella rash illness surveillance is a key component of measles/rubella elimination.

See Appendix C for a flow chart of surveillance of febrile rash illness in countries at the measles/rubella elimination phase.

## 6.1 Case definitions

The following provisional case definitions are recommended for the field test version of this document.

### *Suspected rubella case*

A suspected rubella case is any patient of any age in whom a health worker suspects rubella. A health worker should suspect rubella when the patient presents with fever, maculopapular rash, and one of the following: cervical, sub-occipital, or post-auricular adenopathy; or arthralgia/arthritis.

It will usually be impossible to distinguish rubella from measles, dengue, or a number of other febrile rash illnesses. At the rubella/measles elimination phase, suspected measles and suspected rubella are combined in a single febrile rash illness surveillance category for suspected cases.

### *Laboratory-confirmed rubella case*

Because of the difficulty in clinical diagnosis of rubella, laboratory confirmation is required. A laboratory-confirmed rubella case is a suspected case with a positive blood test for rubella-specific IgM (see Appendix C).

### *Epidemiologically-confirmed rubella case*

An epidemiologically-confirmed rubella case is a patient with febrile rash illness who has not had a blood test but has an epidemiological linkage to laboratory-confirmed case of rubella (see Appendix C).

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## 6.2 Suspected rubella in a pregnant woman

In order to identify CRS cases in infants, it is important to investigate rash illness in pregnant women. The system described below will be most practical in countries where women attend antenatal clinics during the first 16 weeks of pregnancy, as the risk of CRS is low in women infected after the first trimester. If rubella is suspected in a pregnant woman, the laboratory flow chart provided in Appendix D should be followed, along with the steps listed below:

1. The suspected diagnosis should be explained to the patient and a blood specimen obtained.
2. The blood specimen should be tested for rubella-specific IgM at a qualified laboratory.
3. If the result of the blood specimen is positive for rubella-specific IgM, the patient should be counseled accordingly at the next antenatal visit and followed-up (*Remington & Klein 1995*).
4. If the result of the blood specimen is negative for rubella-specific IgM and the first blood specimen was taken in the first six days after rash onset, a second blood specimen should be obtained and tested for rubella-specific IgM.
5. For all laboratory-confirmed cases of rubella infection during pregnancy, the patient's name and other relevant information should be entered into a rubella pregnancy register. Counseling and medical follow-up must be assured.
6. The infant of a woman confirmed to have rubella infection during pregnancy should have a blood specimen sent for rubella-specific IgM testing and should be examined by a qualified physician as soon as possible after birth.

Some countries may wish to consider more complex laboratory procedures for identification of rubella in pregnancy (*Best & O'Shea 1995*).

## 6.3 Case reports

A standard reporting form should be completed for each case of suspected rubella (see example in Appendix E). The following items of information are of major importance:

- Clinical signs and symptoms,
- Date of birth or age,
- Date of rash onset,
- Date of case investigation,
- Date of blood specimen collection,
- Results of IgM blood test,
- Address or addresses during the month before onset of illness,
- History of immunization against rubella and measles.

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## **6.4 Laboratory testing**

Rubella can be confirmed only by laboratory testing. Laboratory confirmation of rubella is made by detection of rubella-specific IgM in a blood specimen, which should be obtained within 28 days after rash onset. Further information on laboratory aspects is provided in section 9 of this document.

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# 7. Investigating outbreaks of febrile rash illness

## 7.1 Outbreak surveillance

During an outbreak of febrile rash illness, a sample of cases should be investigated. For practical purposes, an arbitrary number of cases (5 to 10) should be investigated each month, with serological testing for measles and, if negative, for rubella. Concurrent outbreaks of rubella and measles or other viruses have occurred (*Axton et al. 1979, Bell et al. 1975, EPI 1994, Lee et al. 1992*). Countries which have reached the rubella/measles elimination phase, should investigate every case of febrile rash illness. Some countries may also test for dengue virus (*Dietz et al. 1992*).

## 7.2 Special actions in a known rubella outbreak

Once rubella has been identified as the cause of an outbreak of febrile rash illness, particular attention should be paid to the detection of rubella in women of childbearing age. To identify potential cases of CRS, all febrile rash illnesses in pregnant women should be assessed as described in section 6.2 of this document and Appendix D.

Rubella outbreaks may continue over two or more years (*Marquez & Zapata 1984*), and often a smaller outbreak heralds a larger one (*Swartz et al. 1985*). Thus, there is usually time to identify cases of rubella in women of childbearing age. Obstetricians, paediatricians, neonatologists, midwives, and others who provide health services to women and/or infants should be alerted to the occurrence of the outbreak and its implications, informed of the case definitions for rubella and suspected CRS, and supplied with appropriate case investigation forms. (See Appendix B for an example of a CRS case investigation form.) Surveillance for CRS should continue for at least nine months after the last reported case of rubella.

## 7.3 Active surveillance to detect CRS cases

Active surveillance for CRS cases with special emphasis on follow-up of women exposed in the first 16 weeks of pregnancy can be conducted during a rubella outbreak and for nine months after the last rubella case is reported. Two methods for activating CRS surveillance are:

- In an area where coverage of infants with three doses of diphtheria-pertussis-tetanus (DPT) vaccine is 90% or higher, health care workers can be trained to screen infants attending the DPT3 immunization visit (usually at 14 weeks of age) for signs of CRS and inquire about the maternal history of rubella in pregnancy. Infants who meet the definition for suspected CRS should be referred to a qualified physician for clinical evaluation of CRS and IgM testing.

- 
- In an area where immunization coverage of infants is less than 90%, a house-to-house survey can be conducted to examine every baby born to women living in the outbreak area from the start of the outbreak until nine months after the last case is reported. Infants who meets the definition for suspected CRS should be referred to a qualified physician for clinical evaluation of CRS and IgM testing.

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## 8. Serological studies

Serological studies may be a useful adjunct to clinical surveillance at any stage of rubella control. Rubella serological studies may be carried out by immunization programme managers in collaboration with epidemiologists and other researchers. Relatively simple serological studies may be based on samples obtained from women of childbearing age at antenatal clinics. Large age-stratified community-based serosurveys can evaluate age-specific acquisition of rubella antibodies. This information can be used to develop models that estimate the effects of different CRS prevention and rubella control strategies.

### 8.1 Serosurveillance among women of childbearing age

Because the public health burden of rubella relates to the risk of infection of pregnant women, which in turn may cause CRS in their offspring, many countries have conducted serosurveys to determine the proportion of women of childbearing age who are susceptible to rubella (*Cutts et al. 1997*). An individual who is susceptible to rubella infection will have a negative blood test for rubella-specific IgG.

A single cross-sectional survey of IgG seroprevalence in women of childbearing age is of limited usefulness in demonstrating disease burden. Although a high level (e.g. >20%) of susceptibility is likely to indicate a high risk of CRS in that population, a low level of susceptibility cannot be taken to mean no risk of CRS. Even when susceptibility levels in women are below 10%, CRS can occur (*EPI 1994, Zgorniak-Nowosielska et al. 1996*). Therefore serological surveys are of most use to monitor trends in the proportion of adult women who are susceptible, in particular in countries which have introduced rubella vaccination for women of childbearing age. Long-term rubella antenatal serosurveillance has been used to track progress in protecting women of childbearing age against rubella in Australia (*Cheffins et al. 1998*), Israel (*Fogel et al. 1996*), and Singapore (*Dorasingham & Goh 1981*). Such data will be complementary to rubella vaccine coverage data in the same target group.

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Antenatal clinics and similar facilities are appropriate as locations for these kinds of studies when:

- The proportion of pregnant women who attend at least once is high (>90%);  
**and**
- The pregnant women who attend already have blood specimens drawn for other purposes (e.g., haemoglobin or blood sugar tests) and portions of these specimens are leftover. Epidemiological studies that require the examination of anonymous “leftover “ samples of blood may be conducted without the consent of the individuals concerned, as long as their right to confidentiality is ensured by the study methods (*CIOMS 1993*). Anonymity can be achieved by removing personal identifiers from information collected about persons from whom the specimens were collected;  
**or**
- Serological specimens are being collected from the same population for other purposes ( e.g. for measles, HIV, or hepatitis B) and permission can be obtained to use the samples for rubella tests.

Training in safe blood-taking techniques must be required; supplies and equipment must be provided; and procedures for transporting specimens safely to the laboratory must be established and followed. Further information on laboratory aspects is provided in section 9 of this document.

## **8.2 Age-stratified community-based serosurvey**

In special situations, where financial and technical resources permit, a country can consider conducting an age-stratified serosurvey for rubella. However, this will be a major research study that requires the participation of a virologist whose laboratory is prepared to conduct large numbers of serological tests; one or more epidemiologists to design the study; staff to carry out the field work; and a mathematical modeler experienced in studies of communicable diseases to analyse the results. This type of survey can provide point estimates (with confidence intervals) of the proportion susceptible to rubella for each age-group surveyed. Such data, in conjunction with mathematical modeling, can be used to estimate the average age at rubella infection and to predict the effect of different immunization strategies on the incidence of CRS over different periods of time (*Anderson & May 1991, Massad et al. 1994*).

To carry out such a study, detailed plans must include preparing a study protocol; obtaining the appropriate ethical approval; organizing logistics, including blood specimen transport and storage; and arranging for laboratory support. In particular, it should be ascertained whether the laboratory is prepared to handle a large number of serum specimens and whether blood drawing is acceptable in the community where the study is planned. Further information on laboratory aspects is provided in section 9 of this document.

A cross-sectional community-based survey will be expensive if it is conducted solely for rubella. Much of the cost is related to field work. Combining rubella serosurveys with serological studies of other infections such as measles, tetanus, HIV, papillomavirus, *Helicobacter pylori*, or hepatitis B should be considered to reduce

some of the field work costs and to take advantage of systems for handling and transporting specimens to the laboratory that will already be in place. Previous serosurveys for other diseases may have banked leftover specimens – if so, it would be worth ascertaining whether approval can be obtained to screen these sera for rubella IgG antibodies.

Consultation with a statistician in selecting the sample and making sample size estimates is recommended (see example in Table 5). Cluster sampling (*Bennett et al. 1996*) or simple random sampling may be considered. Since the age at which an individual becomes infected with rubella is likely to vary according to the density of the population, the study population will include both urban and rural areas and the sample size will be adequate to stratify results by urban versus rural residence.

**Table 5: Example of the sample size calculation<sup>1</sup> for a community-based serosurvey to assess age-specific prevalence of rubella-specific IgG**

Age group (years)	Expected prevalence of rubella-specific IgG (%)	95% confidence interval	Number of participants needed <sup>2</sup>
0-4 <sup>3</sup>	45	37-53	360
5-9	55	47-63	360
10-14	65	57-73	330
15-19	70	63-77	400
20-24	75	69-81	355
25-29	80	74-86	410
30-34	85	79-91	330
35-39	90	85-95	330
40-44	95	91-99	275
<b>Total</b>			<b>3150</b>

<sup>1</sup> Sample size in this example was calculated using the cluster sampling method (*Bennett et al 1994*).

<sup>2</sup> Assumes a design effect of two for cluster sampling and allows for 20% non-participation, rounded to nearest convenient number.

<sup>3</sup> Sample size for the 0-4 year age group may need to be greater if more finely age-stratified data are desired for the mathematical model.

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# 9. Laboratory components

## 9.1 Handling blood specimens

1. Strict sterile procedures must be followed in collecting blood and handling specimens. The decision to take blood by venepuncture or capillary samples should be taken locally.
2. If a syringe is used, transfer the blood sample to a sterile plain centrifuge tube, sterile ordinary tube, or a vacutainer tube.
3. Immediately label the tube or vacutainer with the patient's name, the date the sample was collected, and identification number. Make certain the information on the label matches the information on the case investigation form and the laboratory request and results form (Appendix F).
4. Let the blood sample stand at room temperature for 30-60 minutes.
5. To separate the serum, spin the blood sample in an ordinary or refrigerated centrifuge at 1500-2000 revolutions per minute for 15-20 minutes. If a centrifuge is not available, allow the blood sample to stand at room temperature overnight.
6. Use a sterile pipette to transfer the serum to a plain sterile tube or bottle with a screw top. The tube or bottle can be glass or plastic. Use a marker that will not wash off to record the identifying information on the sterile tube or bottle. Alternatively, write the information on an adhesive label using an indelible ink marker. Make certain the identifying information matches the information on the case investigation form.
7. If quantities of sera allow, put the sera into two sterile tubes or bottles so that a backup aliquot can be stored in case the need for retesting arises.
8. Check that the screw tops on bottles or tubes are tightly closed. It is advisable to cover screw tops with parafilm or tape to transport.
9. The serum specimens with copies of the laboratory request form (see example in Appendix F) should be transported to the rubella reference laboratory using standard procedures agreed at the national level.

## 9.2 Storing sera specimens

Storage may be at either 2° to 8°C (refrigerator temperature), or frozen (-20°C or below). It is best to avoid repeated freeze-thawing cycles, though one or two cycles will not affect rubella antibody assays. If transport to the reference laboratory is infrequent (e.g., at more than 48-hour intervals), it may be preferable to freeze sera and transport in an appropriate cold box with wet ice (or dry ice, if available) to the reference laboratory.

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### 9.3 Laboratory assays

A laboratory request form should accompany every blood sample. (See Appendix F for an example.)

The laboratory test will differ depending on the purpose for which the blood specimen has been collected:

- IgM test: to diagnose CRS in infants and to diagnose acute rubella infection.
- IgG test: to measure presence or absence of a protective level of anti-rubella IgG antibody in serosurveys.

### 9.4 IgM tests to diagnose CRS and rubella

For the IgM test, the IgM-capture enzyme immunoassay (EIA) is the test of choice. A list of companies supplying suitable EIA tests for rubella IgM appears in **Table 6**, which also indicates the time required to carry out each test. It is best to use the same kit over time, so there is consistency in data reporting. To conserve resources, it is important to choose a kit that uses the same filter to measure optical density (OD) values as the IgM kit being used to test for measles. If possible, a sample of positive and negative specimens and all inconclusive specimens (stored frozen) should be retested at a reference laboratory.

**Table 6: Selected rubella IgM assays based on the IgM-capture method (adapted from Hudson & Morgan-Capner 1996)**

Product name	Country of manufacture	Format	Duration (hours) <sup>1</sup>
Centocor Rubella M	United Kingdom	8 well strips	2.50
Eurogenetics Rubella IgM ELISA	Belgium	individual wells	2.50
HUMAN Rubella-Virus Direct IgM ELISA	Germany	8 well strips	1.25
Kodak Amerlite Rubella IgM Assay	United Kingdom	individual wells	2.10
Organon Rubenostika IgM	Holland	12 well strips	2.50
Sigma Rubella IgM (Capture)	United States	8 well strips	2.50
Sorin ETI-Rubek M Reverse	Italy	8 well strips	2.50

<sup>1</sup> Incubation times only

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## 9.5 IgG tests for serosurveys

For the IgG test, EIA is the test of choice. The IgG EIA test is available in commercial kits, can be used on a large scale, and could be readily adapted to automation. It is best to use the same kit over time, so there is consistency in data reporting.

Single radial haemolysis could be considered, but this test is not available in commercial kits and would need to be set up in the laboratory. Latex agglutination is a quick and easy test, but interpretation is subjective, so it is not generally recommended for serosurveys. Haemagglutination inhibition (HAI) should not be used, as false positive results may be obtained due to inhibitors of HAI which have not been completely removed from test sera.

Most but not all commercial rubella-specific IgG EIA test kits use a cut-off of 10 to 12 IU/ml and this is usually satisfactory for serosurveys. A cut-off below 10 IU/ml should not be used, as it is not known whether lower levels of antibody are protective and also because some assays are unreliable at low levels. Sera giving equivocal results should be re-tested by an alternative assay in a reference laboratory.

## 9.6 Specimen logbook

The laboratory should keep a specimen logbook to record information on all sera received, showing the date received, location (freezer number) where sera are stored, the assay performed, the date of testing, and the result.

## 9.7 Laboratory quality control

Candidate preparations of rubella-specific IgM antibodies and IgG antibodies are being tested by WHO International Laboratories (*WHO 1998*). When international standards become available, these should be used to calibrate serological tests for rubella-specific IgM and IgG.

Indicators of field and laboratory performance should be monitored, including:

- the proportion of samples received in good condition,
- the proportion of properly completed laboratory request forms, and
- the proportion of results reported within seven days of receipt of the specimen in the laboratory.

Virologists will need to work with the CRS/rubella surveillance coordinator(s) and programme epidemiologists to develop the most useful performance indicators for the full-scale surveillance system.

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# 10. Monitoring rubella vaccine coverage

Rubella vaccine coverage should be reported annually for all target groups receiving rubella vaccine. Both public sector and private sector delivery of rubella vaccine should be considered. Where private sector vaccine delivery data are not routinely reported, coverage surveys can be carried out (*EPI 1991a, WHO 1996b*). Rubella vaccine coverage for children under two years of age should be straightforward, by incorporating information from the national EPI coverage system. If rubella vaccine is delivered to school children, the cooperation of school health authorities and the Ministry of Education may be needed. Monitoring rubella vaccine coverage of women of childbearing age is similar to monitoring coverage of tetanus toxoid vaccine; a lifetime immunization record will be needed. Missed opportunity surveys should be conducted in settings where rubella vaccine is indicated (*EPI 1991b, Hutchins et al. 1990*).

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# Appendices:

**Appendix A : Surveillance of CRS in infants 0-11 months ..... 33**

**Appendix B : Congenital rubella syndrome case investigation form ..... 34**

*This form is to be completed whenever congenital rubella syndrome (CRS) is suspected in an infant. CRS should be suspected when the mother had suspected or confirmed rubella during the pregnancy; OR an infant aged 0-11 months has heart disease, cataract(s), and/or hearing impairment.*

**Appendix C : Surveillance of febrile rash illness in countries at measles/rubella elimination phase ..... 36**

**Appendix D : Laboratory work-up of suspected rubella in pregnancy ..... 37**

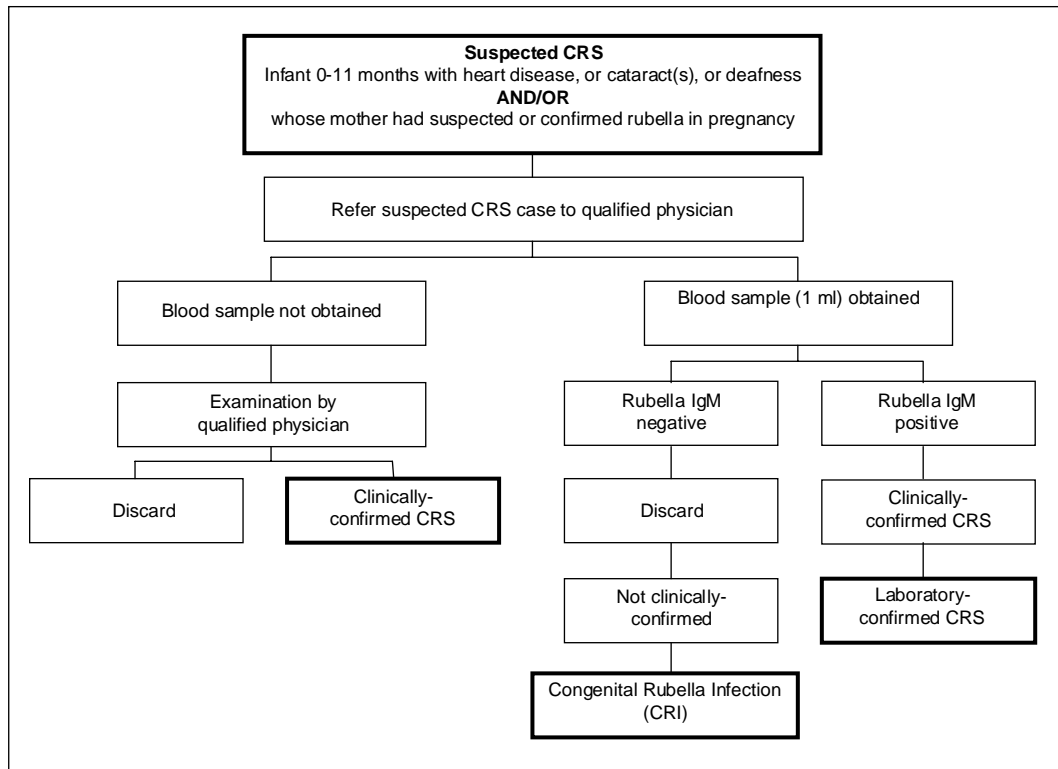
**Appendix E : Suspected measles/rubella case investigation form ..... 38**

*This form is to be completed whenever measles or rubella is suspected in a patient of any age. These patients generally have maculopapular rash with illness fever.*

**Appendix F : Laboratory request and results form ..... 40**

*This form is to accompany the specimen to the laboratory.*

## Appendix A: Surveillance of CRS in infants 0-11 months



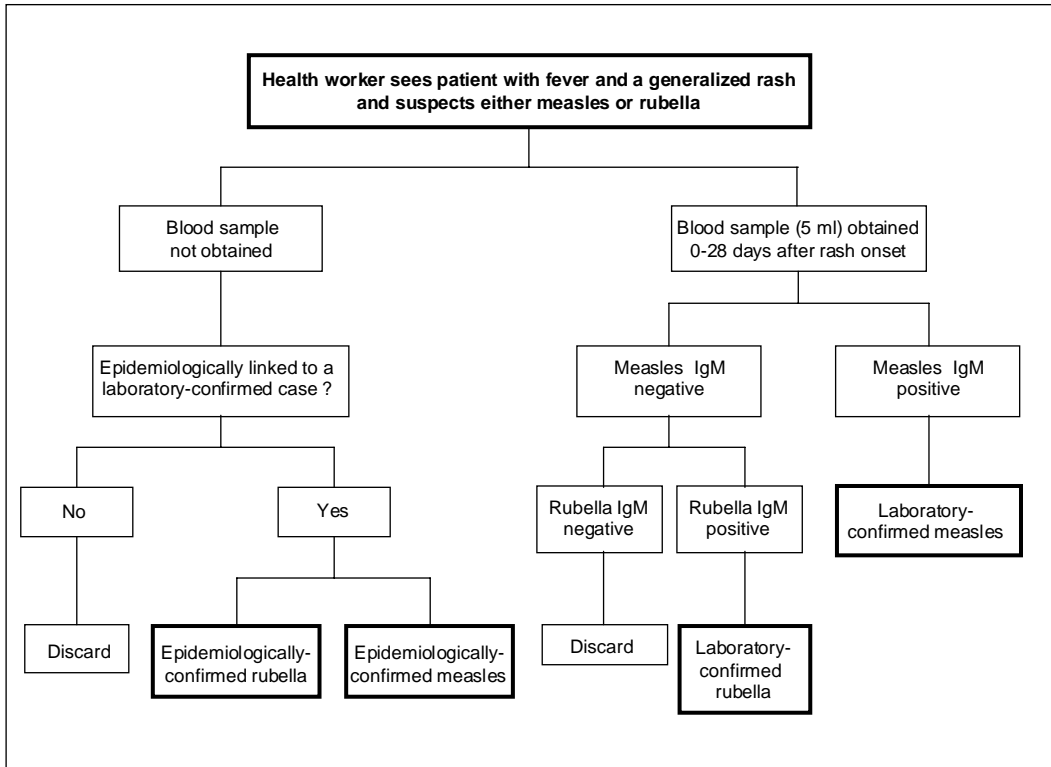
## Appendix B: Congenital rubella syndrome case investigation form

<b>Infant's identification</b>	
Name of child: _____	
Date of birth:     ___ / ___ / ___	
Sex:     M / F           Place infant delivered: _____	
Hospital/clinic record number: _____	
Name of mother: _____	
Address: _____ _____	
<b>Notification</b>	
Source: _____	
Date of notification:   ___ / ___ / ___	
Name of referring health worker: _____	
Address of referring health worker: _____ _____	
Telephone number: _____	
<b>Clinical signs and symptoms</b>	
<b>Group (a)</b>	
Congenital heart disease:	<b>YES / NO</b>
If yes, describe: _____ _____	
Cataract(s):	<b>YES / NO</b>
Pigmentary retinopathy:	<b>YES / NO</b>
Glaucoma:	<b>YES / NO</b>
Hearing impairment:	<b>YES / NO</b>
<b>Group (b)</b>	
Purpura:	<b>YES / NO</b>
Microcephaly:	<b>YES / NO</b>
Meningoencephalitis:	<b>YES / NO</b>
Jaundice:	<b>YES / NO</b>
Other abnormalities:	<b>YES / NO</b>
If yes, describe: _____ _____ _____	
Birth weight (grams): _____   If died, date of death:   ___ / ___ / ___	
Name of physician who examined infant: _____	
Address of physician: _____ _____	
Telephone: _____           Date infant examined:   ___ / ___ / ___	

**App B: Congenital rubella syndrome case investigation form (continued)**

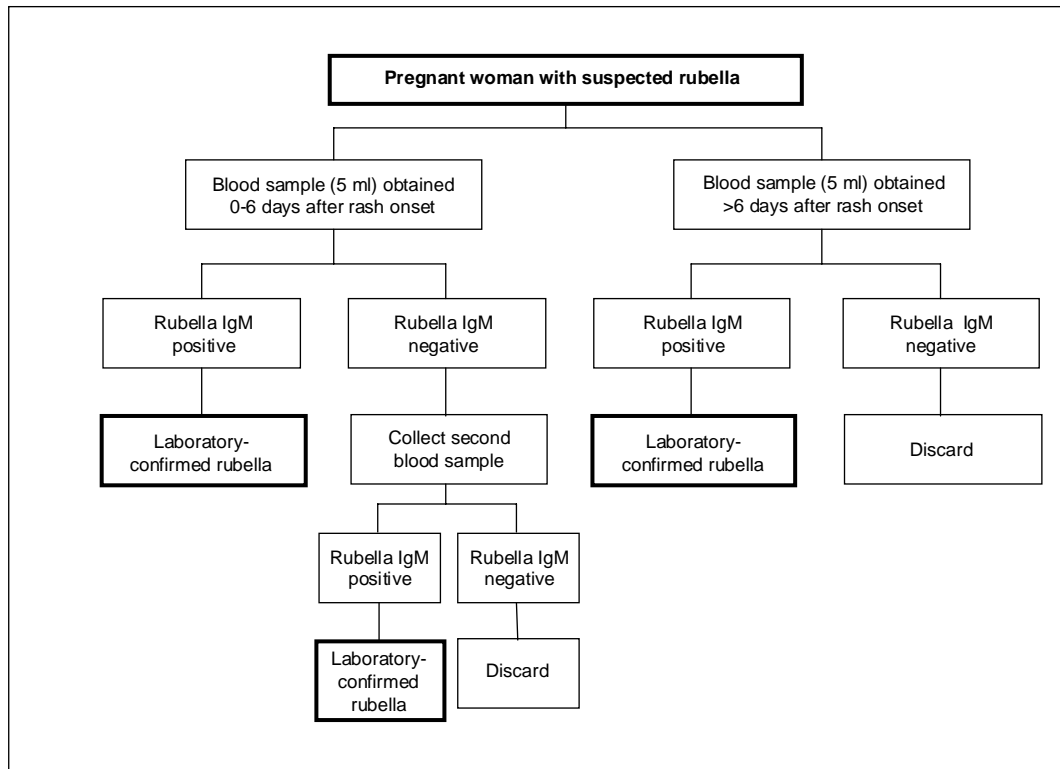
<b>Maternal history</b>		
Mother's age (years) _____		Number of previous pregnancies: _____
Vaccinated against rubella? <b>YES / NO</b>		If yes, give date: ____/____/____
Maculopapular rash illness with fever during pregnancy? <b>YES / NO</b>		If yes, give month: _____
If yes, was rubella laboratory confirmed in the mother? <b>YES / NO</b>		
Exposed during the pregnancy to any person (any age) with maculopapular rash illness with fever? <b>YES / NO</b>		If yes, give month: _____
Travel during pregnancy? <b>YES / NO</b>		If yes, give month: _____
If yes, describe where _____		
<b>Laboratory tests on infant</b>		
Date blood collected: _____		____/____/____
Date serum sent to rubella reference laboratory: _____		____/____/____
Name of rubella reference laboratory: _____		
Address: _____		
Telephone: _____		
Type of IgM test (name of manufacturer): _____		
Results: _____		
Date results received by investigator: _____		____/____/____
Date family informed of results: _____		____/____/____
<b>Final classification of case</b>		
No laboratory test, but clinically consistent with CRS = Clinically-confirmed CRS		
Positive IgM + clinically-confirmed = Laboratory-confirmed CRS		
Positive IgM + no CRS manifestations = Congenital Rubella Infection (CRI)		
<b>Investigator</b>		
Title: _____		
Address: _____		
_____		
_____		
Telephone: _____	Date form completed: _____	____/____/____

## Appendix C: Surveillance of febrile rash illness in countries at measles/rubella elimination phase



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## Appendix D: Laboratory work-up of suspected rubella in pregnancy



## Appendix E: Suspected measles/rubella case investigation form

<b>Patient's identification</b>			
Name of patient: _____			
Age (years): _____	Sex:    M /    F		
Immunized against measles? <b>YES / NO</b>	If yes, give date:    _____ / _____ / _____		
Immunized against rubella: <b>YES / NO</b>	If yes, give date:    _____ / _____ / _____		
Clinic where seen: _____			
Clinic record number: _____			
Address: _____			
_____			
_____			
<b>Notification</b>			
Source: _____			
_____			
Date of notification:    _____ / _____ / _____			
Name of referring health worker: _____			
Address of referring health worker: _____			
_____			
_____			
Telephone number: _____			
<b>Clinical signs and symptoms</b>			
Fever?	<b>YES / NO</b>	If yes, date of onset:    _____ / _____ / _____	
Generalized maculopapular (e.g. not vesicular) rash?	<b>YES / NO</b>	If yes, date of onset:    _____ / _____ / _____	
Duration: _____			
Pigmentary retinopathy:	<b>YES / NO</b>	Hearing impairment:	<b>YES / NO</b>
Conjunctivitis?	<b>YES / NO</b>	Coryza?	<b>YES / NO</b>
Cough?	<b>YES / NO</b>	Lymph nodes swollen?	<b>YES / NO</b>
Arthralgia/arthritis?	<b>YES / NO</b>	Patient hospitalized for this illness?	<b>YES / NO</b>
If yes, name of hospital: _____			
_____			
_____			
Pregnant?	<b>YES / NO</b>		
If yes, due date?    _____ / _____ / _____			
If yes, where will delivery take place? _____			

**App E: Suspected measles/rubella case investigation form (continued)**

<b>Epidemiological contact information</b>	
Was there contact with a suspected measles or rubella case in the month prior to rash onset?	
_____ measles	_____ rubella
_____ no	_____ unknown
Was there a confirmed case of measles or rubella in this area in the month prior to rash onset in this case?	
_____ measles	_____ rubella
_____ no	_____ unknown
Travel of the patient in the month prior to rash onset?	
_____ yes	_____ no
_____ unknown	
If yes, describe where? _____	
Was patient in contact with a pregnant woman since developing symptoms?	
_____ yes	_____ no
_____ unknown	
<b>Laboratory tests</b>	
Date blood collected:	____/____/____
Date serum sent to reference laboratory:	____/____/____
Name of reference laboratory: _____	
Address _____	
Telephone _____	
Measles IgM test result:	<b>POSITIVE / NEGATIVE / EQUIVOCAL / NOT DONE</b>
Rubella IgM test result:	<b>POSITIVE / NEGATIVE / EQUIVOCAL / NOT DONE</b>
Dengue IgM test result:	<b>POSITIVE / NEGATIVE / EQUIVOCAL / NOT DONE</b>
Other lab test results: _____	
Date results received by investigator:	____/____/____
Date patient informed of results:	____/____/____
<b>Final classification of case</b>	
_____ laboratory-confirmed measles	_____ laboratory-confirmed rubella
_____ laboratory-confirmed dengue	
_____ other _____	
_____ epidemiologically-confirmed measles	_____ epidemiologically-confirmed rubella
<b>Investigator</b>	
Title: _____	
Address: _____	
Telephone: _____	Date form completed: ____/____/____

## Appendix F: Laboratory request and results form

Country:	Patient number:	Date: / /			
Patient name:		Sex: M / F			
Date of birth:		Age in months:			
Name of parent of guardian:					
Address:					
Number of doses of measles vaccine:		Date of last dose:			
Number of doses of rubella vaccine:		Date of last dose:			
Date of onset of fever: / /		Date of onset of rash: / /			
Type of rash:					
Provisional clinical diagnosis:					
<b>Specimen</b>	<b>Date of collection</b>	<b>Date of shipment</b>			
(1)	/ /	/ /			
(2)	/ /	/ /			
(3)	/ /	/ /			
Name of person to whom laboratory results should be sent:					
Address:					
Telephone number:		Fax number:	Email:		
<b>For use by receiving laboratory:</b>					
Name of laboratory:					
Name of person receiving the specimen:					
<b>Specimen</b>	<b>Date received by laboratory</b>	<b>Date result</b>	<b>Type of test</b>	<b>Test result</b>	<b>Comment</b>
	/ /	/ /			
	/ /	/ /			
	/ /	/ /			
	/ /	/ /			