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Surveillance Guidelines for Measles, Rubella and Congenital Rubella Syndrome in the WHO European Region

Update December 2012

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ABSTRACT

The WHO Regional Committee for Europe adopted the goal of eliminating indigenous measles transmission in 1998. In 2005, the Regional Committee expanded this commitment to include rubella and set a date for the elimination of both diseases by 2010. Although Member States did make progress, through the implementation of a strategic plan, the goal was not achieved. The WHO Regional Committee for Europe acknowledged at its sixtieth session (2010) that the regional goal of eliminating measles and rubella is achievable, and set a new target date of 2015.

In the document *Eliminating measles and rubella and preventing congenital rubella infection, WHO European Region strategic plan 2005–2010*, key strategies are identified to meet the targets for interrupting transmission of indigenous measles and rubella and preventing congenital rubella infection. Strengthening surveillance systems by vigorous case investigation, including laboratory confirmation, is one of these key strategies.

In line with the elimination goal, *Surveillance guidelines for measles, rubella and congenital rubella syndrome in the WHO European Region* are intended to provide technical advice on the design and implementation of surveillance programmes. Surveillance indicators defined in these guidelines will be critical for assessing whether Member States have achieved the level of disease surveillance necessary for documenting elimination of indigenous measles and rubella transmission, and verifying that the Region's elimination objectives have been reached.

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Acknowledgments

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VPI welcomes any comments and suggestions with regard to this publication ***vaccine@euro.who.int***

Contents

Acronyms 3
1 Introduction 4
1.1 Objectives of surveillance and programme monitoring 4
2 Measles, rubella and CRS: disease description, epidemiology and diagnosis 8
2.1 Measles 8
2.2 Rubella 11
2.3 Congenital rubella syndrome 13
2.4 Rationale for disease elimination and an integrated approach to measles and rubella surveillance in the European Region 14
3 Case definitions for surveillance and reporting of measles and rubella 16
3.1 Measles 17
3.2 Rubella 18
3.3 Classification of cases by origin of infection 21
3.4 Measles and rubella outbreaks 22
4 Measles and rubella surveillance 24
4.1 Laboratory assessment algorithms for measles and rubella infection 26
4.2 Data collection and reporting 28
4.3 Reporting to WHO 30
5 Monitoring and evaluation 31
5.1 Surveillance performance indicators 31
5.2 Indicators for monitoring progress towards elimination 33
6 Surveillance of CRS 35
6.1 Rationale 35
6.2 CRS – clinical features, case classification and laboratory criteria for confirmation 35
6.3 CRS surveillance 39
6.4 Other approaches to identifying CRS cases 40
References 41
Annexes 45
Annex I Integrated measles and rubella case investigation form 46
Annex II Measles and rubella database for case-based reporting – CISID 48
Annex 3 Collection, storage and shipment of specimens for laboratory diagnosis and interpretation of results 51

Annex 4 Measles/rubella aggregate outbreak reporting form 58
Annex 5 Congenital rubella syndrome case investigation form 61
Annex 6. Steps for establishing a CRS surveillance system 63

Acronyms

CRS	congenital rubella syndrome
EBV	Epstein-Barr virus
ELISA	enzyme-linked immunosorbent assay
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
MMR	measles/mumps/rubella
MMRV	measles/mumps/rubella/varicella
MR	measles/rubella
PCR	polymerase chain reaction
RNA	ribonucleic acid
RT	reverse transcription
WHO	The World Health Organization European Region or Regional Office for Europe
VPI	Vaccine Preventable Diseases and Immunization Programme, DCE, WHO Regional Office for Europe
DCE	Division of Communicable Diseases, Health Security and Environment, WHO Regional Office for Europe
UNICEF	United Nations Children's Fund
ECDC	European Centre for Disease Prevention and Control
CDC	US Centers for Disease Control and Prevention
RC	Regional Committee
IVB	Immunization, Vaccines and Biologicals

1 Introduction

The European Region of the World Health Organization (WHO) has adopted the goal of eliminating endemic measles and rubella, which will also lead to elimination of congenital rubella syndrome (CRS). In 2005, in resolution EUR/RC55/R7, the WHO Regional Committee for Europe acknowledged that measles and rubella can be eliminated in the WHO European Region and that congenital rubella infections can be prevented by using combined measles and rubella vaccines in a routine two-dose vaccination schedule within childhood immunization programmes, by achieving and maintaining high coverage and by targeting susceptible populations, including women of childbearing age *(1)*. In 2010, the WHO Regional Committee for Europe recommitted to these goals, and changed the target date for elimination from 2010 to 2015 *(2)*. In 2012, the Global Measles Initiative was expanded to include the rubella goal and a new global strategic plan for measles and rubella was adopted *(3)*.

The key strategies for achieving measles and rubella elimination in the WHO European Region are as follows:

- Achieve and sustain very high vaccination coverage (≥95%), with two doses of measles vaccine and at least one dose of rubella vaccine administered through high-quality routine immunization services.
- Provide measles and rubella vaccination opportunities covering high-risk groups, including supplementary immunization activities, for all populations susceptible to measles and/or rubella.
- Strengthen surveillance systems through rigorous case investigation and laboratory confirmation of suspected sporadic cases and outbreaks.
- Improve the availability and use of high-quality, evidence-based information for health professionals and the public on the benefits and risks associated with immunization against measles and rubella.

1.1 Objectives of surveillance and programme monitoring

The purpose of disease surveillance is to provide information for public health action, i.e. to guide the planning, implementation and evaluation of public health interventions and systems *(4)*. It is important that disease surveillance is considered within the overall

information needs of an immunization programme, and that it supports effective programme management. This includes information about:

- cases and clusters of the disease (epidemiological surveillance);
- vaccination-related adverse events (immunization safety);
- routine immunization coverage (quality of programme delivery); *and*
- the possible accumulation of susceptible persons (epidemiological surveillance, outbreak investigation and seroprevalence surveys).

As the control of measles and rubella becomes more effective and countries approach the point at which these diseases can be eliminated, surveillance systems will be required to detect and facilitate the investigation and laboratory confirmation of all suspected cases. Such systems need to be sensitive, specific and case-based and capable of determining whether cases can be linked, i.e. whether sustained transmission is occurring. Since children and adults of any age can be susceptible to measles and rubella, and cases may occur at any time of the year as a result of importations, surveillance for these diseases must be carried out nationwide, among the general population, all year round.

As part of an elimination strategy, surveillance for measles and rubella has two objectives:

1. To detect, investigate and characterize sporadic cases and outbreaks/chains of transmission, to:
   - ensure proper management of cases and contacts;
   - understand the reasons for the occurrence and transmission of disease (e.g. importation, failure to vaccinate or failure of the vaccine);
   - assess the sustainability of transmission (outbreak size, duration of transmission);
   - identify populations at risk of transmission; *and*
   - ensure a rapid and appropriate public health response.

2. To monitor disease incidence and circulation of the virus in order to:
   - assess the current level of disease incidence and virus circulation;
   - identify the geographical origin of circulating viruses (imported or endemic);
   - provide information for priority-setting, planning, implementation and resource allocation for prevention programmes, and for evaluating control measures;
   - identify changes in risk groups and disease epidemiology;
   - assess the circulation of virus genotypes at national, regional and global levels; *and*

- assess and document progress towards elimination, providing information for verification of measles and rubella elimination.

Monitoring and evaluation of the surveillance system will be critical for assessing its performance by providing evidence of the validity of the data (i.e. the absence of confirmed cases is attributable to the absence of disease rather than to underdetection or underreporting) and identifying areas where surveillance needs to be strengthened.

In addition to disease surveillance, reliable systems to monitor immunization coverage and quality and safety of vaccines should be in place at national and subnational levels. Detailed information on cold-chain monitoring, injection safety and surveillance for adverse events following immunization can be found in other WHO documents at the Immunization, Vaccines and Biologicals (IVB) document centre[1].

Elimination requires the achievement and maintenance of low levels of susceptibility in the population of all ages at each administrative level. The objectives of monitoring susceptibility are to:

- identify population subgroups at higher risk for disease transmission based on age, social or geographical characteristics, and evaluate the risk of outbreaks in these groups; and
- provide information for the planning of interventions to reduce susceptibility in identified population subgroups and thus avoid outbreaks.

The epidemiology of measles and rubella in the European Region varies between countries, reflecting different challenges in controlling these diseases. Despite the availability of highly effective vaccines and very good overall vaccine coverage in most of the 53 Member States, specific population subgroups remain susceptible to these diseases *(5)*. Some young adults remain susceptible to measles and rubella, as they may not have been vaccinated, or may not have contracted the diseases because of the decreasing incidence of measles and rubella following vaccine introduction. In many countries, immunization programmes may not adequately reach minorities or geographically or socially marginalized populations. People holding specific philosophical or religious beliefs may be reluctant to be immunized or actively oppose vaccination *(6-9)*. These and other groups may influence others with misinformation about the safety and effectiveness of vaccines. Susceptible individuals are often geographically clustered, creating “pockets of susceptibility” at a greater risk of large

[1] See http://www.who.int/immunization/documents/en/, accessed 15 December 2012.

outbreaks. At the same time, increased population movements related to migration, immigration and work-related or leisure-related travel, increase the potential for disease transmission from countries with a high incidence of measles or rubella to countries and populations where the incidence is low or the disease has been eliminated. Lack of health care worker awareness of the benefits of vaccination and lack of strong provider recommendations may be contributing to suboptimal vaccination coverage in some countries. A high level of vaccine coverage (≥95%) with two doses of measles vaccine and at least one dose of rubella vaccine must be achieved among susceptible subgroups if measles and rubella are to be eliminated in the Region.

The elimination of measles and rubella is defined as the absence of endemic measles or rubella transmission in a defined geographical area (e.g. region) for at least 12 months in the presence of a well performing surveillance system (10). However, imported cases may still occur in elimination settings.

Progress towards elimination should be monitored and supported by a robust and sensitive surveillance system. Information provided by the surveillance system, along with the information on population immunity, will be crucial for verification of measles and rubella elimination in the Region. Verification of elimination will require the absence of sustained transmission throughout the Region for a period of at least 36 months. The system's performance should be assessed by surveillance indicators, which are discussed later in this document.

The present document, *Surveillance guidelines for measles, rubella and congenital rubella syndrome in the WHO European Region,* primarily addresses issues related to disease surveillance and monitoring of progress towards elimination in the Region. This document provides guidance and recommendations, and describes best practices for surveillance for measles, rubella and CRS. It is intended for national programme managers, and those responsible for such surveillance, to aid them in the development of their country-specific surveillance plans and to provide a framework for monitoring progress and documentation for verification of the elimination of measles and rubella in the Region. This document does not directly address clinical aspects of measles and rubella, e.g. clinical management of measles cases or of pregnant women exposed to rubella.

2 Measles, rubella and CRS: disease description, epidemiology and diagnosis

2.1 Measles

Measles is one of the most contagious viruses, with a secondary attack rate among susceptible individuals higher than 90%. The virus can be transmitted in the air (aerosolized) in respiratory droplets, or by direct or indirect contact with the nasal and throat secretions of infected persons. Individuals with measles are considered infectious from four days before to four days after the onset of rash *(11)*. Following exposure, the incubation period before onset of the first symptoms is usually 10–12 days. The rash usually appears 14 days after exposure (range 7–18 days) *(11, 12)*[2].

Approximately 30% of reported cases of measles involve one or more complication. In developed countries these include otitis media (7–9%), pneumonia (1–6%), diarrhoea (6%), blindness and post-infectious encephalitis (1 per 1000 cases). The risk of serious measles complications is higher in infants and adults. A less common but very serious complication is subacute sclerosing panencephalitis (1 per 100 000 cases) *(12).*

Measles remains a leading cause of death globally among young children, despite the availability of safe and effective vaccines for over 40 years. An estimated 139 000 children died worldwide from measles in 2010, a 74% reduction compared with 2000 *(14)*. The 2005 measles mortality reduction goal established by WHO and the United Nations Children's Fund (UNICEF), which was to reduce the number of measles deaths by 50% from 2000 levels, has now been achieved *(15, 16)*. There is a new goal to achieve a 95% reduction worldwide by 2015, primarily by targeting children in the WHO regions with the highest number of measles deaths (Africa and South-East Asia) *(3)*.

[2] The incubation period from exposure to the onset of rash is with a range of 7–18 days, but rarely, as long as 19–21 days. Use of immunoglobulins in the early stage of infection can prolong incubation. Some countries use 21 days as the longest incubation period *(11, 12, 13)*.

In settings where measles remains endemic, transmission of the virus shows a seasonal trend: in temperate areas, the most intense virus transmission usually occurs in late winter and spring. Before vaccination programmes, childhood infection was almost universal. Measles epidemics occurred in approximately four-year cycles, with periods of very high incidence alternating with low-incidence inter-epidemic periods. With the introduction and increased coverage of measles vaccination, the incidence of the disease during epidemic periods has fallen and the intervals between epidemics have lengthened. Very high levels of population immunity have led to the elimination of the disease in many countries, but if this level of population immunity is not maintained, the cyclical pattern of measles outbreaks will reappear.

In contrast to developing countries, the majority of cases in many European countries occur in adolescents and adults *(17, 18)*. In most countries of the Region, measles vaccination coverage and population immunity among the general population are high and the cyclical pattern of measles is not seen. However, there are still susceptible groups in most countries. While some of these susceptible individuals live within communities with high levels of population immunity to measles and rubella, and are therefore at low risk of exposure to wild measles virus following an importation, others live in settings where the risk of exposure and further transmission between individuals is very high after the virus is introduced.

The case–fatality ratio for measles is highest in infants aged under 12 months. In developed countries, the case–fatality ratio is 0.05-0.1 per 1000 cases, much lower than in developing countries where it can be 3–6% *(15, 19)*. Malnutrition and severe immunodeficiency (e.g. as a consequence of an advanced infection with human immunodeficiency virus) are risk factors for complications, including death.

2.1.1 Laboratory diagnosis of measles

In the European Region, where the incidence of measles is low, a clinical diagnosis of measles in the absence of a confirmed outbreak has a low positive predictive value, and clinical signs are unreliable as the sole criteria for diagnosis. A number of other infections can present with a rash resembling measles, therefore laboratory assessment is required for accurate diagnosis.

Measles-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) are both produced during the primary immune response and can be detected in the serum within days of rash onset, using a sensitive enzyme-linked immunosorbent assay (ELISA). Approximately 70%

of measles cases are IgM-positive at 0–2 days after the rash onset, and 90% are positive 3-5 days after rash onset. IgM antibody levels peak after 7–10 days and then decline, being rarely detectable after 6–8 weeks. IgG antibody levels peak within three weeks and persist long after the infection. Serum and secretory immunoglobulin A (IgA) antibodies are also produced. Re-exposure to measles induces a strong anamnestic immune response with a rapid boosting of IgG antibodies, preventing clinical disease. Measles virus can be isolated from conventional clinical specimens (nasopharyngeal swab, urine or peripheral blood mononuclear cells) up to five days following onset of the rash and may be detected using polymerase chain reaction (PCR) assays on specimens obtained up to seven days or more after onset of the rash. Recommendations for laboratory confirmation of the disease for surveillance have been described in the WHO *Manual for the laboratory diagnosis of measles and rubella virus infection (20)*.

WHO recommends IgM antibody detection by ELISA as the standard test for routine measles surveillance.

In addition to IgM antibody detection, measles can be diagnosed using other methods, including a minimum fourfold increase in IgG titre, antigen detection by immunofluorescence, reverse transcription (RT) PCR to detect measles virus ribonucleic acid (RNA), or isolation of measles virus. False-positive IgM test results may sometimes occur due to cross-reacting IgM antibodies to other agents (e.g. Epstein-Barr virus [EBV], human parvovirus B19), rheumatoid factor or other auto-antibodies, and polyclonal stimulation of IgM response by EBV.

A positive IgM antibody test in recently vaccinated individuals must be interpreted according to the clinical signs and the local epidemiology of disease. Mild rash and low-grade fever, usually without other symptoms of measles (cough, coryza or conjunctivitis), can be observed 1-2 weeks after measles vaccination in some vaccine recipients *(10, 13, 21)*.

In countries with low measles incidence, the use of IgM alone to diagnose a single case of measles without evidence of other cases in the community may not be sufficient, and efforts should be made to confirm the diagnosis using other laboratory methods in addition to the IgM test, and/or to rule out other diseases with similar clinical presentation.

2.2 Rubella

Rubella is an acute viral illness, characterized by mild maculopapular rash often with postauricular or suboccipital adenopathy. Usually mild in children, rubella in adults may be accompanied by low-grade fever, headache and arthralgias. Less common complications are thrombocytopenia and encephalitis (1 per 6000 cases), which may be fatal. Up to 50% of infections with the rubella virus can be asymptomatic. Like measles virus, rubella virus is also transmitted by respiratory droplets and by direct or indirect contact with the nasal and throat secretions of infected persons, but is less contagious. Individuals are most infectious when the rash is erupting, but they may shed virus from seven days before to 14 days after the onset of rash. Following exposure, the incubation period before onset of symptoms is usually 14–18 days (range 12–23 days). The outcome of rubella is most serious when infection occurs during early pregnancy, as it can result in spontaneous abortion, stillbirth or an infant born with a combination of birth defects, known as CRS *(22, 23, 24)*.

In the pre-vaccine era, the epidemiology of rubella was similar to the epidemiology of measles, with seasonal variation and regular epidemic peaks alternating with low-incidence periods. In temperate climates, regular seasonal increases of rubella occurred in spring, with small epidemics every three to four years, and larger epidemics every six to nine years *(22, 23)*.

Rubella vaccination programmes have been highly effective in modifying the epidemiology of rubella, and a number of countries have eliminated the disease, with a similar effect to that of measles vaccination programmes on measles *(22, 25)*. However, in many countries of the Region, rubella vaccination has been introduced in different ways and often much later than measles vaccination. This has resulted in marked differences in rubella susceptibility profiles and rubella epidemiology across these countries. In addition, rubella surveillance is not well established in many countries, making estimates of the true burden in Europe difficult.

2.2.1 Laboratory diagnosis of rubella

A number of infections can present with signs and symptoms compatible with rubella. In addition, up to 50% of infected persons may have minimal or no clinical symptoms. Therefore, a laboratory assessment is critical for confirmation of a clinical rubella diagnosis.

Humoral and cell-mediated immunity develop following natural infection and with immunization. With natural infection, IgM antibodies become detectable within 3–4 days and IgG antibodies within one week of the onset of rash. Rubella-specific IgM can often be detected in individuals up to two months after illness and, in a decreasing percentage of individuals, up to six or seven months after natural infection, vaccination and reinfection *(26)*. In addition, false-positive IgM test results may occur because of cross-reacting IgM antibodies (e.g. to EBV, human parvovirus B19, etc.), rheumatoid factor or other auto-antibodies, and polyclonal immune stimulation by EBV.

Following infection, the virus can be isolated from nasopharyngeal secretions from a few days before to up to seven days after the onset of rash. The detection of viral RNA by RT-PCR may be possible for 3–4 days longer. However, the optimal time to collect specimens is within four days of the onset of symptoms *(20, 22, 26)*.

WHO recommends IgM antibody detection by ELISA as the standard test for routine rubella surveillance.

In countries with low incidence of rubella, a positive rubella IgM result in a person without known exposure to other cases in the community or through travel to endemic countries should be assessed using other laboratory methods in order to distinguish a primary rubella infection from a false-positive result. Recommendations for testing are described in the WHO *Manual for the laboratory diagnosis of measles and rubella virus infection (20)*.

2.2.2 Rubella infections in pregnant women

Cases of rubella in pregnant woman should be reported like any other rubella case and have pregnancy status noted on the report form. A single positive IgM test result is sufficient for classifying a case as laboratory-confirmed for surveillance purposes. However, for clinical management and medical decision-making, additional testing (detection of a significant rise of IgG antibodies, avidity testing, rubella immunoblot, virus detection or virus isolation) may be needed. A consultation with a medical expert is strongly recommended. Although not included in this document, detailed procedures should be in place in all Member States for appropriate screening and follow-up of pregnant women exposed to rubella, given the serious consequences of rubella infection during pregnancy *(27)*.

Pregnant women known to have been exposed to rubella should be assessed for rubella-specific IgG antibody and those found to be negative should be monitored for IgM and IgG

seroconversion and for the outcome of their pregnancies. Pregnant women found to be susceptible should be vaccinated after delivery.

A registry of pregnant women with rubella can be used for recording pregnancy outcomes (e.g. abortion, stillbirth, defects associated with congenital rubella) and for laboratory follow-up of infants (See Chapter 6).

2.3 Congenital rubella syndrome

The most serious consequence of rubella virus infection can develop when a woman becomes infected during pregnancy. Infants infected with rubella virus in utero may have a variety of physical defects, known collectively as congenital rubella syndrome (CRS). This is most likely to develop with maternal infection during the first 12 weeks of pregnancy, although isolated birth defects, particularly sensorineural hearing impairment, can be found in infants with maternal infection at up to 20 weeks of pregnancy *(22)*. CRS is seen in 0.6–2.2 children per 1000 live births during epidemics in countries without rubella immunization programmes *(28)*.

The clinical features associated with CRS are: ophthalmic (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy and chorioretinitis); auditory (e.g. sensorineural hearing impairment); cardiac (e.g. patent ductus arteriosus, peripheral pulmonary artery stenosis, or ventricular septal defects); and craniofacial (e.g. microcephaly). CRS can also present with neonatal manifestations that include meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia and radiolucencies in the long bones (a characteristic radiological pattern of CRS). Thrombocytopenia can be fatal. Interstitial pneumonitis is also a complication of CRS in infancy *(29)*.

Infants with CRS who survive the neonatal period may face serious disabilities (such as visual and hearing impairment) and have an increased risk of developmental delays, type I diabetes mellitus and thyroiditis. A progressive rubella panencephalitis, resembling subacute sclerosing panencephalitis, has been observed in a few individuals with CRS *(22, 30-32).*

Infants with congenital rubella infection will have a positive rubella-specific IgM test at or shortly after birth, at least through the first three months of life. Because some infants do not test positive at birth, a second IgM test should be done shortly after an initial negative result

if there is clinical suspicion. Most infants with CRS will be IgM-positive between three and six months of life; however, the laboratory confirmation of a possible congenital rubella case in an infant aged over six months should not rely on the IgM test alone. In the absence of vaccination or postnatal rubella, congenital rubella can also be confirmed by serial IgG testing for the sustained presence of IgG over several months.[3] All congenitally infected infants, including those without clinical manifestations of CRS, may shed virus for up to at least one year of age and can transmit rubella to others *(27)*.

2.4 Rationale for disease elimination and an integrated approach to measles and rubella surveillance in the European Region

Measles and rubella infections have many similarities. Both are viral diseases caused by pathogens that infect only humans. In the absence of prevention, both can have a serious impact on a population's morbidity and mortality. Both are also preventable with safe and widely used vaccines, which are often given as a combined vaccine. These characteristics make elimination of both diseases feasible.

Strategies recommended for elimination of these diseases depend on local epidemiology, historical vaccination coverage and the ability of the health system to deliver vaccine with high coverage to susceptible groups of people. All Member States currently have routine two-dose measles and rubella vaccination programmes using combined vaccines (usually measles/mumps/rubella (MMR) vaccine). Many countries that have recently introduced rubella vaccine have also undertaken supplementary immunization activities using combined measles and rubella (MR) vaccine with a strategy targeting susceptible children, adolescents and women of childbearing age, or in some cases adults of both sexes.

Integrating rubella and measles surveillance is cost-effective, given that the symptoms of the diseases are similar and both diseases commonly affect the same age groups. Thus, testing of specimens of suspected measles or rubella cases (at least IgM-negative ones) for the

[3] Maternal IgG will be declining or absent after six months of age.

other disease is clinically and epidemiologically sound as it allows to confirm or rule out each of two diseases.

As the incidence of measles and rubella declines, Member States will need to ensure that their surveillance systems remain sensitive to the detection of sporadic cases. Based on the experience of countries that have eliminated measles, the principal benchmark for assessing the quality of surveillance in the absence of, or at low incidence of, measles and/or rubella is the rate of suspected cases which have been investigated and discarded. The rate of discarded cases should be at least 2 per 100 000 population per year at the national level, and in >80% subnational administrative units (additional details are given in Chapter 5).

Achieving this benchmark requires that all sporadic illnesses clinically consistent with measles or rubella be thoroughly investigated and adequate specimens obtained for laboratory confirmation and, if possible, virus isolation. If serum specimens have not been obtained, or were collected outside the time period optimal for IgM detection, other tests or types of specimens should be used to determine etiology. In the absence of laboratory results, cases clinically consistent with measles or rubella which cannot be epidemiologically linked to other confirmed cases should be classified as clinically compatible cases and reported to the surveillance system. In countries with an annual incidence of measles or rubella of <1 per 1 000 000 population, all cases should be either laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case.

3 Case definitions for surveillance and reporting of measles and rubella

Surveillance systems use case definitions designed to standardize reporting across health facilities and at various levels of the health system – subnational, national and international. This facilitates aggregation, analysis and interpretation of data, as well as a comparison between geographical areas and over time. These definitions are for surveillance purposes and do not replace clinical diagnosis. The case definitions for measles and rubella include the following categories: suspected, laboratory confirmed, epidemiologically linked, clinically compatible and discarded cases.

3.1 Measles

The clinical criteria for measles are:

- fever *and*
- maculopapular rash (i.e. non-vesicular rash) *and*
- cough or coryza (runny nose) or conjunctivitis (red eyes).

The laboratory criteria for measles surveillance case confirmation are:

- measles IgM antibody detection *or*
- measles virus isolation *or*
- measles viral RNA detection by RT-PCR *or*
- a significant rise in measles IgG antibody in paired sera.

Box 1 sets out the case classifications for surveillance for measles.

Box 1

Measles case definitions for surveillance purposes

Case category	Definition
Suspected	A case with signs and symptoms consistent with clinical criteria of measles.
All suspected cases have to be investigated and classified based on clinical, laboratory and epidemiological data as one of the following:	
Laboratory confirmed	A suspected case which meets the laboratory criteria for measles case confirmation.
Epidemiologically linked	A suspected case which has not been adequately tested by laboratory and which was in contact with a laboratory-confirmed measles case 7–18 days before the onset of rash.
Clinically compatible	A suspected case which has not been adequately tested by laboratory and has not been epidemiologically linked to a confirmed measles case.
Discarded	A suspected case which was investigated and discarded, either through negative results of adequate laboratory testing for measles or by an epidemiological link to a laboratory-confirmed case of another disease.

3.2 Rubella

The clinical criteria for rubella are:

- maculopapular rash *and*
- cervical, suboccipital or postauricular adenopathy, or arthralgia/arthritis.

The laboratory criteria for rubella surveillance case confirmation are:

- rubella IgM antibody detection *or*
- rubella virus isolation *or*
- rubella viral RNA detection by RT-PCR *or*
- a significant rise in rubella IgG antibody in paired sera.

Box 2 sets out the case classifications for surveillance for rubella.

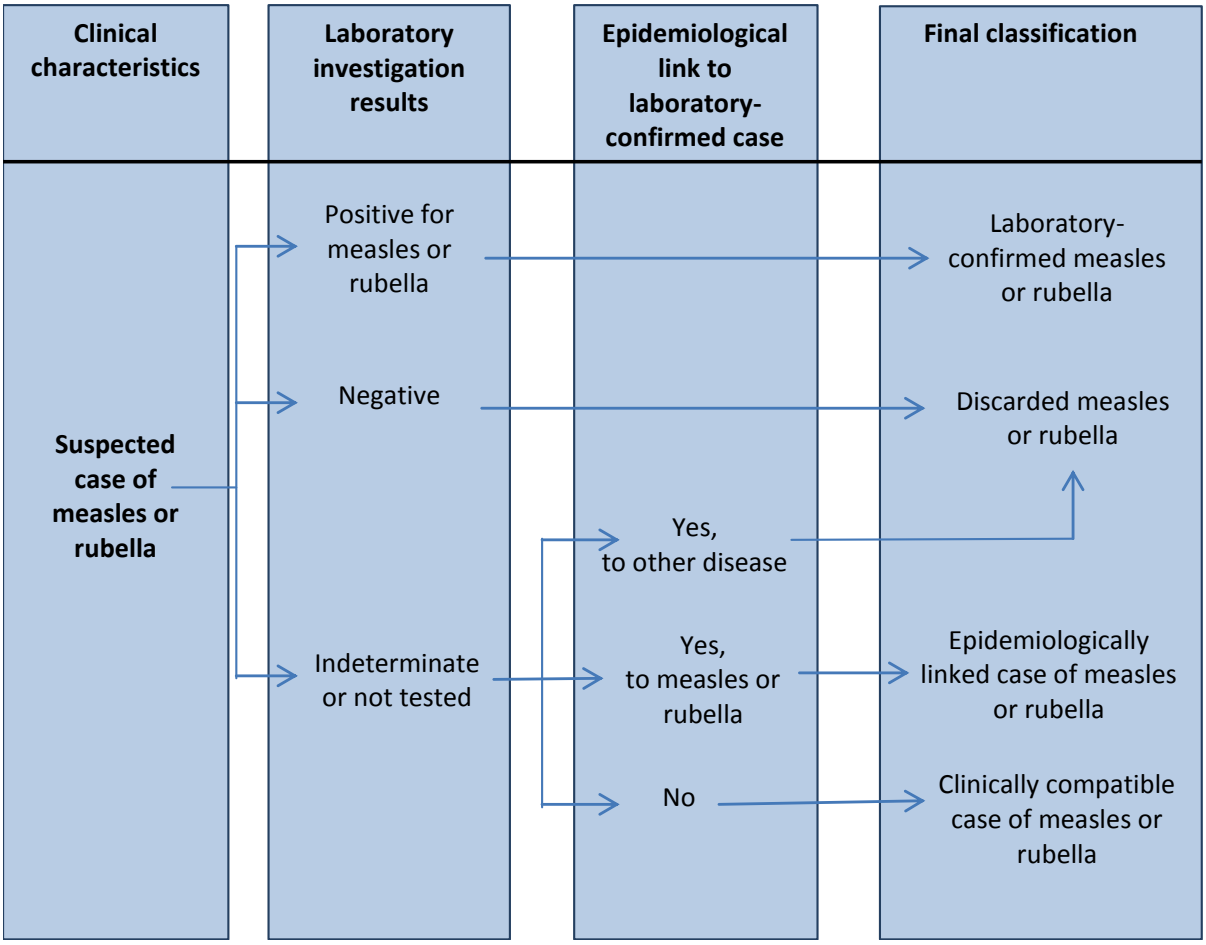
Box 2

Rubella case definitions for surveillance purposes

Case category	Definition
Suspected	A case with signs and symptoms consistent with rubella clinical criteria.
All suspected cases have to be investigated and classified based on clinical, laboratory and epidemiological data as one of the following:	
Laboratory confirmed	A suspected case which meets the laboratory criteria for rubella case confirmation.
Epidemiologically linked	A suspected case which has not been adequately tested by laboratory *and* which was in contact with a laboratory confirmed rubella case 12–23 days before the onset of symptoms.
Clinically compatible	A suspected case which has not been adequately tested by laboratory and has not been epidemiologically linked to a confirmed rubella case.
Discarded	A suspected case which was investigated and discarded, either through negative results of adequate laboratory testing for rubella or by an epidemiological link to a laboratory-confirmed case of another disease.

A case-classification flowchart for measles and rubella surveillance is shown in Fig. 1.

Fig. 1. Case classification algorithm for measles and rubella*



* For operational approach to interpreting positive measles and rubella IgM results in special circumstances, see Box 3.

Box 3

Operational approach to interpreting measles and rubella IgM results in special circumstances

- **Specimen taken early after rash onset**
  In case of negative IgM result in a serum sample taken earlier than four days after onset of the rash, a second sample should be taken between four and 28 days following onset of the rash. If obtaining the second sample is not feasible, the case should be classified based on the results of the available sample.

- **Indeterminate results**
  Specimens with indeterminate IgM results should be retested. If the test result remains indeterminate following repeat testing, the sample may be tested by an alternate method or another sample obtained and tested. If the results continue to remain indeterminate, or additional testing is not feasible, the case should be classified based on the presence of an epidemiological link to another laboratory-confirmed case.

- **Results in recent vaccine recipients**
  Recent recipients of measles and/or rubella vaccine are expected to have detectable IgM for the respective antigens. Serological techniques cannot distinguish between immune responses to natural infection and immunization; only genetic characterization of the virus can help distinguish an IgM response to natural infection from the one induced by the vaccine. Suspected cases with virus characterization performed in which only vaccine, but not wildvirus is detected, should be classified as “discarded”.

  An operational approach to classification of suspected cases with an IgM-positive result which have a recent history of vaccination but in which virus characterization has not been performed, is as follows *(10, 20)*.

  Generally, any suspected case with positive IgM result, including recent vaccine recipients, should be considered laboratory-confirmed, EXCEPT cases which meet ALL of the criteria listed below. These cases should be discarded.

  The criteria for discarding IgM-positive cases in recent vaccine recipients:

  - history of vaccination with relevant vaccine seven days to six weeks prior to specimen collection;
  - rash onset 7-14 days after vaccination;
  - active search in community does not reveal evidence of virus transmission;
  - no history of travel to areas where the virus is known to be circulating.

  The same algorithm applies to recently vaccinated cases with other serological evidence of acute infection (i.e. significant increase in IgG antibodies).

3.3 Classification of cases by origin of infection

As countries approach measles or rubella elimination, cases should be classified both according to the case-confirmation status (i.e. laboratory confirmed, epidemiologically linked, or clinically compatible) and origin of infection (i.e. endemic, imported, import-related or of unknown origin). The definitions and classification of measles and rubella cases by their origin are shown in Box 4.

Box 4

Case definitions for measles or rubella cases by their origin

Case category	Definition
Endemic	A case resulting from endemic transmission of the virus (i.e. virus present at the territory for ≥12 months) as confirmed by laboratory testing or epidemiological linkage.
Imported	A case with virological or epidemiological evidence, or both, of exposure outside the region or country during the 7–18 days (for measles) or 12-23 days (for rubella) prior to rash onset.
Import-related	A case with locally acquired infection but caused by imported virus, as supported by epidemiological or virological evidence, or both. The index case for this infection/chain of transmission is an imported case. If virus transmission related to importation persists for ≥12 months, cases are no longer considered to be import-related, but endemic.
Unknown origin of infection	A case where the origin of infection cannot be determined. There may be objective reasons making classification into one of the above categories impossible, but cases of unknown origin may also be indicative of endemic transmission missed because of suboptimal performance of the surveillance system.

To make this classification possible, national surveillance systems must have reliable epidemiological and virological data on measles and rubella for a minimum period of 12 months, with a comprehensive database of virus genotypes.

The following table illustrates the 12 possible classification categories for every measles or rubella case in low-incidence settings.

Table 1

Classification of measles or rubella cases, by confirmation status and origin of infection

Origin of infection	**Case classification**		
	Laboratory-confirmed	Epidemiologically linked	Clinically compatible
Endemic	a	b	c
Imported	d	e	f
Import-related	g	h	i
Unknown	j	k	l

3.4 Measles and rubella outbreaks

In countries with elimination goals, outbreaks of measles and rubella are defined as follows.

- Measles outbreak – two or more confirmed cases which are temporally related (with onset of rash in cases occurring between 7 and 18 days after exposure), and epidemiologically or virologically linked, or both.

- Rubella outbreak – two or more confirmed cases which are temporally related (with onset of rash in cases occurring between 12 and 46 after exposure), and epidemiologically or virologically linked, or both.[4]

In populations with very high immunity (natural or due to immunization), virus transmission after importation is usually self-limited and results in sporadic cases or small clusters/outbreaks which are resolved without intervention. However, virus introduction into

[4] The timeframe includes two incubation periods owing to the frequency of subclinical rubella infections.

pockets of susceptibles or in population groups with large numbers of susceptibles may result in large-scale, sometimes nationwide, outbreaks.

Outbreaks should be investigated so that their extent and origin can be determined. This information will lead to a better understanding of their epidemiology and help with defining and tailoring interventions in order to decrease the size of susceptible populations and control the outbreaks.

4 Measles and rubella surveillance

Public health surveillance requires prompt dissemination of information to those who need it so that appropriate action can be taken at each level of the health system. It is critical that surveillance and response occur at national and subnational levels. In the case of diseases where the target is elimination, it is also critical that reporting, response and feedback also take place at the international level through:

- prompt communication of data, information and reports between Member States and WHO, European-Union-related institutions and other European networks; and
- provision of samples/strains/sequence data to WHO reference laboratories.

The general logistics of surveillance are presented and discussed in *Making surveillance work. Module 3: logistics management (33).*

With the goal of eliminating measles and rubella in the WHO European Region, it is critical that all countries should implement case-based surveillance to detect, investigate and confirm every suspected measles and rubella case in the community. Comprehensive nationwide surveillance systems based on standardized case definitions are essential to ensure that all necessary information on individual cases is collected and reported through collaboration by clinicians, epidemiologists and virologists. The information sufficient for monitoring progress and documentation for achieving elimination can be obtained only through case-based surveillance, which implies reporting of individual cases rather than reporting aggregated numbers.

National health authorities and technical experts should create protocols for measles and rubella surveillance and case investigation most appropriate for their health system. This protocol should define roles of health institutions and different technical experts in investigation of measles cases, together with standard operating procedures. The regional guidelines should be used as a background document for establishing the surveillance system, as this will assure collection of uniform critical information in all Member States, harmonization of surveillance and response activities, and comparison and analysis of data at the regional level.

Investigation of measles and rubella cases begins with a clinician who suspects measles or rubella in a patient with relevant clinical manifestations and notifies the public health authorities. Under case-based surveillance, epidemiological investigation including laboratory testing should be conducted for all suspected cases of measles and rubella immediately upon notification. The following practical steps should be part of the case investigation:

- A unique identifier (or EPID number) should be assigned to each case (e.g. country code + district code + year + sequential number by order of reporting), to facilitate further collection and merging of clinical, epidemiological and laboratory data. In many systems, the identifier is created by the epidemiology unit after notification.
- Accurate relevant information should be obtained from the case (or the family if necessary), including demographic and clinical information, vaccination status, pregnancy status and travel history. This is usually the responsibility of clinicians and epidemiologists. Availability of accurate and timely information will decrease time needed for investigation and help with laboratory investigation.
- An attempt should be made to identify the source of infection for a case (contact with possible infectious measles or rubella cases, travel in an epidemic area, etc.) and active search for other cases in the area should be carried out.
- Outbreaks should be adequately investigated and documented. Every outbreak should have a unique identifier and all cases from the same outbreak should be coded accordingly. Adequate clinical and epidemiological investigation linking a particular case with an outbreak will decrease the work burden on laboratories.
- As laboratory results are critical for case classification, specimens should be collected for confirmation and virus isolation/detection. This is recommended as a step in the clinician's work during the first (and maybe only) contact with the patient, or as soon as feasible.
- The investigation form should be completed to collect data for further analysis (an example of a form and a list of variables to collect are given in Annexes 1 and 2). Since information will be collected by different institutions and will become available at different times (e.g. laboratory results later than immunization status), it is important to ensure that all participants know which information they have to collect and to whom it should be transmitted.
- Case investigation should include identification of contacts exposed to the case when he/she was infectious, and their family members. They should be interviewed to check their vaccination status, provide appropriate information, encourage them to

consult a clinician if symptoms consistent with measles or rubella appear, and provide appropriate public health interventions, potentially including vaccination.

4.1 Laboratory assessment algorithms for measles and rubella infection

Laboratory investigation has a critical role in measles and rubella elimination because of the unreliability of clinical characteristics of these diseases for accurate diagnosis and the need to distinguish endemic and imported viruses. In order to enhance the cost–effectiveness of integrated surveillance for measles and rubella, laboratory assessment should be based on the epidemiology of measles and rubella in the country, and the clinical and epidemiological information on the case.

The following algorithm is proposed for testing of suspected cases of measles and rubella:

- In countries with high incidence of both measles and rubella:
    - test specimen for measles first
    - if negative, test for rubella.
- In countries with low incidence of measles and high incidence of rubella:
    - test specimen for rubella first
    - if negative, test for measles.
- In countries with low incidence of both measles and rubella:
    - test specimens for both infections.

4.1.1 Collection of samples for measles and rubella testing

The correct timing for the collection of samples is vital for obtaining an adequate sample and interpreting the test results. The diagnostic tests used to confirm measles and rubella infection include both antibody and antigen detection, but the timing of sample collection will determine which tests can be conducted (Table 2). The typical sample for disease confirmation is serum, but alternative specimen types (oral fluid, dried blood spots, etc.) are increasingly used in some countries. Details of the collection, storage and shipment of specimens are provided in the *WHO manual for the laboratory diagnosis of measles and rubella virus infection (20)* and in Annex 3.

Table 2

Clinical samples for measles and rubella collection and recommended time* of collection

Clinical samples	Assays	0–4 days	5–7 days	8–28 days
Serum/dry blood spots	IgM/IgG	✓	✓	✓
	Virus detection	✓	✓	✗
Whole blood	Virus isolation	✓	✗	✗
	Virus detection	✓	✗	✗
Nasopharyngeal secretions	Virus isolation	✓	✗	✗
	Virus detection	✓	✓	✗
Urine	Virus isolation	✓	✗	✗
	Virus detection	✓	✓	✗
Oral fluid	IgM/IgG	✓	✓	✓
	Virus isolation	✓	✓	✗
	Virus detection	✓	✓	✓

*Time measured in days after the onset of rash.

4.1.2 Antibody detection

A single *sample* (e.g. *serum*) obtained **at the first contact** with the health-care system at any time within 28 days after onset is considered adequate for surveillance purposes. Because of the higher proportion of false-negative results found in specimens collected within 72 hours of onset of the rash, in a serum sample taken earlier than four days after onset of the rash which has a negative IgM result, a second sample should be taken between four and 28 days following onset of the rash. If the second specimen has not been obtained, case classification should be based on the results of testing the single specimen.

4.1.3 Virus isolation

In contrast to antibody detection, virus isolation is most successful when clinical specimens are collected during the first four days following onset of the rash. Virus can be isolated from *nasopharyngeal secretions, oral fluid samples, urine and whole blood* collected as soon as possible after the appearance of the rash. Measles and rubella viruses are sensitive to heat, and detection decreases markedly when specimens are not kept cold (4–8^{o}C). It is important that samples are transported under cold conditions as soon as possible following collection.

4.1.4 Reverse transcription PCR

Measles and rubella viruses can be detected by PCR in *nasopharyngeal secretions, urine, serum and whole blood, and dry blood spots* up to seven days after onset of the rash and in *oral fluid* for even longer.

4.1.5 Laboratory testing during outbreaks

In outbreak settings, it is recommended that specimens from 5–10 cases early in the outbreak are submitted for laboratory testing. Once the outbreak is confirmed as measles or rubella, subsequent cases should be primarily confirmed based on epidemiological linkage. If the outbreak continues, an additional 5–10 specimens should be submitted to the laboratory every two to three months to confirm that the illness in question is still measles or rubella and to monitor the implicated virus genotype(s). *An important exception to this rule is a case of suspected measles or rubella in a pregnant woman, when laboratory testing should be performed regardless of the background incidence.* During outbreaks, cases should be reported to WHO using both the case-based reporting form and the outbreak aggregate reporting form (see Annexes 1 and 4 for examples of data collection forms).

4.2 Data collection and reporting

Public health authorities at all levels should establish a well functioning surveillance network that meets the reporting requirements of the elimination stage of measles and rubella. The case notification form or set of core information should be transmitted by the clinician to the local epidemiologist. The notification and investigation information should then be transmitted from local levels to higher administrative levels of the surveillance system, including to the national level. Each administrative health subdivision within a country should be part of the reporting system. The following approach for data transmission can be recommended, based on the incidence of disease in the country:

- Case-based data should be collected at the primary level of the system (see Annex 1 for example of case investigation form).
- Case-based data on all suspected cases that have been investigated and classified, including cases classified as discarded, should be reported from local up to national level, to allow for adequate epidemiological analysis. A line listing of cases (database with all relevant information) in the area under surveillance should be available at all levels of the system.

- All sporadic cases and disease clusters should be reported immediately upon detection, and subsequently to all surveillance levels according to national regulations. During an outbreak, reporting should be weekly after the initial report. If timely case-based reporting during an outbreak is not feasible because of the large number of cases, case-based data should still be collected and entered into the database as soon as it becomes feasible.
- Monthly zero reporting (i.e. reporting even if there are no cases) should be implemented at all levels of the system, in order to monitor quality of surveillance.

Laboratories should confirm sporadic cases by IgM testing within three days of receiving the specimens. Weekly surveillance reports are recommended when transmission is ongoing followed by weekly zero reporting after an outbreak for at least two incubation periods.

Feedback should be provided with similar regularity to data reporting. Comprehensive reports which include an epidemiological description, and implemented activities and recommendations for control, should be compiled at the end of an outbreak. The regional outbreak investigation and reporting form (see Annex 4) may be adapted for reporting purposes in the national health system.

The quality of data collected in the process of an outbreak investigation is critical for determining the control strategy and activities. With adequate investigation of outbreaks, the surveillance system will have information about susceptible populations and explanations for their susceptibility.

The size and duration of outbreaks may be used by national surveillance systems as an indirect indicator of immunity, immunization coverage, quality of surveillance system and adequacy of response and control measures. However, without a thorough outbreak investigation that includes active case-finding and epidemiological linkage of cases, these data can be misleading.

4.3 Reporting to WHO

The objectives of reporting to WHO are to:

- provide a standardized, up-to-date and complete picture of the epidemiology of measles and rubella in the Region, to indicate the burden they place on public health and facilitate response and control measures;
- identify more precisely the geographical areas and populations where particular problems are occurring and action is needed (subnational level or geographical area with specific risk, risk groups by age and gender);
- ensure timely dissemination of critical and accurate information about infectious diseases among public health professionals.

Member States have technical staff in national health institutions designated as the WHO counterparts for measles and rubella surveillance, with a responsibility to provide national surveillance data for the Regional Office through the Centralized Information System for Infectious Diseases (CISID[5]) or sending reports via other means.

Member States should report routine measles and rubella case-based surveillance data monthly to WHO. Complete and accurate data from all suspected cases, including confirmed, epidemiologically linked and clinically compatible cases **and discarded cases**, should be provided. In the absence of disease, countries should provide monthly zero reports. Countries belonging to the European Union send their notifications through the European Centre for Disease Prevention and Control, which transmits these data on a monthly basis to the Regional Office.

Real-time case-based reporting in the national surveillance systems (such as Web-based reporting) allows real-time surveillance of diseases. If cases are properly coded, information about clustering of cases and confirmed outbreaks with all related cases will be immediately available. As real-time reporting is not possible at the regional level (because of the delay in data availability due to monthly reporting), the Regional Office recommends reporting of outbreaks using the form presented in Annex 4. It is expected that surveillance counterparts will send this form twice, at the beginning of the outbreak as a notification form, and at its end as a final report form.

[5] http://data.euro.who.int/cisid/, accessed 15 December 2012.

5 Monitoring and evaluation

Monitoring and evaluation of surveillance systems over time is necessary to identify areas that need strengthening and to verify the relevance and quality of the information obtained. These objectives are particularly important in the context of eliminating measles and rubella.

To help with the routine monitoring of surveillance systems, WHO has defined a set of core indicators for measles and rubella (see Chapter 5.1 “Surveillance performance indicators” below). Together with surveillance indicators, indicators for monitoring progress towards elimination are helpful in determining the current status and activities needed for elimination (see Chapter 5.2 “Indicators for monitoring progress towards elimination” below).

Surveillance performance should be analysed at each administrative level in order to monitor and document local and national progress towards achieving and sustaining elimination. Indicators for monitoring progress must be interpreted with regard to the quality of disease surveillance and also with regard to the immunity profile of specific subgroups (age group, geographical area, etc.) when available.

In addition to routine monitoring, detailed periodic reviews of system performance should be conducted with reasonable frequency (between annually and every five years) to assess system quality and implement modifications based on the review findings.

5.1 Surveillance performance indicators

The following indicators (Table 3) measure the performance of measles and rubella surveillance.

Table 3 Measles and rubella surveillance performance indicators

Indicator	Description	Target
Timeliness of reporting	The number of measles and rubella routine reports submitted before a deadline, divided by the number of reports expected in the reporting month or year × 100%	≥80% of reports received before a deadline
Completeness of reporting	The number of measles and rubella routine reports submitted, divided by the number of reports expected in the reporting month or year x 100%	≥80% of reports received
Laboratory investigation rate	The number of cases with specimens adequate for detecting[1] measles or rubella collected and tested in a proficient laboratory[2] divided by the number of suspected cases × 100%.	Specimens adequate for detecting acute measles/rubella infection should be collected and tested in a proficient laboratory from ≥80% of suspected measles/rubella cases. Any suspected cases that are not tested by the laboratory and are a) confirmed by epidemiologic linkage or b) discarded as non-measles/non-rubella by epidemiological-linkage to a laboratory-confirmed case of another communicable disease or epidemiological-linkage to a measles or rubella IgM-negative case, should be excluded from the denominator.
Rate of discarded cases	The rate of suspected measles or rubella cases that have been investigated and discarded as non-measles or non-rubella cases using laboratory testing in a proficient laboratory and/or epidemiological linkage to another confirmed disease	At least 2 discarded measles/rubella cases should be reported annually per 100,000 population nationwide and in ≥80% of subnational administrative units (e.g. at the province level or its administrative equivalent)
Chains of transmission/outbreaks investigated for virus genotype	The number of measles or rubella chains of transmission/outbreaks investigated for virus' genotype, divided by the number of laboratory-confirmed chains of transmission/outbreaks of that disease × 100%	Samples adequate for virus detection should be collected from ≥80% of laboratory-confirmed chains of transmission/outbreaks and tested in WHO accredited laboratory.
Origin of infection	The number of measles or rubella cases for which an origin of infection is identified (e.g. imported, import-related, or endemic), divided by the total number of cases reported × 100%.	≥80% of cases with identified origin of infection
Timeliness of investigation	The number of suspected measles or rubella cases with an adequate investigation[3] initiated within 48 hours of notification divided by the total number of suspected cases reported × 100%	At least 80% of all reported suspected measles/rubella cases should have had an adequate investigation initiated within 48 hours of notification.

1 See Chapter 4.1 and Annex 3 for instructions
2 A proficient laboratory is a laboratory that uses a validated assay and participates in the laboratory quality assurance programme of the WHO Global Measles and Rubella Laboratory Network (14).
3 An adequate investigation includes collection of all of the following data elements from each suspected measles/rubella case: case identifier, age (or date of birth), sex, date of rash onset, date of specimen collection, vaccination status, date of last vaccination, travel history and contacts.

5.2 Indicators for monitoring progress towards elimination

Vaccination coverage and disease incidence are useful indicators for providing general guidance regarding progress towards elimination. However, they are not sufficient to document elimination by themselves. Rather, an assessment of several lines of evidence (e.g. population immunity, quality of surveillance, molecular epidemiology data, etc.) will be necessary for reliable conclusions to be drawn. In countries with small populations, these indicators should be interpreted with caution.

1. Vaccination coverage

Countries should monitor vaccination coverage continuously to enable population immunity to be assessed. Although high coverage with one dose of the rubella-containing vaccine provides sufficient protection against rubella and is likely to interrupt transmission, all Member States of the European Region have currently implemented a routine immunization programme offering two doses of combined measles and rubella-containing vaccines (MR, MMR, measles/ mumps/ rubella/ varicella – MMRV).

Indicator:

Vaccination coverage of the first and second routine doses of measles/rubella-containing vaccine.

Target:

Achieving and maintaining of at least 95% coverage with both first and second routine doses of measles/rubella-containing vaccine in all districts or their administrative equivalents and at the national level.

2. Incidence

Incidence of measles or rubella is a basic measure of progress in disease elimination, used to describe the overall level of disease control and enable meaningful comparisons across countries and regions. Monitoring incidence is reliable only when the surveillance system meets essential performance indicators.

Indicator:

Incidence of ALL measles or rubella (laboratory confirmed, epidemiologically linked and clinically compatible) cases per million total population. The numerator should exclude imported cases.

Target:

Achievement of a measles/rubella incidence of <1 case per 1 million total population.

Meeting individual indicators for monitoring progress towards elimination does not define measles elimination nor confirm that it has been achieved. Conclusions regarding verification of measles and rubella elimination should be based on examination of several lines of evidence.

6 Surveillance of CRS

6.1 Rationale

The public health justifications for congenital rubella surveillance are to monitor the effectiveness of rubella vaccination programmes, to detect and isolate affected infants rapidly, and to mitigate the consequences of the disease for infants and their families through early provision of appropriate medical care. CRS surveillance allows for detection of infants with clinically apparent manifestations and can be standardized for regional and global reporting and comparison purposes. All Member States should develop a CRS surveillance system that captures the majority of infants with suspected CRS within the country. If there is no surveillance in place, countries may opt to establish CRS surveillance in a few sentinel sites first, then to broaden the surveillance and add additional sites to include more of the population.

Rapid identification of infants with CRS is necessary to ensure that appropriate testing can be conducted and the infant entered into the CRS surveillance system. Detection of infants with CRS is necessary to ensure infection control and prevent further spread of rubella, as infants with CRS may shed virus for prolonged period, up to one year of age or longer. Immediate diagnosis of CRS also facilitates early intervention for specific defects.

This section has been developed to provide a comprehensive framework for developing and monitoring high-quality CRS surveillance.

6.2 CRS – clinical features, case classification and laboratory criteria for confirmation

Classification of cases for CRS surveillance purposes is based on clinical, epidemiological and laboratory data. The case definitions for CRS surveillance include the following categories: suspected, laboratory confirmed, clinically compatible, epidemiologically linked

and discarded. The case definitions for CRS surveillance purposes are given in Box 5. The algorithm for classification of suspected CRS cases is presented in Fig. 2.

The clinical criteria for CRS include the presence of ≥2 clinical features from group A, or one feature from group A and ≥1 from group B in the following list:

Group A	***Group B***
Sensorineural hearing impairment	Purpura
Congenital heart disease	Splenomegaly
Pigmentary retinopathy	Microcephaly
Cataract(s)	Developmental delay
Congenital glaucoma	Meningoencephalitits
	Radiolucent bone disease
	Jaundice with onset within 24 hours of birth

Laboratory criteria for confirmation of suspected CRS cases include the following:

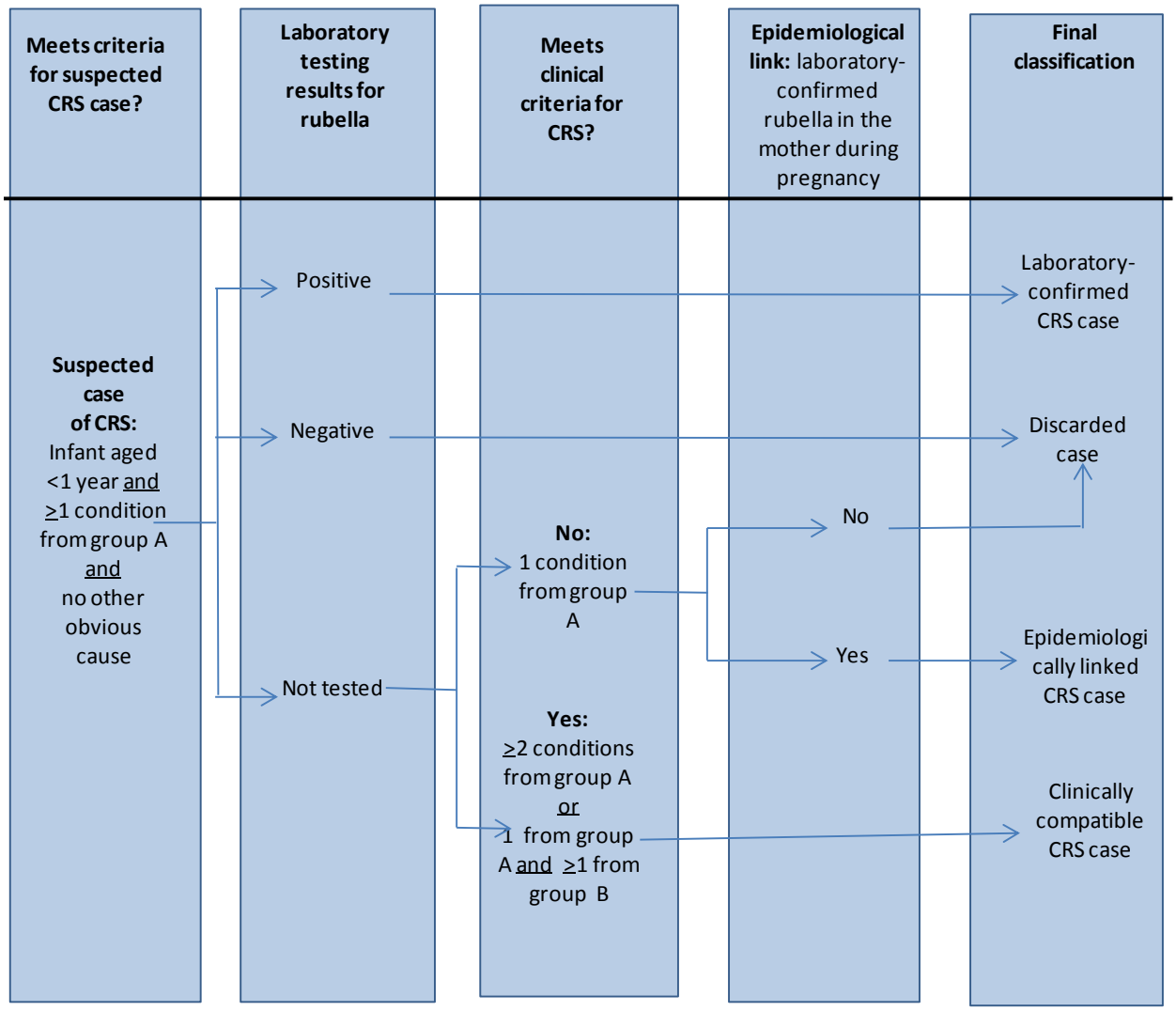
- Rubella IgM antibody detected, *or*
- Sustained rubella IgG antibody level as determined on at least two occasions between 6 and 12 months of age in the absence of receipt of rubella vaccine; *or*
- Rubella virus detection (e.g. nucleic acid detection by RT-PCR or rubella virus isolation) in an appropriate clinical sample (best results come from throat swabs, but nasal swabs, blood, urine, or cerebrospinal fluid specimens are also acceptable).

Box 5

CRS case definitions for surveillance purposes

Case category	Definition
Suspected	Any infant aged <1 year with ≥1 clinical features from group A and no other obvious cause
All suspected cases have to be investigated and classified based on clinical, laboratory and epidemiological data as one of the following:	
Laboratory confirmed	A suspected case which meets the laboratory criteria for CRS case confirmation
Clinically compatible	A suspected case which meets the clinical criteria for CRS **and** has not been adequately tested by laboratory
Epidemiologically linked	A suspected case which does not meet clinical criteria for CRS (i.e. has only one feature from group A), has not been adequately tested **and** has maternal history of laboratory-confirmed rubella during pregnancy
Discarded	A suspected case with negative results of adequate laboratory testing for evidence of rubella virus infection, or a suspected case which does not meet clinical criteria for CRS (i.e. has only one feature from group A), has not been adequately tested, **and** does not have maternal history of laboratory-confirmed rubella during pregnancy

Fig. 2. Classification algorithm for CRS cases



Efforts should be made to obtain clinical specimens for viral isolation from infants at the time of the initial investigation. Infants with congenital rubella, even without clinical features of CRS, will usually be positive for rubella-specific IgM at or shortly after birth. Although IgM antibodies may persist for up to one year, they normally peak within the first six months of life. Because IgM may not be detectable in some infants tested shortly after birth, IgM-negative infants with suspected CRS should be retested at one month of age or shortly thereafter. Laboratory confirmation of CRS in an infant aged over six months should not rely on the IgM test alone if the result is negative. In such cases, serial IgG testing should also be performed to assess for a sustained level of antibody over several months. Infants with congenital rubella should also be tested for shedding of rubella virus through virus isolation techniques. Congenitally infected infants may shed and transmit rubella virus for up to one year of age and be the source of rubella outbreaks *(27)*. Therefore, it is important to continue testing the infant for virus throughout the first year of life so that infection control measures

can continue until virus shedding stops. This has to be confirmed by two negative results of viral testing of specimens obtained one month apart from infants at least three months of age.

Member States are encouraged to report all clinically compatible, laboratory confirmed and epidemiologically linked cases of CRS to the WHO Regional Office. A standard reporting form should be completed for each suspected case of CRS (see Annex 5).

6.3 CRS surveillance

All Member States of the WHO European Region need a CRS surveillance system that has the ability to capture the majority of infants with suspected CRS within the country. Routine surveillance for CRS should focus on identifying infants under one year of age, although some defects associated with CRS surveillance may not be detectable until an older age *(34)*. The most common congenital defects related to CRS – cataracts, heart defects and hearing impairment – are the primary conditions under CRS surveillance. These conditions are most likely to be seen at secondary and tertiary health-care facilities, which should be included as sentinel sites for CRS surveillance.

National health authorities should define the objectives and overall structure of the CRS surveillance system, which should be aligned with the existing communicable-disease surveillance system, health-care structure and capacities. The process may vary depending on differences between national health systems, but in most Member States CRS surveillance will be integrated into existing surveillance of vaccine-preventable diseases and into measles and rubella elimination activities. Member States should report CRS cases to WHO according to national surveillance system capacities, at least annually.

The following steps, discussed in more detail in Annex 6, should be implemented to establish CRS surveillance *(34)*.

1. Identify national CRS surveillance coordinators responsible for epidemiological and laboratory components of the system.
2. Determine the health-care facilities at which infants with CRS are likely to be seen and enrol these facilities as sentinel surveillance sites; identify a CRS surveillance coordinator at each facility or group of facilities.
3. Conduct initial and refresher training for participating providers.

4. Initiate CRS surveillance activities.
5. Conduct quality assessment and monitoring of CRS surveillance.
6. Expand CRS surveillance and include other sites, as appropriate.
7. Analyse CRS surveillance data on an annual basis, or more frequently if necessary.
8. Provide periodic feedback to all stakeholders involved in the CRS surveillance system.

CRS surveillance that identifies the majority of infants with suspected CRS in a Member State is optimal for documentation of the elimination process. This does not mean that all health-care providers/institutions must participate in surveillance. Participation of the sentinel secondary and tertiary care facilities most likely to treat infants with eye, ear and heart defects, is sufficient.

6.4 Other approaches to identifying CRS cases

6.4.1 Rubella in pregnancy registries

Rubella in pregnancy registration can be used for follow-up of pregnant women exposed to rubella and their pregnancy outcome(s), as well as for identification of CRS cases. Rubella in pregnancy registries should be maintained at the local level so that comprehensive follow-up of pregnant women can occur, and if applicable, infants born with CRS can be identified and diagnosed immediately and obtain early interventions for any associated defects. The registry should include maternal contact data and demographic data, disease case classification for the pregnant women (laboratory confirmed, clinically compatible or epidemiologically linked) and pregnancy outcome (e.g. miscarriage, termination, infant with CRS, etc.).

6.4.2 Retrospective searches for CRS cases

Retrospective searches allow for a rapid identification of infants with CRS by reviewing medical records of infants with defects or signs consistent with CRS. Retrospective searches can help determine a baseline for the burden of CRS in a country. However, one limitation of this approach is that retrospectively identified cases usually do not have laboratory confirmation. Several studies on conducting retrospective searches for CRS cases are available as possible models *(35-37)*.

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Annexes

Annex I Integrated measles and rubella case investigation form

Recommended basic set of data for case-based reporting in national surveillance system

Case ID:_____Region:_____District: _____

Date of notification:____/____/____ Date of investigation:____/____/____ Date of report:____/____/____

Initial clinical diagnosis: 1. Clinical measles ☐ 2. Clinical rubella ☐ 3. Others ☐ 9. Unknown ☐

Outbreak-related: 1. Yes ☐ 2. No ☐ 9. Unknown ☐ Outbreak ID: _____

A. Personal data and immunization status

Name*: _____*WHO Europe does not collect this information – please provide only Case ID number _____

Sex: 1. Male ☐ 2. Female ☐ 9. Unknown ☐

Date of birth: _/___/_____if not available, age in years ____or for younger than a year, age in months_____

Address*: _____*WHO Europe does not collect this information _____

For female cases

Is case pregnant? 1. Yes ☐ 2. No ☐ If yes, gestation age:_____weeks

Vaccination status

Measles: 1. Yes ☐ 2. No ☐ 3. Unknown ☐ If yes, no. of doses___ | ***Last vaccination date:***

Source of vaccination status: 1. Medical record ☐ 2. Parent or guardian ☐ | ___/___/___

Rubella: 1. Yes ☐ 2. No ☐ 3. Unknown ☐ If yes, no. of doses___ | ***Last vaccination date:***

Source of vaccination status: 1. Medical record ☐ 2. Parent or guardian ☐ | ___/___/___

B. Clinical information

Maculopapular rash 1. Yes ☐ 2. No ☐ 9. Unknown ☐

Date of rash onset: _____/_____/____ Duration of rash (days): _____

Other symptoms		Presence of complications	Yes ☐ No ☐
Fever	Yes ☐ No ☐ Unknown ☐	Pneumonia	Yes ☐ No ☐ Unknown ☐
Coryza	Yes ☐ No ☐ Unknown ☐	Malnutrition	Yes ☐ No ☐ Unknown ☐
Cough	Yes ☐ No ☐ Unknown ☐	Diarrhoea	Yes ☐ No ☐ Unknown ☐
Conjunctivitis	Yes ☐ No ☐ Unknown ☐	Encephalitis	Yes ☐ No ☐ Unknown ☐
Adenopathy or arthralgia or arthritis	Yes ☐ No ☐ Unknown ☐	Other (specify)	Yes ☐ No ☐ Unknown ☐

Hospitalized: 1. Yes ☐ 2. No ☐ 9. Unknown ☐ Name of hospital: _____

Clinical outcome: 1. Dead: date of death __/____/___ 2. Survived ☐ 3. Lost to follow-up ☐ 9. Unknown ☐

Cause of death: _____

C. Epidemiological investigation

Did the patient have contact with confirmed case of measles (within 7-18 days) or rubella (within 12–23 days) prior to rash onset? 1. Yes ☐ 2. No ☐ 9. Unknown ☐
If yes:
Who (case ID/name): _____
Where (country/address): _____
When (dates): _____

Were there confirmed cases of measles and/or rubella reported in the area prior to this case?
1. Measles ☐ 2. Rubella ☐ 3. Both ☐ 4. No ☐ 9. Unknown ☐

Did the patient travel within 7–23 days before onset of rash? 1. Yes ☐ 2. No ☐ 9. Unknown ☐
If yes:
Where (country/address): _____
When (dates): _____
Travel details: _____

Is the case epidemiologically linked to imported confirmed case? 1. Yes ☐ 2. No ☐ 9. Unknown ☐
If yes:
Who (case ID/name): _____
Where (country/address): _____
When (dates): _____

Was the case in contact with a pregnant woman since development of the symptoms?
1. Yes ☐ 2. No ☐ 9. Unknown ☐ If yes, please provide name and address _____

_____

D. Laboratory investigation

Specimen collected: 1. Yes ☐ 2.No ☐ 3. Unknown ☐
If yes, type of specimen:
Serum ☐ Saliva/oral fluid ☐ Nasopharyngeal swab ☐ Dry blood spot ☐
Urine ☐ EDTA whole blood ☐ Other ☐_____

Date of specimen collection:_____/___/___ Date specimen sent to lab:___/___/___

Measles IgM: Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐
Rubella IgM: Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐

Date of laboratory result (first validated result):_____/___/___

Measles virus detection: Not tested ☐ Positive ☐ Negative ☐ In process ☐ Genotype _____
Rubella virus detection: Not tested ☐ Positive ☐ Negative ☐ In process ☐ Genotype _____

E. Final classification

0 Discarded ☐

1 Measles – laboratory-confirmed ☐ 2 Measles – epidemiologically linked ☐ 3 Measles – clinical ☐

6 Rubella – laboratory-confirmed ☐ 7 Rubella – epidemiologically linked ☐ 8 Rubella – clinical ☐

Source of infection: 1. Imported ☐ 2. Endemic ☐ 3. Import-related ☐ 9 Unknown ☐

Date of final classification:___/___/___

Investigated by: Name_____

Position: _____

Annex II Measles and rubella database for case-based reporting – CISID

Example of coding fields, definitions and possible entry field data types

Field name	Label	Definition	Possible entry	Rules
CaseID	CaseID	Unique identifier for the case	Free text (limit of 50 characters)	(Country code) (province code) (district code) (year)(case number). Example of EPID numbers: RU204602006003 (Russian Federation, St Petersburg city, case number 3)
IniDiag	Initial diagnosis	Initial diagnosis	1 Clinical measles 2 Clinical rubella 3 Other 9 Unknown	
AreaID	Country; first administrative level; second administrative level	One code defines country and first and second administrative levels of residence of patient when illness was contracted	Updated information can also be obtained in the "area code reference" function of the WHO Europe Web site	A code defining at least the first administrative level must be provided
DRash	Date of onset of rash	Date of onset of rash	dd/mm/yyyy	Must be reported in first report. Cannot be a future date: DRash must be on or after (>=) DBirth
GenderID	Gender	Gender	1 Male 2 Female 4 Unknown	Must be reported at first report
Pregnant	Pregnant	Pregnant	1 Yes 2 No 9 Unknown	
DBirth	Date of birth	Date of birth	dd/mm/yyyy	Must be reported at first report if age at onset of rash is not provided. Cannot be a future date: DRash>=DBirth
AgeAtRashOnset	Age at rash onset	Age at onset of rash	Positive integer. Child is 0 years until 1st birthday, 1 year until 2nd birthday, etc.	Must be reported at first report if date of birth is not provided
NumOfVaccines	Number of measles vaccines	Number of measles vaccines from vaccination card or by verbal history	Positive integer. Use 9 if the number of vaccines received is unknown	
Dvaccine	Date of last measles vaccination	Date of last measles vaccination	dd/mm/yyyy	Dvaccine>=Dbirth. Cannot be a future date
NumOfRVaccines	Number of rubella vaccines	Number of rubella vaccines from vaccination card or by verbal history	Positive integer. Use 9 if the number of vaccines received is unknown	
DRVaccine	Date of the last rubella vaccination	Date of the last rubella vaccination	dd/mm/yyyy	Dvaccine>=Dbirth. Cannot be a future date
DNotification	Date of notification	Date when case is first reported or notified to public health authorities	dd/mm/yyyy	DNotification>=DBirth DNotification>=DRash Cannot be a future date

Field name	Label	Definition	Possible entry	Rules
DInvestigation	Date of investigation	Date of epidemiological investigation of case by public health authorities	dd/mm/yyyy	DInvestigation>=DBirth DInvestigation>=DRash Cannot be a future date
ClinFever	Fever	Presence of fever	1 Yes 2 No 9 Unknown	
ClinCCC	Cough or coryza or conjunctivitis	Presence of one or more of cough, coryza or conjunctivitis	1 Yes 2 No 9 Unknown	
ClinAAA	Adenopathy, arthralgia/ arthritis	Presence of one or more of adenopathy, arthralgia or arthritis	1 Yes 2 No 9 Unknown	
ClinRashDuration	Duration of rash	Number of days when rash is present	Positive integer. Use 9 if duration of rash is unknown	
ClinOutcome	Outcome	Outcome of case. Death is defined as death due to measles or its complications within two months of onset of measles	1 Death 2 Alive 3 Lost to follow-up or unknown	
ClinHospitalization	Hospitalization	Patient was hospitalized	1 Yes 2 No 9 Unknown	
SrcInf	Source of infection	Case is part of a chain of transmission originating with an imported case	1 Yes, imported 2 Endemic 3 Import-related 9 Unknown	
SrcOutbreakRelated	Outbreak-related	Case is part of an outbreak	1 Yes 2 No 9 Unknown	
SrcOutbreakID	Outbreak ID	Unique identifier for that outbreak	Free text (limit of 50 characters)	Can only be filled in if SrcOut-breakRelated=1. When a case is part of an outbreak, the outbreak should be reported in the measles outbreak section. Unique identifier for that outbreak
CompComplications	Complications	Patient had complications	1 Yes 2 No 9 Unknown	
CompEncephalitis	Encephalitis	Patient suffered from encephalitis	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplications=1
CompPneumonia	Pneumonia	Patient suffered from pneumonia	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplications=1
CompMalnutrition	Malnutrition	Patient suffered from malnutrition	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplications=1
CompDiarrhoea	Diarrhoea	Patient suffered from diarrhoea	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplications=1

Field name	Label	Definition	Possible entry	Rules
CompOther	Other	Patient suffered from other complications	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplications=1
FinalClassification	Final classification	Final classification of the case	0 Discarded 1 Measles laboratory-confirmed 2 Measles epidemiologically linked 3 Measles clinically 6 Rubella laboratory-confirmed 7 Rubella epidemiologically linked 8 Rubella clinically	Should be provided 30 days after date of onset of rash. Final classification can only be measles laboratory-confirmed if MeaslesIgM=1 or MeaslesVirusDetection=1 or both. Final classification can only be rubella laboratory-confirmed if RubellaIgM=1 or RubellaVirusDetection=1 or both
DSpecimen	Date of collection	Date when first specimen was collected from Patient regardless of test results	dd/mm/yyyy	DSpecimen>=DBirth DSpecimen+4days>= DRash. Cannot be a future date
Specimens	Type of specimen	Type of specimen collected	1 Serum 2 Saliva/oral fluid 3 Nasopharyngeal swab 4 Dry blood spot 5 Urine 6 EDTA[6] whole blood 7 Other specimen	Several types of specimen can be specified, separated by a comma Example: 1,2 means that a serum sample and a saliva sample have been taken
DLabResult	Date of laboratory result	Date when laboratory results become available (first validated result)	dd/mm/yyyy	DLab Result>= DBirth DLabResult>=DSpecimen Cannot be a future date
MeaslesIgm	Measles IgM	Validated result of measles IgM testing, whether on serum or oral fluid or other, at patient level	0 Not tested 1 Positive 2 Negative 3 In process 4 Inconclusive	
MeaslesVirusDetection	Measles virus detection	Validated result of measles isolation or detection by, for example, RTPCR[7] at patient level	0 Not tested 1 Positive 2 Negative 3 In process	
RRLMeaslesGenotype	Measles virus genotype	Measles virus genotypes	Text	
RubellaIgm	Rubella IgM	Validated result of rubella IgM testing, whether on serum or oral fluid or other at patient level	0 Not tested 1 Positive 2 Negative 3 In process 4 Inconclusive	
RubellaVirusDetection	Rubella virus detection	Validated result of rubella isolation or detection by, for example, RT-PCR at patient level	0 Not tested 1 Positive 2 Negative 3 In process	
RRLRubellaGenotype	Rubella virus genotype	Rubella virus genotypes	Text	
CommentsEpi	Comments	Comments	Free text. Should contain (if relevant): 1. whether case is the index case of an outbreak;2. name of country where patient acquired the disease	

[6] EDTA – ethylenediaminetetraacetic acid
[7] RT-PCR – reverse transcription polymerase chain reaction

Annex 3 Collection, storage and shipment of specimens for laboratory diagnosis and interpretation of results

I. Clinical specimens for IgM and IgG antibody detection

Clinical samples for the diagnosis and surveillance of measles and rubella should be obtained at the first contact between the patient with the clinical case and the health care system, irrespective of the stage of disease at which the patient presents. Depending on the country, blood obtained by venipuncture, dried capillary bloodspots on filter paper and/or oral fluid may be used.

Fig. 1. Measles and rubella laboratory request and result form

Country:_____Date:_____Case ID:_____

Patient Name:_____ Gender M☐ F☐ Date of birth:_____

Age in months:_____ Name of parent or guardian:_____

Address:_____

Date of onset of rash:_____ Date of last vaccination for measles/rubella:_____

Case ID – unique identifier for the case should be obtained from epidemiologist. For date please use: dd-mm-yyyy (e.g. 20-10-2002).

Specimen ID	Specimen type	Date of collection	Date of shipment	Date received at laboratory	Condition	Date of result	Measles test		Rubella test	
							IgM	Other*	IgM	Other*
1										
2										
3										

Comment: _____*Other methodology (specify): _____

_____

Laboratory results should be sent to (name):_____

Address: _____

Telephone/ Fax number/E-mail_____

For use by the receiving laboratory:

Name of laboratory: _____

Name of the person receiving specimen: _____

Notes:

[a] The Specimen No. should be exactly as written on the sample container.

[b] Specimen type may include: serum, whole blood (ethylenediaminetetraacetic acid (EDTA), heparinized), dried blood spot, swab (oral fluid, throat, nasal), aspirate (nasopharyngeal, respiratory), urine (whole sample, pelleted) and others.

[c] Additional comments of importance to the epidemiological investigation or the laboratory, such as: patient died; patient's relationship to another case under investigation; second set of samples collected from same patient; samples exposed to suboptimal conditions prior to shipment.

I.A. Whole blood for IgM and IgG antibody detection

Blood collection for serum by venipuncture and handling

Blood should be collected in a sterile tube (5 ml for older children and adults and 1 ml for infants and younger children) and labelled with the patient's name and/or identification number and the collection date.

Whole blood can be stored at 4−8°C for up to 24 hours before the serum is separated, but **it must not be frozen.**

Whole blood should be allowed to clot and then centrifuged at 1000 × gravitational units (g) for 10 minutes to separate the serum. If there is no centrifuge, the blood can be kept in a refrigerator (4–8oC) until there is complete retraction of the clot from the serum (no longer than 24 hours).

The serum should be carefully removed with a fine-bore pipette to avoid extracting red cells, and transferred aseptically to a sterile vial labelled with the patient's name or identifier, date of collection and specimen type.

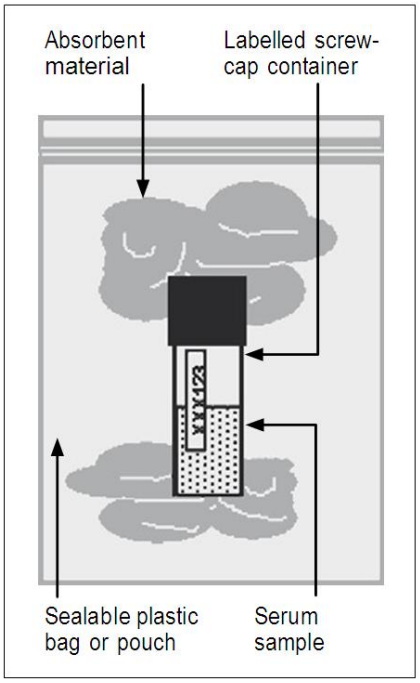
A measles/rubella laboratory request form should be fully completed when the specimen is collected and must accompany all specimens sent to the laboratory (Fig. 1).

Storage and shipment of serum samples

Serum should be stored at 4−8°C until shipment takes place, or for max. 7 days.

When kept for longer periods, serum samples should be frozen at –20°C or lower and transported to the testing laboratory on frozen ice packs. Repeated freezing and thawing of serum samples for IgM testing should be avoided, as it may have detrimental effects on the stability of IgM antibodies.

Fig. 2. Example of packaging of a serum sample for shipment



As a general rule, serum specimens should be shipped to the laboratory as soon as possible. The shipment should not be delayed for the collection of additional specimens.

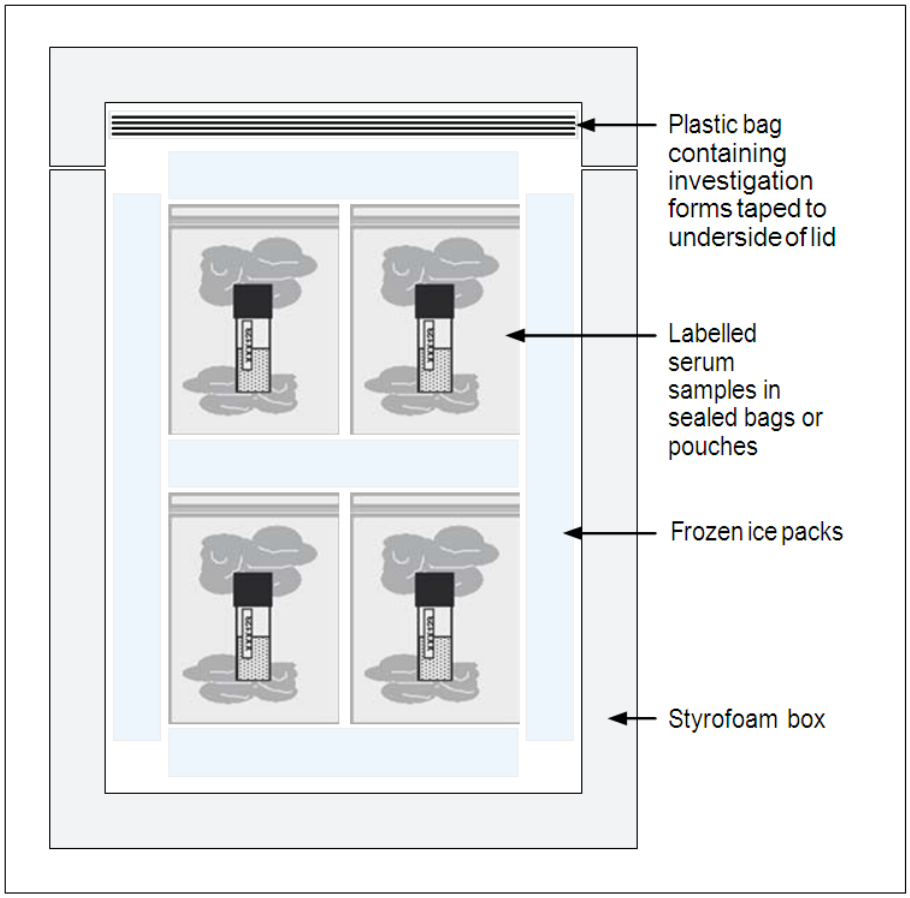
Serum specimens, in their uniquely labelled, sealed vials, should be placed in sealable plastic bags or pouches containing absorbent materials such as cotton wool to soak up any leakage that may occur (Fig. 2).

Styrofoam boxes or an insulating (vacuum) flask should be used to contain the sealed

bags or pouches. The specimen form and investigation form for each specimen should be placed in a separate plastic bag and taped securely to the inner surface of the top of the styrofoam box or the outside of the vacuum flask (Fig. 3).

If ice packs (which should be frozen) are used, they should be placed at the bottom and along the sides of the styrofoam box. The samples should then be placed in the centre and more ice packs placed on top.

Fig. 3. Example of packing several sera into one container for shipment



A shipping date should be arranged between the sample collectors and the laboratory. When arrangements have been finalized, the addressee should be informed of the time and manner of transportation. More details on the packaging and transportation of samples are provided in the Manual for the laboratory diagnosis of measles and rubella virus infection (1).

I.B. Dried blood spots for IgM and IgG antibody detection

Collection and handling of dried blood spots

Clean each participant's finger (or heel in the case of very young children) with alcohol and prick with a sterile, disposable microlancet.

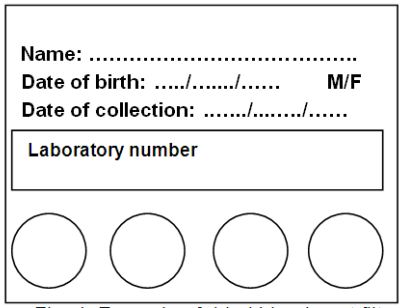


Fig. 4. Example of dried blood spot filter paper collection form

Collect up to four drops of whole blood on standardized filter paper (such as Whatman Chromatography paper no 3®, Schleicher and Schuell #903® or another high-quality paper).

The filter paper should be marked up, either by hand or laser-printed, in a standard format that includes 14–15 mm circles within which to place the blood drops. Spaces should be marked to write the name, age and sex of the patient, with a space provided to write the laboratory or specimen number (Fig. 4).

The filter paper should be allowed to dry thoroughly (for at least 60 minutes) at room temperature. Filter papers may be placed in a slide holder or similar receptacle during the drying process.

Storage and shipping of dried blood spots

Each dried filter paper should be wrapped individually in paper, foil or plastic to prevent possible cross-contamination.

Filter papers should be stored away from sunlight and inside a plastic bag to protect them from dust and moisture.

Dried blood spot samples are not considered biohazardous and can be shipped without special requirements or special documentation from the site of collection to the laboratory.

Although samples do not need to be kept refrigerated or frozen during transport, it is advisable to store them in a cool place and transport them to the laboratory as soon as possible.

I.C Oral fluid for IgM and IgG antibody detection

Collection and handling of oral fluid

Crevicular fluid exuded from the interface between the gums and teeth contains low levels of IgM. A number of swab collection devices (such as the Orocol®) have been developed specifically to collect this fluid from the mouth.

The swabs are designed to be used like a toothbrush and should be rubbed along the gum until the swab is wet. This usually takes one minute.

The wet swab should be placed inside the clear plastic transport tube, which has an area on the outside to write the name and details of the patient and the date of collection.

Some devices have virus transport medium incorporated within the plastic transport tubes, while others require that a small volume of transport medium be added. Specific instructions provided by the manufacturer of the device should be followed.

Storage and shipping of oral fluid

Once a sample has been collected, the device should be sealed according to the manufacturer's instructions.

If the daily ambient temperature is below 22°C, samples should be shipped to the laboratory within 24 hours.

At higher temperatures samples should be kept in a refrigerator (4–8oC) until they can be shipped to the laboratory on ice.

The samples are usually not considered biohazardous and can be shipped without special requirements or special documentation from the site of collection to the laboratory.

II. Clinical specimens for virus isolation

Clinical samples for virus isolation should be collected as soon after onset of the rash as possible, and at least within seven days of onset.

II. A. Urine for isolation of measles and rubella virus

Collection of urine samples

It is preferable to obtain the first urine passed in the morning. Urine (10–50 ml) should be collected in a sterile container and held at 4–8°C before centrifugation.

Urine must not be frozen before the concentration procedure is carried out. A refrigerated centrifuge is recommended, but otherwise start with urine that has been chilled at 4°C.

Urine should be centrifuged at 500 × g (approximately 1500 rpm) at 4°C for 5–10 minutes, preferably within 24 hours after specimen collection. The supernatant should be discarded and the sediment resuspended in 2–3 ml sterile transport medium, tissue culture medium or phosphate-buffered saline.

If centrifugation facilities are not available, whole urine can be shipped directly to the laboratory in well-sealed containers at 4°C immediately after collection. Do not freeze.

Storage and shipping of urine samples

The resuspended pellet may be stored at 4°C and shipped within 48 hours to a measles reference laboratory.

Alternatively, it may be frozen at –70°C or lower in viral transport medium and shipped on dry ice in a well-sealed screw-capped vial to protect against CO2 contamination.

II. B. Nasopharyngeal specimens for isolation of measles and rubella virus

Collection of nasopharyngeal samples

Nasopharyngeal specimens may be taken as follows (in order of increasing yield of virus):

- nasal aspirates are collected by introducing a few millilitres of sterile saline into the nose with a syringe fitted with fine rubber tubing and collecting the fluid in a screw-capped centrifuge tube containing viral transport medium;

- throat washes are obtained by asking the patient to gargle with a small volume of sterile saline and collecting the fluid in viral transport medium;

- nasopharyngeal swabs are obtained by firmly rubbing the nasopharyngeal passage and throat with sterile cotton swabs to dislodge epithelial cells; the swabs are placed in a sterile viral transport medium in labelled screw-capped tubes.

Storage and shipping of nasopharyngeal samples

Nasopharyngeal specimens should be refrigerated and shipped at 4–8°C to arrive at the testing laboratory within 48 hours.

If arrangements cannot be made for rapid shipment, swabs should be shaken in the medium for elution of the cells and then removed.

The medium or nasal aspirate should be centrifuged at 500 × g (approximately 1500 rpm) at 4°C for five minutes and the resulting pellet resuspended in cell culture medium.

The suspended pellet and the supernatant should be stored separately at –70°C or lower and shipped to the testing laboratory on dry ice in well-sealed screw-capped vials to protect against CO2 contamination.

II.C. Whole blood for isolation of measles and rubella virus

Collection of whole blood for virus isolation

Measles virus is often detectable in peripheral blood mononuclear cells (PBMC) from a few days before to at least seven days after onset of rash. Samples collected for virus isolation should normally be collected as soon as possible and within two days of onset of rash.

For isolation of PBMC for subsequent virus isolation, blood should be collected by venipuncture in a sterile tube supplemented with ethylenediaminetetraacetic acid (EDTA). A minimum blood volume of 5 ml is recommended.

The plasma fraction can be used to determine the measles-specific IgM antibodies. The tube should be labelled with the patient's identification number and the date of collection.

Storage and shipment of whole blood

Whole blood samples may be shipped in well-sealed tubes at 4°C.

EDTA-supplemented whole blood should be processed for virus isolation within 48 hours after collection and must not be frozen at any time prior to processing.

III. Samples for reverse transcription processing of specimens

Although not recommended as a primary screening test, several laboratories have the capacity to use reverse transcription polymerase chain reaction (RT-PCR) for measles and/or rubella as a supplementary or confirmatory test.

Any sample collected for virus isolation and transported to the laboratory can be used for RT-PCR analysis.

Measles and rubella virus can often be detected by RT-PCR in whole blood (PBMC) for three to four days after onset of rash, and in urine and nasopharyngeal samples for a few days longer.

Oral fluid and dried blood spots can be used for RT-PCR analysis if they have been collected within seven days of onset of rash (oral fluid even longer) and transported to the laboratory under nondenaturing conditions.

IV. Processing of specimens on arrival at the laboratory

As each specimen is logged in, a laboratory identification number and information about the patient and the specimen should be recorded in the spreadsheet. The specimen information may be helpful in identifying problems that may contribute to difficulty with antibody detection and/or to loss of virus and inability to make isolations. Problems in shipment or with the samples should be reported to the sender.

The following important data should be recorded:

Patient information	Specimen information
Case ID	Specimen No.
Age	Type (urine/throat swab/nasal washing/blood)
Date of birth	Volume (urine)
Date of onset of rash	Condition/temperature on arrival
Date of collection of sample(s)	Action taken (centrifugation, storage location)
IgM result	
Last measles and/or rubella vaccination date(s)	

Reference

WHO Expanded Programme on Immunization. Manual for the laboratory diagnosis of measles and rubella virus infection, 2nd ed. Geneva, World Health Organization, 2006 (http://www.who.int/immunization_monitoring/LabManualFinal.pdf, accessed 15 December 2012).

Annex 4 Measles/rubella aggregate outbreak reporting form

Outbreak Identification	Cases detail	Lab Detail	
Outbreak ID	No. of suspected cases - Male	No. Suspected cases with specimen	
Country	No. of suspected cases - Female	No. Lab conf. measles cases	
1st admin level	No. of suspected cases - Total	No. Lab conf. rubella cases	
2nd admin level	No. Deaths	Genotype	
Date of rash onset of first case	No. Encephalitis		
Date of rash onset last case	No. Hospitalized		
Outbreak Notification Date	**Only rubella cases:** No. Pregnant Women		No. WCBA
Current Outbreak Status	Name and contact detail of the person reporting this outbreak		Date of this report to WHO Europe
Outbreak end date			
Importation (Y/N)			
If yes, from which country			

Epidemiological detail of confirmed cases (lab confirmed, epi linked and final clinical)

Age Group / Vaccination Status	<1 year	1–4 years	5–9 years	10–19 years	20–29 years	> 30 years	Unknown	Total
0 dose								
1 dose								
2+ doses								
Vaccination status not known								
Vaccinated with unspecified number of dose								
Total								

Description of outbreak

Measures taken to prevent/control further spread of outbreak

Sub-national outbreak spread detail (please provide this detail if available)

Province	District	Date of first cases	Total reported cases	Cases investigated	comments

INSTRUCTION INSTRUCTIONS FOR FILLING IN THE MEASLES/RUBELLA AGGREGATE OUTBREAK REPORTING FORM FOR REPORTING OUTBREAKS TO WHO REGIONAL OFFICE FOR EUROPE

Please report using routine ways – through the Regional Office or ECDC's TESSy, as you do for reporting cases of measles or rubella disease, or for sending monthly reports.

Please submit this form for each measles or rubella outbreak in your country. This form should be submitted as soon as an outbreak is reported, by the referent national surveillance health institution (the one in charge of outbreak response). A second, final report should be submitted when the outbreak is finished (following national regulation and epidemiology of disease) and should capture the most accurate and updated data. A minimum of two reports per outbreak should be sent. Additional updates may be sent if the country wishes.

Outbreak identification

Outbreak ID: Outbreak ID is used to identify, trace, match and update outbreak information. The ideal outbreak ID is MEA-CCC-YYYY-99. (CCC is 3 character ISO3 code of the country, YYYY is year of outbreak and 99 is series starting from 01 to number the outbreaks sequentially).

Country: Enter the name of the country.

1st and 2nd admin level: Specify the location of the outbreak onset. Enter the name of the first and second administrative level in the country, according to territorial organization (e.g. 1st level region, 2nd district; 1st level province, 2nd municipality; 1st level oblast, 2nd rayon.)

Date of rash onset of first case: Indicate the date of rash onset for the index case.

Date of rash onset of last case: Indicate the date of rash onset for the last case notified in the outbreak. [NOTE: This information should be indicated only in the final outbreak report.]

Outbreak Notification Date: Indicate the date when the outbreak was notified to the referent surveillance health institution (e.g. reported by MD or health-care institution). Considering differences between the surveillance and health systems in Member States, this date should be the actual date when the planning and performing of outbreak control measures started in the referent institution.

Current Outbreak Status: Indicate "Ongoing" or "Finished".

Outbreak end date: Indicate the date when outbreak finished. Considering differences between the surveillance and health systems in the Member States, as well different health regulations, the suggestion is to use date of the last case notification as the outbreak end date (if in the period of one maximal incubation for the outbreak causing disease there are no other notified cases). [NOTE: This information should be indicated in the final outbreak report.]

Importation (Y/N): Indicate with "Yes" or "No" whether outbreak is imported from another country. Imported measles cases are cases exposed outside the country during the 7 to 18 days prior to rash onset as supported by epidemiological and/or virological evidence. If the index case came from or was exposed and infected by contact with a person from another administrative territory in the same country, that is NOT an importation. In the following cell of the form enter the name of the country where the index case was exposed.

Case detail

No. of suspected cases: (3 cells; Male, Female and Total) – indicate the number of suspected cases of measles or rubella by gender and as a total. A suspected case is any person who is under epidemiological, clinical and/or laboratory investigation during the outbreak, because of present clinical symptoms meeting the case definition for measles or rubella and/or a possible epidemiological link with another suspected/confirmed case.

No. Deaths: Indicate the number of deaths caused by disease during the outbreak.

No. Encephalitis: Indicate the number of cases diagnosed with encephalitis during the outbreak.

No. Hospitalized: Indicate the number of cases hospitalized due to measles or rubella during the outbreak.

Lab Detail

No. Suspected cases with specimen: Indicate the number of suspected cases from whom specimens were collected for laboratory diagnostic procedures (detection of anti rubella or measles IgM). According to WHO

Guidelines for elimination of measles, rubella and congenital rubella syndrome (CRS), we expect that cases from the beginning of investigation (when cluster of cases is recognized) will be tested for both diseases (IgM for measles and IgM for rubella). Later, when outbreak is confirmed by IgM results, countries with low incidence of both diseases should continue with testing of suspected case for measles and rubella for DDg, regardless which disease is actually a cause of outbreak. Look for more information in surveillance guidelines.

No. Lab conf. measles cases: Indicate the number of measles cases that are confirmed IgM positive. No. Lab conf. rubella cases: Indicate the number of rubella cases that are confirmed IgM positive. Genotype: Indicate the genotype of virus (with isolation or by PCR only), if performed.

Only rubella cases

This information should be provided for a rubella outbreak investigation AND for cases that are lab. confirmed rubella cases in measles outbreak investigation.

No. Pregnant Women: Indicate the number of suspected rubella cases in pregnant women during the rubella outbreak OR indicate the number of confirmed rubella cases in pregnant women during the measles outbreak.

No. WCBA: Indicate the number of suspected rubella cases in women of childbearing age during the rubella outbreak OR indicate the number of confirmed rubella cases in women of childbearing age during the measles outbreak.

About report

Name and contact detail of the person reporting this outbreak: Enter the contact information of the person that WHO Regional Office for Europe can contact if there is a need for additional information.

Date of this report to WHO Europe: Indicate the date when this report was sent to WHO Regional Office for Europe.

Epidemiological detail of confirmed cases (lab confirmed, epi linked and final clinical)

Enter information about confirmed cases during the outbreak regarding their age and immunization status. This information should be only for the diseases causing the outbreak and the related immunization status (for example, not rubella lab-confirmed cases during a measles outbreak or rubella immunization status of cases). The totals for rows and columns will be automatically calculated.

Description of outbreak

Indicate the main epidemiological findings: any specificity regarding characteristics of affected institutions and communities, special populations, professional exposure, immunization status, age of cases, dominating diagnoses for hospitalization, high number of cases with severe form of disease or other epidemiologically important findings.

Measures taken to prevent/control further spread of outbreak

Indicate the main measures taken to prevent/control further spread of outbreak, the outbreak response measures (e.g. school immunization). If it is possible, in the final closing outbreak report form indicate the risk management measures and potential long-term measures that are based on the lessons learned during this outbreak.

Subnational outbreak spread details (please provide if available)

In the case that epidemiological and laboratory findings are able to link other measles or rubella outbreaks or clusters in other administrative territories of the country, please enter information following the title row of the table. Depending on national regulations, these cases may be considered as clusters of the reported outbreak or as individual outbreaks. If they are considered as separate outbreak(s), please enter this information in cell of “Comments” row and fill in the additional form for that outbreak(s).

Annex 5 Congenital rubella syndrome case investigation form

Recommended basic set of data for case-based reporting in national surveillance system

Fill in this form for investigation and reporting of a clinically suspected case of congenital rubella syndrome

Case ID:_____Region:_____District: _____

Date of notification:___/___/___Date of investigation:____/___/___ Date of reporting:_____/___/___

A. Identification

Name of the child:_____ Sex: Male ☐ Female ☐

Date of birth:___ /___ /___ if not available – age in months_____ Address:_____

_____

Place infant delivered:_____ Name of mother:_____

B. Clinical signs and symptoms

Gestational age (weeks) at birth:_____ Birth weight (grams): _____

Group A (please complete all)				**Group B** (please complete all)			
Congenital heart disease:	Y es ☐	No ☐	Unknown ☐	Purpura:	Yes ☐	No ☐	Unknown ☐
Cataracts:	Yes ☐	No ☐	Unknown ☐	Microcephaly:	Yes ☐	No ☐	Unknown ☐
Congenital glaucoma:	Yes ☐	No ☐	Unknown ☐	Meningoencephalitis	Yes ☐	No ☐	Unknown ☐
Pigmentary retinopathy:	Yes ☐	No ☐	Unknown ☐	Jaundice:	Yes ☐	No ☐	Unknown ☐
Hearing impairment:	Yes ☐	No ☐	Unknown☐	Splenomegaly:	Yes ☐	No ☐	Unknown ☐
				Developmental delay:	Yes ☐	No ☐	Unknown ☐
				Radiolucent bone disease:	Yes ☐	No ☐	Unknown ☐

Other abnormalities: Yes ☐ No ☐ If yes please describe:_____

_____

Name of physician who examined infant:_____

City/town/village:_____ Telephone:_____

Present status of infant: Alive ☐ Dead ☐

If dead, cause of death: _____

Autopsy conducted: Yes ☐ No ☐ Unknown ☐

Autopsy findings:_____

Autopsy date:_____/____/_____

C. Maternal history/Antenatal care

Number of previous pregnancies:_____Mother's age (years): _____

Vaccinated against rubella:	Yes ☐	No ☐	Unknown ☐	If yes, give date: ___/___/___
Conjunctivitis:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Coryza:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Cough:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Maculopapular rash:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Lymph nodes swollen:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Arthralgia/arthritis:	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___
Other complications	Yes ☐	No ☐	Unknown ☐	If yes, date of onset___/___/___

Was rubella laboratory-confirmed in the mother Yes ☐ No ☐ Unknown ☐

If yes, when (date): ___/___/___

Was the mother exposed during pregnancy to person of any age with maculopapular (e.g. not vesicular) rash illness with fever Yes ☐ No ☐ Unknown ☐ If yes, when (date): ___/___/___

Month of pregnancy:_____Describe where:_____

_____

Did the mother travel during pregnancy: Yes ☐ No ☐ Unknown If yes, when (date): ___/___/___

Month of pregnancy:_____ Describe where:_____

_____

D. Infant/child laboratory investigations

Specimen collected: Yes ☐ No ☐ Unknown ☐

If yes, type of specimen: Serum ☐ Throat swab ☐ Urine ☐ Cerebrospinal fluid ☐ Other ☐

Date of specimen collection: ___/___/___ Date specimen sent: ___/___/___

Rubella IgM: Not tested ☐ Positive ☐ Negative ☐ In process ☐ Inconclusive ☐

Sustained IgG level*: IgG not tested ☐ Yes ☐ No ☐ In process ☐

*(*sustained IgG level on at least 2 occasions between 6 and 12 months of age)*

Rubella virus isolation: Not tested ☐ Positive ☐ Negative ☐ In process ☐

Rubella PCR: Not done ☐ Positive ☐ Negative ☐ In process ☐ Genotype_____

Date of laboratory result (first validated result): ____/____/____

E. Final classification

CRS ☐ Discarded ☐ If discarded, please specify:_____

Case classification as Laboratory-confirmed ☐ Epidemiologically linked ☐ Clinical ☐

Classification by origin: Endemic ☐ Imported ☐ Import-related ☐ Unknown ☐

Date of final classification: ____/____/____

Investigator:_____

Annex 6. Steps for establishing a CRS surveillance system

1. Identify national CRS surveillance coordinators responsible for epidemiological and laboratory components of the system.

Responsibilities of these coordinators include the following.

Epidemiological coordinator oversees:

- development of a protocol for CRS surveillance;
- development of necessary training materials;
- training on the CRS surveillance system;
- monitoring of surveillance performance and data quality;
- adequacy of collection and transportation of specimens for laboratory testing;
- maintenance of the CRS surveillance database;
- coordination with laboratory activities, to ensure linkage of laboratory and epidemiological data;
- coordination of activities with national measles and rubella elimination programme in country, including reporting to WHO;
- feedback on the CRS surveillance to participating health-care providers and facilities and relevant public health authorities.

Laboratory coordinator oversees:

- adequacy of laboratory testing, standard operating procedures (SOPs), necessary accreditations and an ongoing quality assurance programme;
- interpretation and reporting of test results for CRS;
- monitoring duration of virus shedding by CRS cases;
- coordination with epidemiological activities, to ensure linkage of laboratory and epidemiological data;
- laboratory-related training.

2. Determine facilities at which infants with CRS are most likely to be seen.

The facilities at which infants with most common defects associated with CRS – cataracts, heart defects, or deafness, as well as infants with maternal history of rubella during pregnancy – are likely to be seen should be included in the CRS surveillance system. As these defects are most likely to be evaluated and treated at secondary and tertiary care facilities, adequate sentinel surveillance for CRS can be conducted at these facilities, without including primary health-care providers and facilities in the CRS surveillance system. This will help to avoid overwhelming general health-care providers with having to identify, report, and follow-up on cases of CRS.

The types of facilities/providers most likely to evaluate and treat infants with CRS:

- secondary care providers/facilities, particularly ophthalmologists, cardiologists, audiologists, neonatologists;
- tertiary care facilities, particularly those that provide surgical services for the eyes, ears, and heart;
- specialist care centres (e.g. children's hospitals; centres for hearing and blindness);
- obstetric centres or private clinics involved in the care of pregnant women with rubella.

If providers and facilities included in the CRS surveillance system capture the majority of infants with suspected CRS within a country, the CRS surveillance system can be considered adequate.

It is recommended that countries with newly established CRS surveillance systems pilot test their system with a few facilities to ensure adequacy of developed protocols and SOPs. Protocols may then be updated with feedback from the piloted sites.

Responsibilities of local surveillance coordinators at sentinel sites include the following:

- ensure adherence to the national protocol and SOPs for CRS surveillance;
- assist as needed in training health-care providers and staff at the facilities concerned;
- ensure collection of clinical and epidemiological data and completion of case investigation forms;
- ensure appropriate collection and transportation of specimens with all relevant data, ensuring that laboratory data can later be linked to clinical and epidemiological information;
- maintain a line listing of suspected CRS cases in the assigned facilities;

- provide periodic feedback for health-care providers at their respective sites;
- maintain contact with the national coordinator regarding identification and follow-up of suspected cases of CRS identified in the area.

3. Conduct initial and refresher training for participating providers.

Training for providers from the sentinel facilities participating in CRS surveillance activities should be conducted on an annual basis, and more frequently as needed (e.g. for new staff).

Training should include information regarding clinical features of CRS, evaluation of infants with suspected CRS, appropriate laboratory testing of suspected cases, follow-up of CRS cases, the importance of completing case investigation forms, infection control measures to prevent rubella virus spread from infants with CRS, and reporting cases in a timely manner.

4. Initiate CRS surveillance activities.

Reporting of suspected CRS cases should be initiated once the coordinator and participating sites have been identified and participating providers have been trained in SOPs for CRS surveillance.

5. Conduct surveillance quality assessment and monitoring.

Surveillance quality assessments need to be conducted at the sentinel sites at least every six months to assess completeness of CRS surveillance at the site:

- this should be done by review of hospital records by the site-level coordinator to identify any missed cases;
- missed cases can be identified by comparing the list of reported CRS cases with the list of all cases that meet the entry criteria for CRS surveillance (i.e. criteria for suspected CRS case); the proportion of missed cases at a sentinel site can be assessed as the percentage of missed cases identified by the coordinator, among all cases that meet the CRS surveillance entry criteria (total of both reported and unreported cases);
- similarly, the proportion of suspected CRS cases that have been reported but have not been tested by laboratory can be assessed as the percentage of reported cases without laboratory testing among all reported suspected CRS cases (both tested and not tested).

Monitoring surveillance data quality means that CRS surveillance case reports should be assessed for any missing variables. If records are incomplete, the findings should be discussed with providers at the site and the need for completeness of data and case reporting should be emphasized.

6. **Expand CRS surveillance and include other sites, as appropriate.**

In countries that have conducted limited pilot testing of CRS surveillance systems or in countries where assessments have shown that the majority of infants within the country are not included in CRS surveillance, the surveillance should be expanded to include more sites, with the ultimate goal of establishing sentinel site surveillance that captures the majority of infants in the country.

7. Analyse the CRS surveillance data annually, or more frequently if necessary.

Epidemiological variables that should be assessed include:

- number of cases reported throughout time frame assessed (e.g. year);
- case classification status;
- geographical location of CRS cases within country;
- whether or not cases were clustered and/or associated with rubella outbreaks;
- maternal characteristics (age, race/ethnicity, country of birth);
- location of maternal exposure to rubella.

8. Provide feedback for stakeholders involved in the CRS surveillance system

Feedback should include information on the status of the epidemiology of CRS, including, if necessary, any updates and recommendations for improvements.

WHO
Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

Member States

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Estonia
Finland
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Switzerland
Tajikistan
The former Yugoslav Republic of Macedonia
Turkey
Turkmenistan
Ukraine
United Kingdom
Uzbekistan

The WHO Regional Committee for Europe adopted the goal of eliminating indigenous measles transmission in 1998. In 2005, the Regional Committee expanded this commitment to include rubella and set a date for the elimination of both diseases by 2010. Although Member States did make progress, through the implementation of a strategic plan, the goal was not achieved. The WHO Regional Committee for Europe acknowledged at its sixtieth session (2010) that the regional goal of eliminating measles and rubella is achievable, and set a new target date of 2015.

In the document *Eliminating measles and rubella and preventing congenital rubella infection, WHO European Region strategic plan 2005-2010*, key strategies are identified to meet the targets for interrupting transmission of indigenous measles and rubella and preventing congenital rubella infection. Strengthening surveillance systems by vigorous case investigation, including laboratory confirmation, is one of these key strategies.

In line with the elimination goal, *Surveillance guidelines for measles, rubella and congenital rubella syndrome in the WHO European Region* are intended to provide technical advice on the design and implementation of surveillance programmes. Surveillance indicators defined in these guidelines will be critical for assessing whether Member States have achieved the level of disease surveillance necessary for documenting elimination of indigenous measles and rubella transmission, and verifying that the Region's elimination objectives have been reached.

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