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

RATORY SURVEILLANCE CASE-BASED INVESTIGATION REPORTING DOCUMENTATION ASSESSMENT RUBELLA ELIMINATION
G VALIDATION CLASSIFICATION PROGRESS CASE DEFINITIONS LABORATORY INDICATORS CRS MONITORING MEASLES CL

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ABSTRACT
Measles and rubella remain important causes of vaccine-preventable diseases in the WHO European Region. The WHO Regional Committee for Europe formally 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. In the document *Eliminating measles and rubella and prevention congenital rubella infection, WHO European Region strategic plan 2005–2010*, key strategies are identified to meet the targets for interrupting the transmission of indigenous measles and rubella and preventing congenital rubella infection, and strengthening surveillance systems to include vigorous case investigation. Laboratory confirmation is one of these key strategies. *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 for these diseases in line with the elimination goal. Surveillance indicators defined in these guidelines will be critical for assessing whether Member States have achieved the level of disease surveillance necessary for monitoring progress towards eliminating the transmission of indigenous measles and rubella and verifying that the Region's elimination objectives have been reached.

Keywords

EPIDEMIOLOGIC SURVEILLANCE
MEASLES – elimination
RUBELLA – elimination
RUBELLA SYNDROME, CONGENITAL – prevention
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Abbreviations

CISID	Centralized Information System for Infectious Diseases
CRI	congenital rubella infection
CRS	congenital rubella syndrome
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EU	The European Union
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
MR	measles and rubella
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
UNICEF	The United Nations Children's Fund
WHO	The World Health Organization

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The team will be grateful for any comments and suggestions with regard to this publication addressed to vaccine@euro.who.int

1 Introduction

In 2005, the World Health Organization Regional Office for Europe published *Eliminating measles and rubella and preventing congenital rubella infection, WHO European Region strategic plan 2005–2010 (1),* identifying five key areas for action with the objective of eliminating measles and rubella. These are: the development of national policy, surveillance, the quality and safety of immunization, communication and advocacy, and the development of a verification process. Five key strategies are also identified:

- maintaining of very high coverage (≥95%) with two doses of measles vaccine and at least one dose of rubella vaccine through high-quality routine immunization services;
- ensuring provision of measles vaccination opportunities through supplementary immunization activities in populations susceptible to measles;
- providing rubella vaccination opportunities, including supplementary immunization activities, to all rubella-susceptible children, adolescents and women of childbearing age;
- strengthening of surveillance systems that include rigorous case investigation and laboratory confirmation of clinical cases; and
- increasing the availability of high-quality valuable information for health professionals and the public about the benefits and risks associated with vaccinations against measles and rubella.

Ensuring and sustaining high routine childhood vaccination coverage (≥ 95%) for 2 doses of measles-containing vaccine and 1 dose of rubella vaccine in each birth cohort is critical for the elimination of measles and rubella.

1.1 Objectives of surveillance and programme monitoring

Surveillance guidelines for measles, rubella and congenital rubella syndrome in the WHO European Region primarily addresses disease surveillance and monitoring towards elimination. It is important that disease surveillance is considered within the overall information needs of an immunization programme, which support effective programme management. These information needs include:

- information about cases and clusters of the disease (epidemiological surveillance);
- information about vaccination-related adverse events (immunization safety);
- information about the immunization coverage routinely achieved (quality of programme delivery); and
- information about the possible accumulation of susceptible persons (outbreak investigation and forecasting and sero-prevalence surveys).

The purpose of disease surveillance is to provide information for public health action as and when needed, i.e. to guide the planning, implementation and evaluation of public health interventions and systems *(2)*.

As the control of measles and rubella becomes more effective and countries approach the point at which these diseases are eliminated, surveillance systems will be required to detect and facilitate the investigation and laboratory confirmation of all clinical cases. Such sys-

tems need to be countrywide, sensitive, specific and case-based and be able to determine whether cases can be linked, i.e. whether sustained transmission is occurring. Since both children and adults are 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 at the national level among the general population year-round.

Surveillance for measles and rubella under an elimination strategy has the following two objectives.

1. Detect, investigate and characterize sporadic cases and clusters[1] in order 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 (size, duration of clusters);
   - identify populations at risk of transmission; and
   - ensure a rapid and appropriate public health response to the event.
2. Monitor of disease incidence and circulation of the virus in order to:
   - provide information for priority-setting, planning, implementation and resource allocation for preventive programmes, and for evaluating control measures;
   - assess and document progress towards elimination targets;
   - identify changes in risk groups and disease epidemiology;
   - assess the circulation of virus genotypes at national, regional and global levels.

Monitoring and evaluation of the surveillance system will be critical to 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 under-detection or under-reporting) and identifying areas where surveillance needs to be strengthened.

In addition to disease surveillance, reliable systems for monitoring the 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 (http://www.who.int/immunization/documents/en/).

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

- identify subgroups of the population at higher risk for disease transmission based on social or geographical characteristics, and thus predict or evaluate the risk for outbreaks; and
- provide information to plan relevant interventions to decrease the susceptibility of specific population subgroups and thus avoid outbreaks.

The epidemiology of measles and rubella in the Region varies among countries, reflecting different challenges for 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 *(3)*. Some young adults who have not been vaccinated have not been naturally infected as children due to the decreasing incidence of disease resulting from the adoption of routine measles and rubella childhood immuniza-

[1] Aggregation of measles cases in space and/or time.

tion. Immunization programmes may not adequately reach minorities and geographically or socially marginalized populations in many countries. People holding specific philosophical or religious beliefs may be reluctant to be immunized or actively oppose vaccination *(4-7)*. These groups may influence others with misinformation about the safety and effectiveness of vaccines. While some susceptible individuals benefit from the immunity of the surrounding vaccinated population (as known as herd immunity), geographical clustering of susceptible individuals leads to a greater risk for large outbreaks. At the same time, increased population movements related to migration, immigration and work- or leisure-related travel increase the potential for disease transmission from countries with high incidence of measles or rubella to countries and populations where the incidence is low or the disease has been eliminated.

A high level of vaccine coverage (≥ 95%) 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 interruption of indigenous transmission. There may still be imported cases, but circulation of the virus following importation ends naturally without intervention, usually after a limited number of generations of disease transmission *(8)*.

Progress towards elimination should be monitored and supported by a robust and sensitive surveillance system, assessed by simple but accurate indicators, that allows countries to identify evidence of transmission and information relevant for targeting susceptible groups and to document chains of transmission and their potential relationship to an importation. Sustained incidence rates below one case per million inhabitants are an important indicator for the elimination of measles or rubella but are only verifiable when the quality of surveillance is adequate, including a laboratory assessment of all sporadic clinical cases of measles and rubella. While the incidence of measles and rubella is low in the majority of countries in the Region, verifying the achievement of the Region's disease elimination targets requires accurate information on individual cases to be documented promptly in each country and reported to WHO.

Member States will be asked to document their achievement towards the elimination targets. In this process, all countries will need to provide evidence for the verification of the information they have submitted.

This document provides guidelines and recommendations and describes best practices for surveillance for measles and rubella. 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 the elimination of the diseases in the Region by 2010.

2 Surveillance for measles and rubella

2.1 Measles

Measles virus only infects humans, making elimination feasible. However, it is one of the most contagious viruses, with >90% secondary attack rates among susceptible individuals. The virus can be transmitted in the air (aerosolized) in respiratory droplets, or by direct or indirect contact with 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. Following exposure, the incubation period before onset of the symptoms is usually 10–12 days (range 7–18 days) *(9)*.

Approximately 30% of reported cases of measles involve one or more complications. 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) *(9)*.

Measles remains a leading cause of death globally among young children, despite the availability of safe and effective vaccines for the past 40 years. An estimated 242 000 children died worldwide from measles in 2005 *(10)*. The 2005 measles mortality reduction goal, established by WHO and the United Nations Children's Organization, of reducing the number of measles deaths by 50% from 2000 levels was achieved *(10)*. There is a new goal to achieve a 90% reduction by 2010, primarily by targeting children in the WHO regions (Africa and South-East Asia) with the highest number of measles deaths *(11)*.

There are still susceptible groups within countries in the Region

In settings where it remains endemic, transmission of the measles 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.

Measles in adolescents and adults in the European Region

In many European countries, in contrast to developing countries, the majority of cases occur in adolescents and adults *(12)*. In most countries of the Region, measles vaccination coverage and the level of 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 transmission between individuals is very high after the virus is introduced.

In developed countries, the case–fatality ratio for measles is 0.05-0.1 per 1000 cases, much lower than in developing countries where it can be 3–6% *(10, 13)*. The highest case–fatality rates are seen in infants aged under 12 months. Malnutrition and severe immunodeficiency (e.g. as a consequence of an advanced infection with human immunodeficiency virus) are risk factors for complications, including death.

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, so that a laboratory assessment is required to distinguish measles.

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 a few days of rash onset, using a sensitive enzyme-linked immunosorbent assay (ELISA). Approximately 70–90% of measles cases are IgM-positive at 0–2 and 3–5 days post-rash onset, respectively. 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 *(14)*.

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

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 (14)*. 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.

The interpretation of a positive IgM antibody test in recently vaccinated individuals must be made according to the clinical signs and the local epidemiology of disease, because mild rash and low-grade fever can be observed after measles vaccination in 2% and 5%, respectively, of vaccine recipients.

In countries with measles incidence under one per million (the elimination threshold), the use of IgM alone to diagnose a single case of measles without evidence of other cases in the community may not be adequate, 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 maculopapular rash illness, but infection with the rubella virus can frequently occur without noteworthy clinical signs and symptoms. As humans are the only known host, it is possible for the disease to be eliminated. While the rubella virus is less

contagious than measles, it is also transmitted by respiratory droplets and by direct or indirect contact with the nasal and throat secretions of infected persons. Individuals are most infectious when the rash is erupting, but they may shed virus from 7 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). Infants with congenital infection may shed a large quantity of virus through pharyngeal secretions and urine for up to one year and sometimes longer *(15)*.

Arthralgia and arthritis are commonly observed in adults with rubella, and chronic arthritis has been reported. Other less common complications are thrombocytopenia and encephalitis (1 per 6000 cases), which may be fatal. There is a rare late syndrome of progressive rubella panencephalitis *(16,17)*.

Rubella vaccination programmes have been highly effective in modifying the epidemiology of rubella and a number of countries have eliminated the disease

The epidemiology of rubella was similar to the epidemiology of measles in the prevaccine era, with seasonal variation and regular epidemic periods alternating with low incidence periods. In temperate climates, regular seasonal peaks of rubella occurred in spring, with small epidemics every three to four years and larger epidemics every six to nine years. In tropical regions, epidemics occur but are often unrecognized due to no apparent or only mild clinical symptoms in young children *(15, 16)*.

Rubella vaccination programmes have been highly effective in modifying the epidemiology of rubella and a number of countries have eliminated the disease, similar to the effect measles vaccination programmes have had on measles *(15,18)*. Rubella vaccination has, however, been introduced in different ways and often much later than measles vaccination in many countries of the Region. This has resulted in marked differences in the rubella susceptibility profile and rubella epidemiology among these countries. In addition, rubella surveillance is not well-established in many countries, making estimates of the true burden in Europe difficult.

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 to no clinical symptoms. Thus, a laboratory assessment is critical to confirm the diagnosis.

Humoral and cell-mediated immunity develop following natural infection and with immunization. With natural infection, IgM antibodies are becoming detectable within 3–4 days and IgG antibodies within one week of the onset of rash. Following vaccination, the appearance of IgG and IgM antibodies is somewhat delayed and peak levels are lower compared to natural infection. 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 to seven months after natural infection, vaccination and re-infection *(19)*. In addition, false-positive IgM test results may occur due to cross-reacting IgM antibodies (to Epstein Barr virus, 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 at least 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 after onset of symptoms. Detection of the virus is also possible in a certain percentage of vaccinated individuals *(14, 15, 19)*.

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

In countries with rubella incidence under one per million (the elimination threshold), 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 confirm a primary rubella infection versus a false-positive result.

Rubella in pregnancy

A single IgM result is sufficient for rubella surveillance purposes but not for clinical management of a case. Detection of a significant rise in IgG antibody is essential. Rubella IgM-positive results in pregnant women without clinical illness or defined contact with a rubella-like illness have a low positive predictive value and should be interpreted with caution. For medical decisions additional tests are necessary, such as avidity testing, rubella immunoblot, virus detection or virus isolation. A consultation with a medical expert is strongly recommended.

The laboratory confirmatory testing criteria recommended for surveillance purposes should not be used for the confirmation of rubella infection during pregnancy.

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 who develop a rash illness consistent with rubella and are found to be rubella IgM-positive should be referred to a specialist for further assessment of their risk for and likelihood of rubella infection, using additional assays.

A national registry of pregnant women with confirmed or clinical rubella can be used to record pregnancy outcomes (e.g. abortion, stillbirth, defects associated with congenital rubella) and the laboratory evaluation of infants.

Congenital rubella

All member States should undertake surveillance for CRS

Congenital rubella infection (CRI) is defined as any case with evidence of rubella infection, either by laboratory testing or clinical symptoms of congenital rubella syndrome (CRS), which is present at birth. Congenital rubella infection may occur when a susceptible woman has rubella at any stage of her pregnancy, although the risk of malformations is greatest earlier in the pregnancy. The risk of congenital infection also increases at the end of pregnancy, when the placental barrier is not as strong. Spontaneous abortions or stillbirths may occur following rubella infection in early pregnancy. Infection between the 11th to 17th week of gestation may result in single anomalies and isolated sensorineural hearing defects; defects are rarely found in children whose mothers were infected after 20 weeks gestation *(15)*.

Congenital rubella infection includes CRS, the clinical features of which also depend on the gestational age of maternal infection. Rubella acquired in the first 11 weeks of gestation is associated with the highest risk (70–90%) for signs and symptoms of classical and expanded CRS. CRS is seen in 0.6–2.2 children per 1000 live births during epidemics in countries without rubella immunization programmes *(20)*.

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 steno-

sis, 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 *(21)*.

Infants with CRS that survive the neonatal period may face serious developmental disabilities (such as visual and hearing impairment) and have an increased risk of developmental delay, including autism, type I diabetes mellitus and thyroiditis. A progressive rubella panencephalitis, resembling subacute sclerosing panencephalitis, has been observed in a few individuals with CRS *(15,22–24)*.

Integrating rubella and measles surveillance is cost-effective and a sound public health strategy

Infants with CRI 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 test should be done shortly after an initial negative result if there is clinical suspicion. At least 85% of infants with CRS will be IgM-positive between 3 to 6 months of life and some remain IgM-positive for 18 months. IgM-capture enzyme assays are more reliable than indirect assays for the detection of low levels of IgM, especially in congenital rubella cases after the third month of life. The laboratory confirmation of a possible congenital rubella case in an infant aged over six months should not rely on the IgM test alone but also include serial IgG testing to assess for a sustained level of antibody over several months. IgG antibodies have been detected in 95% of CRS cases beyond 6 to 11 months of age, when rubella vaccination has not been done. All infants with CRI, and in particular those with CRS, may shed virus in decreasing amounts up to at least one year of age and can transmit rubella to others *(25)*.

Recommendations for surveillance of CRS are discussed in further detail in Annex 1.

2.3 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 only infect 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. Almost all countries in the Region administer measles and rubella vaccines 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 on the ability of the health system to deliver vaccine to susceptible groups of people with high coverage. All Member States currently have routine two-dose measles vaccination programmes, and most have introduced two-dose rubella vaccination programmes, using combined measles-rubella vaccines (usually measles-mumps-rubella vaccine). Many countries that have recently introduced rubella vaccine have also undertaken supplementary immunization activities using MR vaccine with a strategy targeting susceptible children, adolescents and women of childbearing age.

Integrating rubella and measles surveillance is cost-effective given that the symptoms of the diseases are very similar. Both diseases commonly affect the same age groups. Thus, the

testing of measles or rubella IgM-negative specimens for the other disease is clinically and epidemiologically sound.

2.4 Adapting surveillance to local epidemiology and moving to case-based reporting

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. Thus, benchmarks by which the quality of surveillance are assessed have been developed: at least 2 measles- or rubella-like illnesses per 100 000 population per year at the national level, and at least 1 per 100 000 per year in all first subnational administrative divisions which are determined to be negative. These benchmarks are based on the experience of countries that have eliminated measles. This will require that all sporadic illnesses clinically consistent with measles or rubella be thoroughly investigated epidemiologically and adequate specimens obtained for laboratory confirmatory testing and, if possible, virus isolation and/or detection following positive results. If adequate specimens do not exist, or were collected outside the optimal IgM time period, other tests should be used (where appropriate) to determine etiology. In the absence of laboratory results, infections clinically consistent with measles or rubella should be classified as clinical cases and reported to the surveillance system.

In the elimination phase, all countries should conduct case-based surveillance. It includes epidemiological investigation and laboratory confirmation of all sporadic illnesses clinically consistent with measles or rubella

If an initial IgM test is negative for one of the two diseases, the specimen should be sequentially tested for other diseases.

In countries with an annual incidence of measles or rubella of under 1 per 100 000, all cases should be either laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case.

It is recommended that specimens from at least 5–10 cases associated with a recognized outbreak are submitted for laboratory testing. If the outbreak continues, additional specimens should be submitted to the laboratory every two to three months to confirm that the illnesses are still measles and/or rubella and to document changes in virus genotype. *An important exception to this rule is a case of clinically-compatible measles or rubella in a pregnant woman, when laboratory testing should be performed regardless of the background incidence.* During outbreaks, cases should be notified to WHO using both the case-based reporting form and the outbreak aggregate reporting form (see Annexes 2-5 for examples of data collection forms).

3 Case definitions for surveillance and reporting of measles and rubella

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 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 (26)*.

Case definitions for surveillance are not meant for medical case management. They are designed to standardize the reporting of similar cases 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. The general case definitions are as follows:

Clinical case	a person with an illness consistent with the clinical criteria;
Laboratory-confirmed case	a person with a clinical illness consistent with the clinical criteria and who has laboratory evidence of acute infection, using a WHO-recommended laboratory test;
Epidemiologically linked case	a person with a clinical illness consistent with the clinical criteria and who is linked to a place and time consistent with exposure and disease incubation with a laboratory-confirmed case; this is considered a confirmed case;
Discarded case	a person with signs and symptoms consistent with clinical criteria that are investigated and confirmed to be neither, either through laboratory testing or an epidemiological link to a case that is laboratory-confirmed to be another disease.

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[2] 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 classifications for surveillance

Clinical case	A person with signs and symptoms consistent with measles clinical criteria.
Laboratory-confirmed case	A person with signs and symptoms consistent with measles clinical criteria ***and*** who meets the laboratory criteria for measles surveillance case confirmation ***or***, if recently vaccinated, someone with an epidemiological link.
Epidemiologically-linked case	A person with signs and symptoms consistent with measles clinical criteria ***and*** who was in contact with a laboratory-confirmed case 7–18 days before the onset of symptoms.
Discarded case	A person with signs and symptoms consistent with measles clinical criteria with negative laboratory tests or who is epidemiologically linked to a case of laboratory-confirmed disease that is not measles (e.g. roseola, *erythema infectiosium*).

[2] See an operational approach to characterize a disease-specific IgM result in recent measles and/or rubella vaccine recipients on p. 14, Box 3.

3.2 Rubella

The clinical criteria for rubella are:
- maculopapular rash *and*
- cervical, suboccipital *or* post-auricular adenopathy, *or* arthralgia/arthritis.

The laboratory criteria for rubella surveillance case confirmation *in non-pregnant cases* are:
- rubella IgM antibody detection[3] *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 classifications for surveillance

Clinical case	A person with signs and symptoms consistent with rubella clinical criteria.
Laboratory-confirmed case	A person with signs and symptoms consistent with rubella clinical criteria ***and*** who meets the laboratory criteria for rubella surveillance case confirmation **or**, if recently vaccinated, someone with an epidemiological link.
Epidemiologically linked case	A person with signs and symptoms consistent with rubella clinical criteria ***and*** who was in contact with a laboratory-confirmed case 12–23 days prior to onset of the disease.
Discarded case	A person with signs and symptoms consistent with rubella clinical criteria with negative laboratory tests or who is epidemiologically linked to a case of laboratory-confirmed disease that is not rubella (e.g. roseola, *erythema infectiosium*).

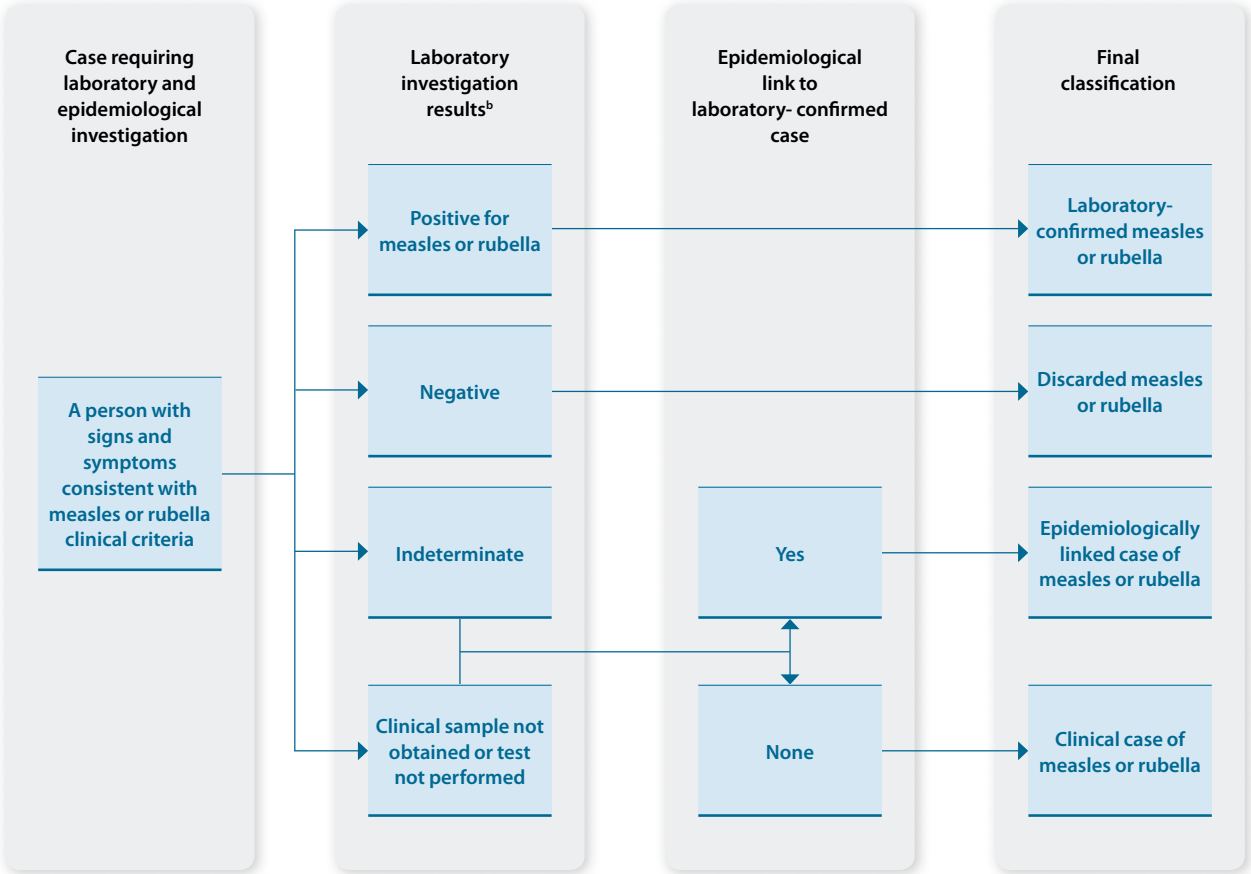
Case – classification flow-chart for measles and rubella surveillance is shown in Fig 1.

Rubella infections in pregnant women

For surveillance purposes, a case of laboratory-confirmed rubella infection in a pregnant woman (as defined above) should be reported on the reporting form as a case of rubella with documentation of the pregnancy. If the pregnancy comes to term, the newborn baby should be tested at birth. Neonates found to be positive for rubella infection in the absence of clinical features of congenital conditions should be reported as having laboratory-confirmed rubella. Any stillbirth should be reported through other surveillance systems (such as national pregnancy outcome registries or vital statistics).

[3] See an operational approach to characterize a disease-specific IgM result in recent measles and/or rubella vaccine recipients on p. 14, Box 3.

Fig. 1. Classification scheme for cases of measles or rubella[a]



[a] In non-pregnant cases; for classification of rubella infections in pregnancy see more on pp. 8 and 13.

[b] See an operational approach to characterize disease-specific IgM results in recent measles and/or rubella vaccine recipients, Box 3.

Box 3. Operational approach to characterize a disease-specific IgM result

- In the case of negative results in a serum sample taken earlier than 4 days after onset of the rash, a second sample should be taken, if possible, between 4 and 28 days following onset of the rash.
- If a sample investigation reveals an equivocal or indeterminate result following repeat testing, the sample may be tested by an alternate method or another sample obtained and tested. If the results remain indeterminate, the case should be classified based on the presence of an epidemiological link to another laboratory-confirmed case(s).
- Recipients of measles and/or rubella vaccine are expected to have detectable IgM after vaccination to the respective antigens used. Serological techniques cannot distinguish between immune responses to natural infection and immunization; thus only isolation and genetic characterization of the virus can distinguish between an IgM response to natural infection and one induced by the vaccine. An operational approach to characterize individuals with an IgM-positive result, without virus isolation or detection, and a recent history (within *six weeks* before onset of rash) of vaccination is as follows *(14)*:

Final case classification (recently vaccinated)	**Epidemiological findings**
Laboratory-confirmed case	Epidemiological link to laboratory-confirmed case(s)
Discarded case	Active search in community does not reveal evidence of virus transmission
	No history of travel to areas where virus is known to be circulating

3.3 Congenital rubella syndrome (CRS)

The clinical criteria for CRS are: an infant aged under one year with clinical features of at least one congenital condition in group A and one in group B below.

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

The clinical criteria suggesting CRS and indicating further laboratory and epidemiological investigation are: an infant aged under one year with clinical features of at least one congenital condition in group A.

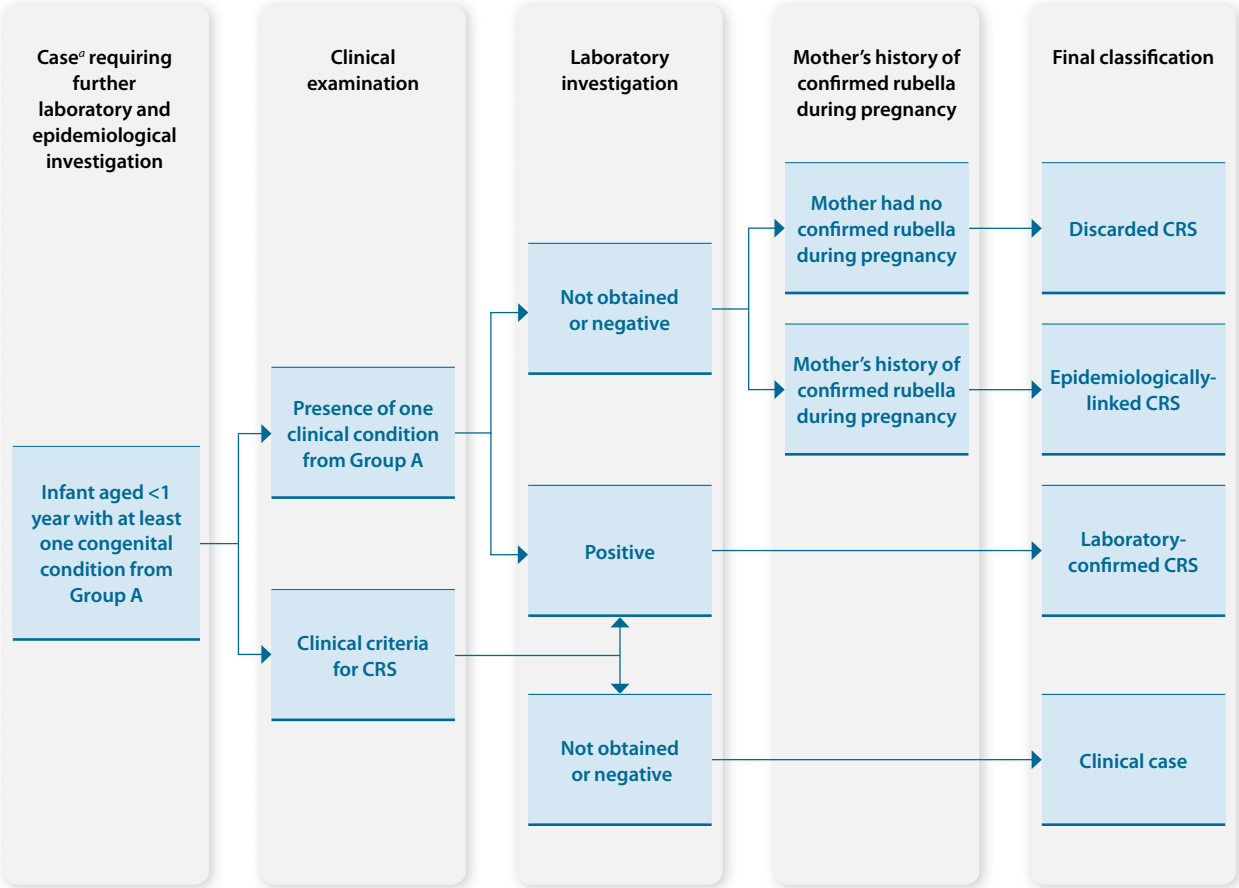
The laboratory criteria for CRS surveillance case confirmation are:

- 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.

The rationale for CRS surveillance and specific recommendations for implementation are in Annex 1. Fig. 2 and Box 4 give the classification scheme for CRS.

Box 4. Congenital rubella syndrome case classification	
Clinical CRS case	An infant with no other defined etiological explanation in whom a physician detects at least two of the clinical features in group A or one from group A and one from group B.
Laboratory-confirmed CRS case	An infant having at least one clinical feature listed in group A and meeting the laboratory criteria for congenital rubella infection.
Epidemiologically-linked CRS case	An infant with at least one clinical feature from group A and whose mother had confirmed rubella during pregnancy.
Discarded case	An infant with at least one feature from group A that does not meet any other classification criteria for clinical, laboratory-confirmed or epidemiologically-linked CRS.

Fig. 2. Classification scheme for CRS cases



[a] With no other defined etiological explanation of congenital conditions.

4 Investigation of measles and rubella cases

Under case based surveillance, epidemiological investigation including laboratory confirmation for all clinical cases of measles or rubella should be conducted immediately upon notification. The following practical steps should be part of the case investigation:

- a unique identifier should be assigned to each case (e.g. country code + district code + date + other);
- the case (or the family if necessary) should be interviewed to obtain demographic and clinical information, vaccination status, pregnancy status and travel history;
- an attempt should be made to identify the source of infection (contact with possible infectious measles or rubella cases, travel in an epidemic area, etc.);
- specimens should be collected for confirmation and virus isolation/detection from cases, if this has not already done by physicians;
- the investigation form should be completed to collect data for further analysis (an example of a form and list of variables to collect are given in Annexes 2 and 3);
- contacts exposed to the case when he/she was infectious, or the families of the contacts, 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

In order to enhance the cost-effectiveness of integrated surveillance for measles and rubella, laboratory assessment can be based on the epidemiology of measles and rubella in the country.

In countries where both measles and rubella incidence are high (i.e. where specimens have been submitted for laboratory testing for at least 5–10 cases associated with a recognized outbreak in a district):

- test for measles first
- test for rubella if the result for measles is negative.

In countries with a low incidence of measles and a high incidence of rubella:

- test for rubella first
- test for measles if the results for rubella are negative.

In countries with a low incidence of measles and rubella (i.e. where at least 80% of clinically compatible cases are laboratory-tested):

- test for both infections.

Collection of samples for measles and rubella testing

The correct timing for the collection of samples with respect to clinical signs is vital for obtaining a valid 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 1). 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 (14)* and in Annex 6.

Table 1. Clinical samples for measles and rubella testing 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	✓	✓	✓

* days of onset of rash

Antibody detection

A single *serum sample* obtained **at the first contact** with the health care system at any time within 28 days after onset is considered adequate for surveillance purposes. A higher proportion of false negative results are found in specimens collected within 72 hours after onset of the rash. In case of negative results in a serum sample taken earlier than 4 days after onset of the rash, a second sample should be taken, if possible, between 4 and 28 days following onset of the rash.

Virus isolation

In contrast to antibody detection, virus isolation, necessary for genotyping, 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 °C). It is important that samples should be transported under cold conditions as soon as possible following collection.

Reverse transcription PCR

Measles and rubella viruses can be detected 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.

4.2 Collection, collation and transmission of data

Public health authorities at different levels should ensure functioning and sustaining of the surveillance reporting network that matches the reporting requirements of the elimination stage of measles and rubella. The case notification form 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.

- Individual data should be collected at the primary level of the system (see Annex 7 for examples of variables to collect).
- Case-based data are reported up to the national level. A line listing of cases should be available at all levels of the system according to the area under surveillance.
- All sporadic cases should be reported immediately.
- During a cluster of cases or an outbreak, reporting should be weekly after the initial report.
- Zero reporting should be implemented at all levels of the system, in order to monitor disease elimination at every level.
- As incidence approaches one per million, epidemiological data on all clinically suspected (including discarded) cases should be reported.

As incidence approaches one per million, laboratory data on all discarded cases should be reported

4.3 Reporting to WHO and European Union

Member States should report monthly to WHO. Countries belonging to the European Union will send their notifications through the European Centre for Disease Prevention and Control or EUVAC.NET, the dedicated surveillance network collaborating with the Centre. The Centre has agreed to transmit these data on a monthly basis to the Regional Office.

The objectives of notification to WHO are to:

- provide a standardized, up-to-date and complete picture of the epidemiology of measles and rubella;
- indicate the burden they place on public health;
- identify more precisely the geographical areas where particular problems are occurring and action is needed;
- permit the sharing of data at subnational level to identify specific geographical areas of risk and risk groups by age and gender; and
- disseminate rapidly critical and up-to-date information about infectious diseases to public health professionals.

For these purposes, the Regional Office has developed an online data entry and analysis tool, the Centralized Information System for Infectious Diseases (CISID), and strongly encourages non-EU Member States to use this mechanism for reporting.

The principal features of CISID are:

- a user-friendly interface in English, French, German and Russian;
- data entry that allows easy submission of aggregate and case-based data;
- easy and rapid access to case-based data;
- production of tables and charts that can be saved and exported to other applications;
- a security policy designed to protect the integrity of data.

CISID allows aggregate and case-based reporting. If Member States are not able to report online, the Regional Office should be informed of the technical difficulties they encounter (contact: measles@euro.who.int). Member States can also report monthly measles/rubella surveillance data using an MS Excel form which is available on CISID for download. CISID

also offers the possibility to e-mail (measles@euro.who.int) or fax (+45 39 17 18 18) the corresponding forms (completeness + aggregated report or completeness + case-based report). Information on CISID can be found at the Regional Office CISID home page (http://data.euro.who.int/cisid/, accessed 24 August 2009).

5 Monitoring and evaluation

The monitoring and evaluation of surveillance systems over time are necessary to identify areas that need strengthening and to provide evidence demonstrating 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, WHO has defined a set of indicators that should be calculated for measles and rubella for every level of the system and regularly reported (see Surveillance performance indicators on page 22).

In addition to routine monitoring, regular in-depth evaluation of the system should be conducted periodically to assess its quality, completeness, usefulness and effectiveness.

Surveillance data should be analysed at each administrative level in order to monitor and document the progress towards achieving and sustaining elimination in all Member States (see Indicators for monitoring progress towards elimination on page 23).

Indicators for monitoring progress must be interpreted in regard to the quality of the disease surveillance. These indicators must also be interpreted with regard to the immunity profile of specific subgroups (age group, geographical area, etc.), when available.

Main definitions for the control and elimination of measles and rubella are presented in Annex 8.

5.1 Surveillance performance indicators

The following indicators measure the performance of measles and rubella surveillance.

1. Timeliness of reporting to national units and WHO

The number of subnational reports received at the national level and the number received by WHO from countries by the 25th of the following month, divided by the number of reports expected in the reporting year (or according to the expected frequency of reporting) × 100%.

Target: ≥80% of countries submit reports timely for all months.

2. Completeness of reporting to national units and to WHO

The number of subnational reports received at the national level, and the number of national reports received by WHO, divided by the number of reports expected by that time in the reporting year × 100%.

Target: ≥80% of countries submit complete reports.

3. Laboratory investigation rate

The number of cases with specimens adequate for detecting measles or rubella IgM collected and tested in a proficient laboratory[4] divided by the number of cases reported × 100%.

Target: >80% of clinical measles/rubella cases tested in a proficient laboratory (except in high-incidence countries with large outbreaks).
(*Note:* any cases that are epidemiologically linked to a laboratory-confirmed case of measles or other communicable disease should be excluded from the denominator.)

4. Detection rate (for countries with an incidence lower than 1 per 1 000 000 population

A rate of clinically 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.

Target: At national level, an annual rate of 2 clinically suspected measles/rubella cases discarded as non-measles/non-rubella cases per 100 000 population should be considered a minimum. In addition, at least 1 non-measles/non-rubella clinically suspected measles/rubella case should be reported annually per 100 000 population in at least 80% of the administrative units at 1st subnational level (e.g. a province) or at an administrative level that has an average population of at least 100 000.

5. Chains of transmission with virus genotype data

The number of measles or rubella chains of transmission with genotype information, divided by the number of the chains of transmission of that disease × 100%.

Target: >90% of chains of transmission with genotype information.

6. Source of infection identified (for countries with an incidence lower than 1 per 1 000 000 population)

The number of measles or rubella cases for which a source of infection is identified (e.g. imported, import-related or endemic), divided by the total number of cases reported × 100%.

Target: >80% cases with source of infection identified.

7. Adequacy of Investigation

The number of clinically suspected measles or rubella cases with an adequate[5] investigation initiated within ≤48 hours of notification, divided by the total number of clinically suspected cases notified × 100.

Target: At least 80% of all reported clinically suspected measles or rubella cases should have had an adequate investigation

Footnotes 4 and 5 on page 23

5.2 Indicators for monitoring progress towards elimination and targets suggesting elimination of the disease(s)

Each of the following indicators has a target, the achievement of which would suggest the disease(s) has/have been eliminated. Because country-specific scenarios can lead to misinterpretations of indicators for monitoring progress towards elimination, the proposed indicators should not be used seperately. Rather, an assessment of all four is necessary for reliable conclusions to be drawn. The indicators are useful for providing general guidance and may not apply to small populations (particularly isolated small populations such as on small islands). WHO will request MS to perform a standardized in-depth review of surveillance and immunization data to verify and confirm that the country has eliminated the disease(s).

1. Vaccination coverage	
Countries should monitor vaccination coverage continuously to enable the population's immunity to be assessed.	
Indicator:	vaccination coverage of first and second routine doses of measles/rubella-containing vaccine.
Target:	achievement and maintenance of at least 95% coverage with both first and second routine doses of measles/rubella-containing vaccine·
2. Outbreak size	
The rationale for monitoring the size of an outbreak is to show that chains of transmission are self-limiting as a result of very high population immunity to measles and rubella. The use of an indicator that monitors outbreak size is intended to encourage countries to conduct thorough outbreak investigations. Data on the size of an outbreak can be misleading in the absence of a thorough outbreak investigation that includes active case-finding and epidemiological linkages of cases.	
Indicator:	monitoring of the size of ALL outbreaks, including outbreaks in closed settings and outbreaks where interventions have taken place to stop the outbreak.
Target:	At lease 80% of outbreaks should have less than 10 confirmed measles or rubella cases.
3. Incidence	
Indicator:	measles/rubella incidence per million population per year should be used to monitor progress towards elimination. The numerator should exclude measles/rubella cases confirmed as imported.[6]
Target:	achievement of a measles/rubella incidence of less than one confirmed case of measles per million population per year, excluding cases confirmed as imported.[7]
4. Endemic measles/rubella virus strain(s)	
Countries should try to detect all epidemiological links to importation and determine the measles/ rubella virus sequence information for all chains of transmission. These data can be used to provide evidence of the absence of endemic measles/rubella transmission and that all measles/rubella viruses are imported.	
Indicator:	number of measles/rubella cases caused by an endemic virus strain.
Target:	0 cases of measles/rubella caused by an endemic virus strain for at least 12 months.

Footnotes page 22

[4] A proficient laboratory is a WHO network laboratory that uses a validated assay and has passed the annual WHO proficiency test.

[5] An adequate investigation includes at a minimum collection of all of the following data elements from each suspected measles case; name or identifiers, age (or date of birth), sex, date of rash onset, date of specimen collection, vaccination status, date of last vaccination, travel history and district. In addition, it should include an investigation of all epidemiological links (as defined at the country/Regional level).

Footnotes page 23

[6] All laboratory-confirmed, epidemiologically-linked and clinical cases.

[7] All import-related cases and sporadic or endemic measles/rubella cases that are not imported should be included.

5.3 General supervision and evaluation

With the marked decrease in incidence of measles and rubella in almost all countries in the Region, these diseases are no longer common causes of rash and fever illnesses and their clinical diagnosis without laboratory confirmation is not specific. The notification of all clinically-suspected cases is not, therefore, relevant for evaluation of virus circulation as most cases will not be confirmed as measles or rubella as a result of the laboratory assessment. Investigation of clinical cases that are discarded following laboratory assessment does, however, provide evidence of the absence of circulation, and countries and subnational administrative areas need to be aware of and regularly monitor the number of clinical cases investigated. Areas not investigating at least 2 cases per 100 000 population also need to be assessed to determine whether clinical cases are not being investigated. This can best be done through site visits with a review of patients' files, if necessary, to identify clinical cases.

Surveillance staff at all administrative levels should regularly review areas that do not report cases for extended periods to ensure that clinical cases are being investigated.

5.4 Frequency of reporting and feedback

In all countries, sporadic cases and disease clusters should be reported immediately to upper administrative levels. Laboratories should confirm sporadic cases within three days of receiving the relevant specimens. Weekly updates are indicated when transmission is active, including weekly zero reporting in the aftermath of an outbreak. In countries with a high incidence of disease, the frequency of reporting sporadic cases must be adapted to the local situation but similar principles should be applied when possible.

Feedback should be provided with similar regularity and quality as data reporting. If weekly notifications are required during an outbreak, weekly feedback summarizing the situation since the beginning of the outbreak and current developments should be made available. More complete reports should also be made available at the end of an outbreak, which should include an appropriate summary of the epidemiological facts together with recommendations for control and a description of the control activities carried out.

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Annex 1 Surveillance for Congenital Rubella Syndrome

Rationale for Congenital Rubella Syndrome (CRS) surveillance

The primary benefit of rubella vaccination is directly linked to the prevention of foetal infection during pregnancy. The frequency and gravity of congenital rubella infection have been described *(1,2)*. The various birth defects described with CRS markedly affect the life of the patient. As a result of their disabilities, some patients need expensive medical or social care and lifelong support in assisted care settings. Some affected infants can also shed the virus throughout the first year of life, increasing the risk of disease transmission in health care settings. Infants meeting the clinical criteria for CRS can be recognized by alert health professionals. However, congenital rubella does not always present as CRS, and these other infants may not be easily diagnosed. Some children will also be asymptomatic but can still shed the virus for several months.

Since the Region aims to eliminate the transmission of indigenous rubella virus, it also aims to prevent all outcomes of intrauterine rubella infection regardless of the clinical features of the infant at birth or whether a pregnancy comes to term or not.

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 potentially to reduce the consequences of the disease on infants and their families through early provision of appropriate medical care.

All Member States should undertake surveillance for CRS.

Even though surveillance for CRS does not capture the entire picture of the burden of rubella infection in pregnancy, it is feasible for the detection and reporting of cases with clinical features. Attempts to include all congenitally-infected fetuses in estimates of the burden of congenital rubella could result in non-standardized estimates that are not congruent with the target goal, which is expressed as a rate per 100 000 live births per year. Furthermore, up to 50% of rubella infections are subclinical and may not be detected, which further complicates obtaining an accurate rate of miscarriages and stillbirths attributable to rubella infection in pregnancy.

Almost all the Member States of the WHO European Region have implemented rubella vaccination programmes. It is recognized, however, that the strength and type of existing rubella and congenital rubella surveillance activities vary greatly among the 53 Member States. Health systems within the Region are also very diverse, and comprehensive surveillance for most outcomes of congenital rubella infection is not feasible in many Member States. Countries that collect statistics on rubella-associated terminations of pregnancy, or who have a systematic mean for documenting miscarriages and stillbirths, may be used in further assessing the outcomes of rubella in pregnancy and in documenting the effect of the rubella vaccination programme.

Recommendations for implementation

CRS should be suspected and further laboratory and epidemiological investigation should be conducted in all infants with clinical features of at least one congenital condition from group A.

When CRS is suspected, blood and urine specimens should be collected as soon as possible. For surveillance purposes, a single blood specimen is generally considered adequate to confirm CRS during the first six months of life. If the first specimen is negative for rubella IgM and there exists a compelling clinical and/or epidemiological suspicion of congenital rubella, a second blood specimen should be requested and both specimens assessed for IgG and IgM. If the initial blood specimen is collected six or more months after birth, the second specimen for IgG testing should be collected several months later.

A standard reporting form should be completed for each clinically suspected case of CRS (Annex 3).

Appropriate isolation procedures should be considered for a young infant suspected of having CRS, particularly if he/she is hospitalized or in a group care setting. Only persons known to be immune to rubella should have contact with these infants in isolation. Infants with CRS may be infectious for rubella during their first year of life unless appropriate laboratory methods have shown them to be virus-negative.

Susceptible pregnant women **must not be exposed** to infants with congenital rubella.

Health professionals working with young children or their mothers should be aware of CRS surveillance activities and receive appropriate training and information. Information should be systematically provided to these health professionals, including:

- standard case definitions;
- procedures for investigating and reporting clinical congenital rubella cases;
- copies of congenital rubella case investigation forms;
- information on handling specimens and shipping them to the appropriate laboratory; and
- reports and results of surveillance activities.

The following health professionals should be provided with information and guidelines on congenital rubella and given regular feedback and training:

- public health and health care professionals routinely participating in surveillance for vaccine-preventable diseases (including epidemiologists, nurses and community health workers);
- public and private health professionals involved in paediatric and antenatal activities, including family doctors;
- staff in neonatal wards and neonatal intensive care units;
- staff in obstetrics services, including obstetricians and midwives;
- staff in general hospitals, including paediatric wards;
- staff in referral hospitals;
- paediatricians;
- cardiologists and cardiac surgeons;
- ophthalmologists, optometrists and primary eye care workers;
- otologists and audiologists; and
- infectious diseases physicians.

Surveillance for CRS is a challenge because infants with less severe manifestations and those with hearing loss (the most common defect among congenital rubella cases) are more likely to be detected later in infancy, when laboratory confirmation is more difficult. Earlier detection of clinical CRS is possible in countries with routine neonatal screening for hearing, using the methods of otoacoustic emissions or auditory brainstem responses.

Newborns who fail hearing screening tests should be tested for rubella-specific IgM antibodies to rule out congenital rubella.

When a surveillance programme is being implemented, a review of historical records of similar sources of information should be considered. This can allow a comparison for assessment of the previous disease burden and a basis for monitoring completeness of notification. Sources of information that may be considered for historical and continuing review are:

- birth-defects registers (access to data may be limited for confidentiality reasons);
- rare disease registers;
- national statistics on causes of death; and
- laboratory testing of autopsy specimens in countries performing routine autopsies of infants; testing of abortion products may also be considered, according to the practices in the countries.

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Annex 2 Integrated measles and rubella case investigation form

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. Identification

Name: _____

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: _____

_____

For female cases

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

Vaccination status

Last vaccination date:

Measles: Yes ☐ No ☐ Unknown ☐ If yes, no. of doses ___ ___/___/___

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

Last vaccination date:

Rubella: Yes ☐ No ☐ Unknown ☐ If yes, no. of doses ___ ___/___/___

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:	Yes ☐ No ☐ Unknown ☐
		Please specify	_____

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. Possible source of infection

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 (cases ID/name): _____

Where (country/address): _____

When (dates): _____

If there were confirmed cases of measles , rubella or measles and 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 (cases 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 data

Specimen collected: Yes ☐ No ☐ 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. Classification

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. Not imported, not import-related ☐ 3. Import-related ☐ 9. Unknown ☐

Date of final classification: ___ /___ /___

Investigated by: Name _____ Position: _____

Annex 3 Congenital rubella syndrome case investigation form

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): _____ Birth weight (grams): _____

Group A (please complete all)

Congenital heart disease: Yes ☐ No ☐ Unknown ☐

Cataracts: Yes ☐ No ☐ Unknown ☐

Congenital glaucoma: Yes ☐ No ☐ Unknown ☐

Pigmentary retinopathy: Yes ☐ No ☐ Unknown ☐

Hearing impairment : Yes ☐ No ☐ Unknown ☐

Group B (please complete all)

Purpura: Yes ☐ No ☐ Unknown ☐

Microcephaly: Yes ☐ No ☐ Unknown ☐

Meningoencephalitis: Yes ☐ No ☐ Unknown ☐

Jaundice: 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 (please describe): _____

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: 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 any 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: _____ 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: _____

Laboratory-confirmed ☐ Epidemiological link ☐ Clinical ☐

Imported ☐ Not imported, not import-related ☐ Import-related ☐ Unknown ☐

Date of final classification: ___ /___ /___

Investigator: _____

Annex 4 Rubella Aggregated Monthly Reporting to WHO/EURO

Form Updated: Dec 2007. measles@euro.who.int or fax to +45 39 17 18 63

Identification	Reporting
Country	Year of report
Name of the responsible person	Month of the report
Email	New suspected cases reported in the month
Telephone	Number of districts reporting
Current date	Total number of districts in the country

Vaccination status and Age of confirmed rubella (Lab-Confirmed, Epi-linked, Clincal) cases

Vaccination status	<1 year	1 - 4yrs	5 - 9yrs	10 - 14yrs	15-19yrs	20-29 yrs	30+	age unknown	Total
0 doses									
1 dose									
2+ doses									
Unknown Vaccination Status									
Total									

Classification and Age of confirmed rubella cases

Case Classification	<1 year	1 - 4yrs	5 - 9yrs	10 - 14yrs	15-19yrs	20-29 yrs	30+	age unknown	Total
Laboratory Confirmed cases									
Epi linked cases									
Clinical cases									
Other Information									
Reported cases of Rubella who were pregnant at the time of infection									

Instructions

Rubella cases to report: All cases with illnesses consistent with the rubella clinical criteria should be reported as new clinically suspected rubella cases regardless final classification: A person with the following signs and symptoms: maculopapular rash, and cervical, suboccipital or post-auricular adenopathy, or arthralgia/ arthritis.

All the cases should be finally classified or discarded.

Finally classified cases: Countries using an aggregated reporting format should report to WHO all laboratory-confirmed, epidemiologically linked and clinical cases:

Laboratory-confirmed case: A person with a clinical illness consistent with the clinical criteria and who has laboratory evidence of acute infection, using a WHO-recommended laboratory test.

Epidemiologically linked case: A person with a clinical illness consistent with the clinical criteria and who is linked in time appropriate for the disease incubation period and place to a case who has been laboratory confirmed.

Clinical case: A person with an illness consistent with the clinical criteria.

Annex 5

Measles/Rubella Aggregate Outbreak Reporting Form

(Please fill this form after each measles rubella outbreak investigated and email to measles@euro.who.int or Fax +45 39171863)

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

Instructions to fill-in the Measles/Rubella Aggregate Outbreak Reporting Form for reporting measles or rubella outbreaks to WHO Regional Office for Europe

Please report using routine ways - through WHO Europe or EUVAC.NET, 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 as soon as an outbreak is reported by referent national surveillance health institution (the one in charge for 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.

Additional updates can be sent if the country would like to report, however at a minimum two reports per outbreak should be sent.

Outbreak Identification: 11 information cells

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 the country, YYYY is year of outbreak and 99 is series starts 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's 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 municipalities; 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, 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" if outbreak is imported from another country. Measles imported case are cases exposed outside the country during the 7 to 21 days prior to rash onset as supported by epidemiological and/or virological evidence. If the index case came from or was exposed and infected due to contact with a person from another administrative territory in the 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.

Cases detail: 6 information cells

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 that is under epidemiological, clinical and/or laboratory investigation during the outbreak; and that the person has clinical symptoms meeting the case definition for measles or rubella and/or possible epidemiological link with other 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: 4 information cells

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 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.

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: 2 information cells; to fill in 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.

Name and contact detail of the person reporting this outbreak: Enter the contact information of the person that WHO EURO 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 EURO.

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 and 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 sever 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 eventual long term measures that are based on the lessons learned during this outbreak.

Sub-national outbreak spread detail (please provide this detail 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. According to the national regulations, these cases can 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 6 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. Example of specimen request form

Measles and rubella laboratory request and result form

Country: _____ If yes, when (date): _____ Date: _____ Case ID: _____

Patient Name: _____ 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 local epidemiologist. **For date please use: dd-mm-yyyy (like 20-10-2002).**

Specimen No.[a]	Specimen type[b]	Date of collection	Date of shipment	Date received at laboratory	Condition	Date of result	Measles test		Rubella test	
							IgM	Other*	IgM	Other*

Comment: [c] _____ *Other methodology (specify): _____

Name of the person whom the laboratory results should be sent: _____

Address: _____

Telephone number: _____ Fax number: _____

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 (ethylenediaminetetra-acetic 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.

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**.

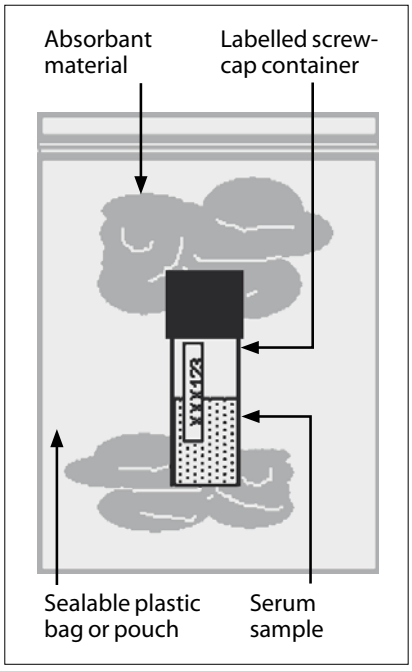
Whole blood should be allowed to clot and then centrifuged at 1000 × gravitational units (g) for 10 minutes to separate the serum. If there is no centrifuge, the blood can be kept in a refrigerator (4–8 °C) until there is complete retraction of the clot from the serum (no longer than 24 hours).

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

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



Serum should be stored at 4–8 °C until shipment takes place, or for a maximum of 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 the serum samples for IgM testing should be avoided, as it may have detrimental effects on the stability of IgM antibodies.

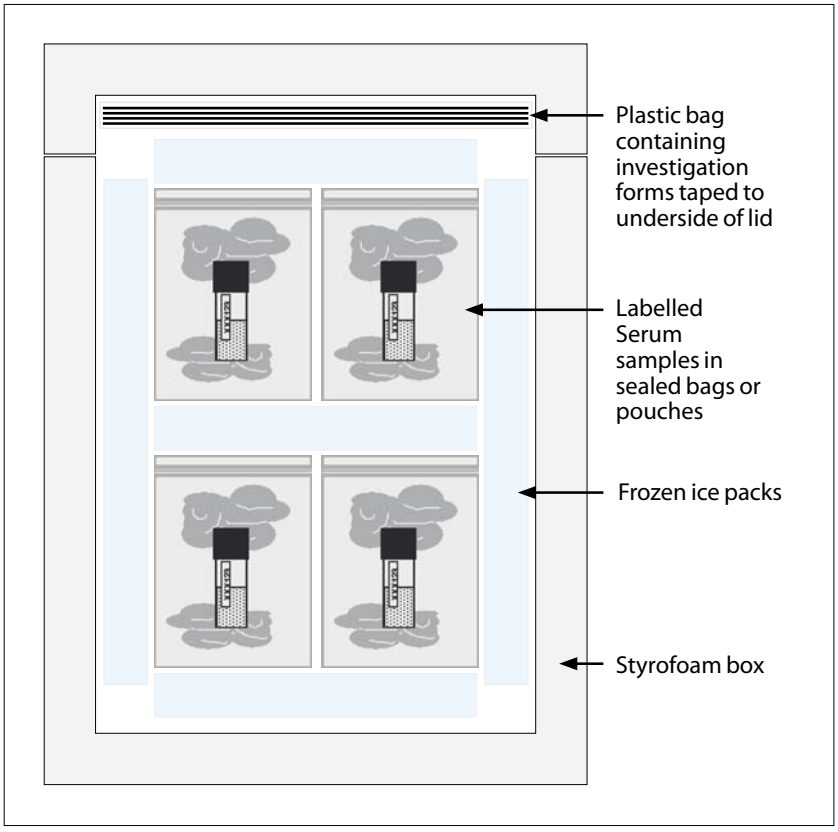
As a general rule, serum specimens should be shipped to the laboratory as soon as possible. The shipment should not be delayed for the collection of additional specimens.

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)*.

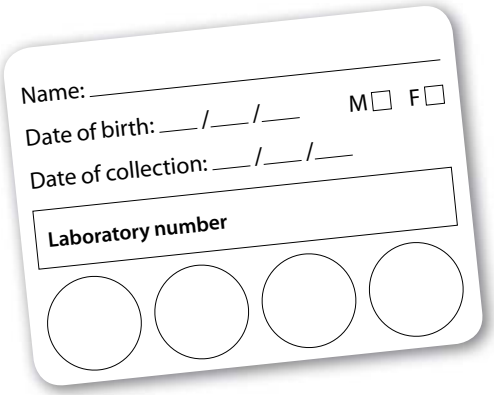


Fig. 4. Example of dried blood spot filter paper collection form

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 micro-lancet.

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.

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 these 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 that 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 (4–8 °C) 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 after onset.

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 CO_2 contamination.

B. Nasopharyngeal specimens for isolation of measles and rubella virus

Collection of nasopharyngeal samples

Nasopharyngeal specimens can 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 CO_2 contamination.

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 ethylenediaminetetra-acetic 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 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 non-denaturing 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, Annex 6

1. 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 17 March 2009).

Annex 7 Data Fields and Definitions for Case-Based Reporting

Field name in database	Label	Definition	Possible answers	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 website	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 at 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 in database	Label	Definition	Possible answers	Rules
DInvestigation	Date of investigation	Date of epidemio-logical 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 conjuctivitis	1 Yes 2 No 9 Unknown	
ClinAAA	Adenopathy, arthralgia/ arthritis	Presence of one or more of adenopathy, arthralgia/ 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	
ClinHospitalisation	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 Not imported, not import- related 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 SrcOutbreakRelated=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 CompComplication=1
CompPneumoniae	Pneumoniae	Patient suffered from pneumoniae	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplication=1
CompMalnutrition	Malnutrition	Patient suffered from malnutrition	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplication=1
CompDiarrhoea	Diarrhoea	Patient suffered from diarrhoea	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplication=1

Field name in database	Label	Definition	Possible answers	Rules
CompOther	Other	Patient suffered from other complications	1 Yes 2 No 9 Unknown	Answer is only possible if CompComplication=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 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, RT-PCR 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 the case is the index case of an outbreak; 2. name of country where the patient acquired the disease.	

Annex 8 Main definitions for the control and elimination of measles and rubella

Adequate investigation includes at a minimum collection of all of the following data elements from each suspected measles case: name or identifiers, age (or date of birth), sex, date of rash onset, date of specimen collection, vaccination status, date of last vaccination, travel history and district. In addition, it should include an investigation of all epidemiological links (as defined at the country/regional level).

Chain of transmission/outbreak is the situation when two or more confirmed cases are temporally related with sufficient time between them to allow for an incubation period, and epidemiologically linked by exposure history and/or genetically linked by viral typing.

Endemic virus strain is a genotype of any measles virus that occurs in an endemic chain of transmission. Any genotype that is found repeatedly in locally acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.

Imported case is defined as a case which has its source of infection outside the country; travelled outside of the country during the incubation period prior to onset of the rash (measles: 7–18 days; rubella: 12–23 days) and supported by epidemiological and/or virological evidence of foreign-acquired infection.

Import-related case is a case epidemiologically linked to an imported case, as supported by epidemiological and/or virological evidence. All import-related cases are to be considered as indigenous cases.

Incidence rate by age group is calculated to detect changes in the epidemiology of disease. It can be interpreted in relation to the susceptibility profile and vaccine coverage by age group, if available.

Incidence rate: CRS Number of cases in a defined geographical area (excluding imported cases) reported as a ratio indexed to the number of live births in the same geographical area during a specific period of time.

Incidence rate: measles and rubella Number of cases in a defined geographical area (excluding imported cases but including import-related cases) reported as a function of the total population of the same geographical area during a specific period of time.

Indigenous case is a case which cannot be proven to be an imported or import-related case, or any sporadic case with unknown source of infection.

Outbreak/cluster size refers to the number of cases, including all chains of transmission, that are epidemiologically and/or genetically linked. As countries approach and achieve the elimination phase, at least 80% of outbreaks should consist of fewer than 10 cases.

Proficient laboratory is a WHO network laboratory that uses a validated assay and has passed the annual WHO proficiency test.

Proportion of imported cases is the number of measles or rubella cases classified as imported as a result of a thorough epidemiological investigation, divided by the total number of cases of that disease. In an elimination phase, the proportion of imported cases increases.

Proportion of vaccinated cases can help detect problems with vaccine effectiveness. This indicator can be used to calculate the effectiveness of vaccine in the aftermath of an outbreak.

Re-establishment of endemic transmission is a situation in which epidemiological and laboratory evidence of a chain of transmission of a laboratory-confirmed virus continues uninterrupted for a period of 12 months or more.

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.

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Measles and rubella remain important causes of vaccine-preventable diseases in the WHO European Region. The WHO Regional Committee for Europe formally 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. In the document *Eliminating measles and rubella and prevention congenital rubella infection, WHO European Region strategic plan 2005–2010*, key strategies are identified to meet the targets for interrupting the transmission of indigenous measles and rubella and preventing congenital rubella infection, and strengthening surveillance systems to include vigorous case investigation. Laboratory confirmation is one of these key strategies. *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 for these diseases in line with the elimination goal. Surveillance indicators defined in these guidelines will be critical for assessing whether Member States have achieved the level of disease surveillance necessary for monitoring progress towards eliminating the transmission of indigenous measles and rubella and verifying that the Region's elimination objectives have been reached.

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