World Health Organization

European Region

Eliminating measles and rubella in the WHO European Region

Integrated guidance for surveillance, outbreak response and verification of elimination

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Abstract

Member States of the WHO European Region share the goal of eliminating endemic transmission of measles and rubella viruses, which will also result in the elimination of congenital rubella syndrome. Significant progress has been made in the Region in recent years towards achieving and documenting interruption of endemic transmission of measles and rubella viruses. However, as evidenced by the occurrence of outbreaks, primarily of measles, the achievement of these goals at the Regional level has been delayed. It is essential that all Member States maximize efforts to achieve and maintain high vaccination coverage. In addition, the implementation of the WHO recommendations for elimination-standard surveillance for the rapid detection of outbreaks must be given the highest priority. Adherence to these surveillance standards for enhanced outbreak detection will provide the opportunity to deploy a timely and effective response to cases and outbreaks.

This document provides guidance on conducting elimination-standard surveillance and how to implement a rapid and appropriate response to outbreaks of measles and rubella. The reader will gain an understanding of the necessary epidemiological and laboratory evidence that is critical for documenting the interruption of transmission and eventual elimination of these viruses through the established regional verification process.

Keywords

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Abbreviations

ASU	Annual Status Update (report)
CRI	congenital rubella infection
CRS	congenital rubella syndrome
DBS	dried blood spots
DSId	distinct sequence identifier
EIA	enzyme immunoassay
EIA2030	European Immunization Agenda 2030
eJRF	electronic Joint Reporting Form
ETAGE	European Technical Advisory Group of Experts on Immunization
GMRLN	Global Measles and Rubella Laboratory Network
IgG	immunoglobulin G
IgM	immunoglobulin M
IHR	International Health Regulations
MCV	measles-containing vaccine
MeaNS	WHO Measles Nucleotide Surveillance online database
MMR	combined measles, mumps and rubella vaccine
MMRV	combined measles, mumps, rubella and varicella vaccine
MR	combined measles and rubella vaccine
NP	nasopharyngeal
NVC	national verification committee for measles and rubella elimination
OF	oral fluid
ORI	outbreak response immunization
PBS	phosphate buffered saline
RDT	rapid diagnostic test
RT-PCR	reverse transcription-polymerase chain reaction
RubeNS	WHO Rubella Nucleotide Surveillance online database
RVC	European Regional Verification Commission for Measles and Rubella Elimination
SIA	supplementary immunization activity
VTM	viral transport media

Introduction

The WHO European Region is committed to achieving the goals of eliminating the endemic transmission of measles and rubella viruses. The successful elimination of rubella will in turn eliminate new cases of congenital rubella syndrome (CRS). In 2010, all 53 Member States of the Region reaffirmed their commitment to achieving these goals *(1)*, which were also included as a priority in the European Vaccine Action Plan 2015–2020 *(2,3)* and are an important component of the European Immunization Agenda 2030 (EIA2030) *(4)*.

This document integrates three previous WHO Regional Office for Europe documents *(5–7)*, includes updates from current WHO global guidance and considers developments in the elimination process of measles and rubella in the Region.

High population coverage with measles- and rubella-containing vaccines in Member States has resulted in substantial progress toward achieving these goals. In 2012, the European Regional Verification Commission for Measles and Rubella Elimination (RVC) was established to assess the elimination status of measles and rubella in each Member State. Since then, more and more countries have provided documentation demonstrating interruption of transmission and ultimately, elimination *(8,9)*. However, outbreaks of measles continue to occur throughout the Region particularly in countries with persisting immunity gaps in the population and where outbreak control responses are inadequate (Box 1).

Furthermore, the quality of the surveillance of these diseases may be insufficient for early case detection and effective outbreak response. Preparedness and timely response to outbreaks are core components of the regional measles and rubella elimination strategy and are embedded in the EIA2030 *(4)*.

Box 1.
Factors contributing to measles outbreaks

• Accumulation of susceptible individuals, including older children and young adults who were not targeted by immunization schedules or who missed routine vaccination in their childhood, and did not get the natural diseases due to reduced opportunities for exposure with the decline of measles and rubella incidence after vaccination introduction.

• Existence of pockets of low vaccination coverage in some population groups due to lack of access to health services or resistance to vaccination based on religious or philosophical beliefs.

• Declining public acceptance of immunization, due to the lack of concern about disease severity and unfounded perceptions of the risks and benefits of vaccination.

• Lack of strong provider recommendations to vaccinate during the patient encounter, leading to missed opportunities and contributing to suboptimal vaccination coverage in some countries of the Region.

• Ongoing reforms in the health systems of countries in transition, affecting funding, organization and availability of immunization services and surveillance activities.

Aim of this document

Section 1 - Surveillance guidelines of this document provides guidance on how to conduct elimination-standard surveillance for measles, rubella and CRS. **Section 2 - Outbreak investigation and response guidelines** provides guidance for early detection of measles and rubella outbreaks and describes how to conduct a rapid and appropriate response. Verifying the interruption of endemic transmission of measles and rubella viruses and the eventual elimination of the diseases is a process that relies upon appropriate documentation of both the epidemiology of cases and the quality of the surveillance of these diseases in every Member State. **Section 3 - Framework for the verification of measles and rubella elimination** explains this process and provides specific advice on the documentation required for verification by Member States. This document is targeted for use by public health authorities, technical experts at the national level and members of national verification committees in the Member States of the Region.

Diseases' characteristics, aetiology, transmission and vaccines

Both measles and rubella are highly contagious acute viral diseases characterized by maculopapular rash. Both viruses are transmitted via the respiratory route (aerosolized in respiratory droplets) or by direct or indirect contact with nasal and throat secretions of infected persons. Measles virus is particularly contagious, with > 90% secondary attack rates among susceptible individuals. Infected persons shed the viruses and are contagious shortly before the onset of clinical symptoms and for several days afterwards. Rubella virus infections are asymptomatic or subclinical in 20–50% of instances, but infected persons can still transmit the virus to susceptible individuals. Characteristics of infection with measles and rubella viruses are shown in Table 1.

In the pre-vaccination era in temperate climates, the incidence of these diseases was usually higher in late winter and spring, and epidemics occurred periodically every few years, followed by inter-epidemic intervals with lower incidence. As vaccination became more widespread, disease incidence declined and the inter-epidemic periods became longer with eventual almost disappearance of the cyclical pattern. Also, with higher vaccination levels, infections tended to occur later in life than was typical in the pre-vaccination era. The average age of cases increased due to reduced opportunities for exposure as the incidence of disease decreased. In elimination settings, where most infections result from importations, cases can occur at any time during the year. The size and duration of outbreaks are related to the number and distribution of susceptible individuals and the efficiency of responses to control the outbreaks.

Measles or rubella transmission that results in an outbreak can occur in communities and congregate settings such as households, workplaces, day-care centres, schools, universities and military installations. The setting, extent of spread and size of the outbreak will determine the magnitude of the response. Because measles infection is uniformly a symptomatic one, including a characteristic maculopapular rash, outbreaks of measles are more easily recognized than outbreaks of rubella, as rubella cases have a milder course of illness overall and are often asymptomatic.

Measles

Measles is one of the most contagious diseases for humans, manifesting as a febrile rash illness. It is caused by the measles virus, a member of the genus *Morbillivirus*. The incubation period for measles is generally 10–14 days (range 7–23 days) from exposure to symptom onset *(10)*. The initial symptoms (prodrome) typically consist of fever, malaise, cough, conjunctivitis and coryza. These symptoms may be present 1–5 days prior to rash (see Fig. 1 for a timeline of infectivity and additional clinical details). The characteristic maculopapular rash appears 2–4 days after onset of the prodrome. Infected individuals are usually contagious from about four days before rash onset until four days after its appearance. The source of infection

is frequently unknown because the individual is often infected by someone in the pre-rash prodrome stage.

Measles complications such as pneumonia, diarrhoea and encephalitis can occur in up to 30% of persons depending on age and predisposing factors such as malnutrition or the existence of medical conditions that adversely affect the immune response. The complications resulting from measles infection usually occur 2–3 weeks after rash onset. Measles can infect anyone of any age, but the burden of disease globally remains highest among children under 5 years of age.

Rubella

Rubella is an acute disease caused by the rubella virus, a member of the genus *Rubivirus*. Its public health importance is due mainly to the teratogenic potential of the virus, causing harm to an embryo or foetus including CRS, and may result in foetal loss or stillbirths *(11)*. The incubation period of rubella is 14 days, with a range of 12–23 days (see Fig. 2). Apart from the congenital infection, rubella is generally a mild self-limiting illness that usually occurs during childhood; however, it is more severe in infants and adults. During the second week after exposure, there may be a prodromal illness consisting of fever, malaise and mild conjunctivitis. Prodromal symptoms are more common in adults than in children. Postauricular, occipital and posterior cervical lymphadenopathy is characteristic, and typically precedes the rash by 5–10 days. The maculopapular, erythematous and often pruritic rash occurs in 50–80% of rubella-infected persons. The rash, usually lasting 1–3 days, starts on the face and neck before progressing down the body. Joint symptoms (arthritis, arthralgia), usually of short duration, may occur in up to 70% of adult women with rubella but are less common in men and children. Post-infectious encephalitis occurs in approximately 1/6000 rubella cases, but occasionally incidences based on different studies have been reported as high as 1/500 and 1/1600 *(12)*.

Table 1.
Selected features of measles and rubella infection

FEATURES	MEASLES	RUBELLA
Aetiological agent	Measles virus	Rubella virus
Genus, family	*Morbillivirus, Paramyxoviridae*	*Rubivirus, Matonaviridae*
Incubation period range (most common onset of symptoms post exposure)	7–23 days (10–14 days)	12–23 days (14 days)
Infectious period		
Before the rash onset	4 days	7 days
After the rash onset	4 days	7 days
With congenital infection	Not applicable	Up to 1 year
Rash duration	4–8 days	1–3 days
Collection of specimen for IgM detection relative to rash onset (day 0)[a]		
Optimal: best IgM sensitivity	Optimal range: day 4–28	Optimal range: day 4–28
Adequate: for surveillance	Adequate range: day 0–28	Adequate range: day 0–28
Maximal virus present relative to rash onset (day 0)[b]	Day of onset of rash to day 5	Day 7 before rash onset to day 5 after rash onset

Notes:

IgM = immunoglobulin M

a. For serum specimen tested by enzyme immunoassay (EIA).
b. For best sensitivity of virus detection by reverse transcription-polymerase chain reaction (RT-PCR). Adequate collection timeframe of specimens for virus detection depends on type of specimen (Table 2).

Fig. 1. Timeline of infectivity, clinical disease and laboratory findings for measles virus infection

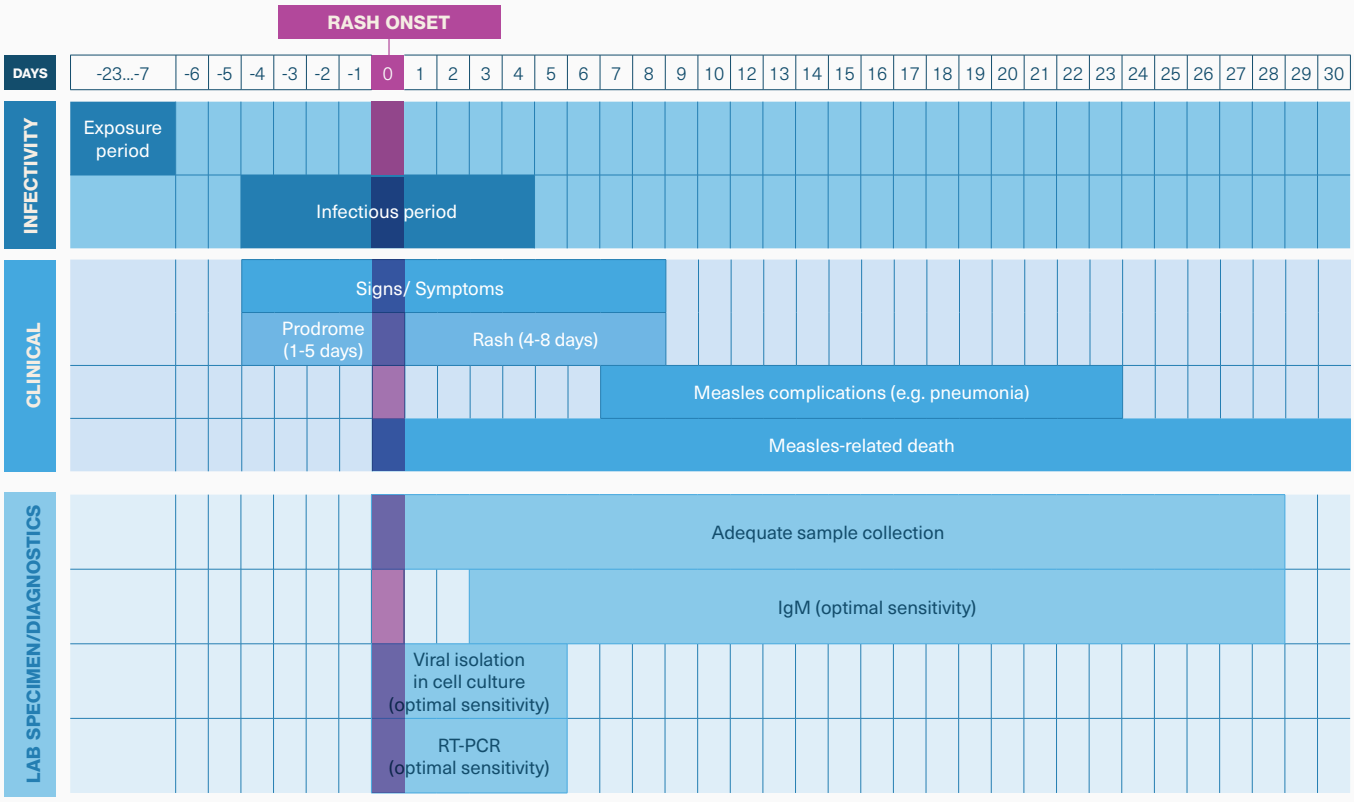
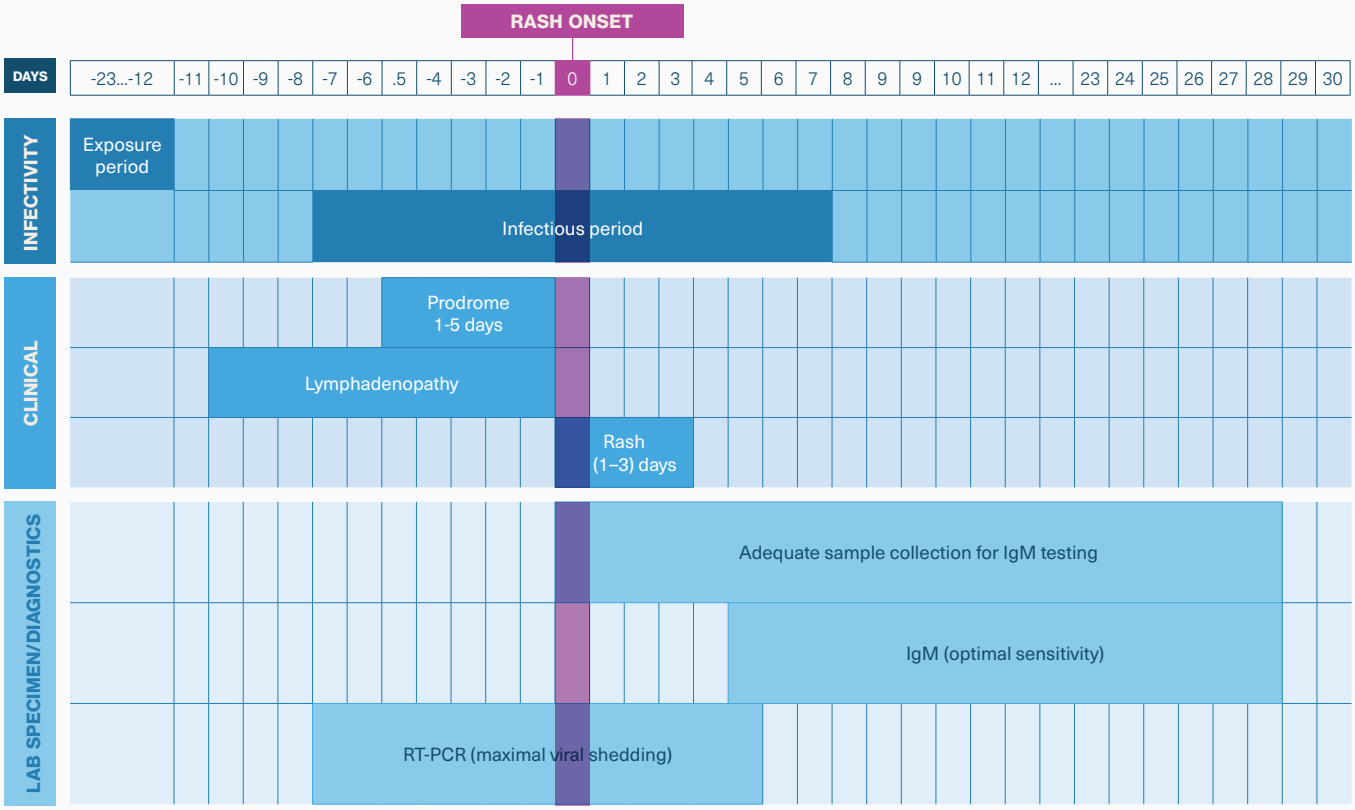


Fig. 2. Timeline of infectivity, clinical disease and laboratory findings for rubella virus infection



Horizontal bars represent range of possible days, with day 0 as the day of rash onset. For laboratory specimens/diagnostics, bars represent the range of days in which that particular test would be positive.

Congenital rubella syndrome

Rubella infection in pregnant women, occurring just before conception and through the first 8–10 weeks of gestation, may result in miscarriage or stillbirth, or in multiple fetal abnormalities (known as congenital rubella syndrome) in up to 90% of cases. CRS risk is unrelated to severity of symptoms in the mother.

The CRS defects can affect any organ system, including ophthalmic, auditory, cardiac, neurological, hepatic and haematological. The most common defects of CRS are hearing impairment and deafness, eye defects (cataracts, congenital glaucoma or pigmentary retinopathy) and cardiac defects. Infants with CRS can shed high amounts of rubella virus from body secretions for up to one year, thus potentially causing outbreaks. Infants that survive the neonatal period may face serious developmental disabilities (such as deafness) and have an increased risk for developmental delay (such as autism) and autoimmune diseases (diabetes type 1, thyroiditis). In some cases of rubella infection during pregnancy, particularly after 20 weeks of gestation, the fetus can be infected but not develop the signs and symptoms of CRS. These infants are classified as having congenital rubella infection (CRI) and are capable of shedding rubella virus.

Measles and rubella vaccines

The attenuated live measles- and rubella-containing vaccines are highly effective, yielding seroconversion rates of 95% or more in persons over 12 months old. Almost all children who fail to respond to the first dose will respond to the second, thus ensuring seroconversion rates of 95% after two doses. As a result of the high transmissibility of the measles virus, the herd immunity threshold is very high, and coverage of ≥ 95% is necessary to interrupt measles virus transmission. The herd immunity threshold for rubella is 86%. Therefore, high coverage with a measles and rubella combination vaccine can provide an effective tool for interrupting transmission of both viruses.

Before the widespread use of measles vaccination, almost everyone was infected in early childhood and acquired life-long immunity. Before 1980, measles killed an estimated 2.6 million children globally each year *(13)*. The widespread adoption of the measles vaccine in national immunization programmes since the establishment of the Expanded Programme on Immunization in 1974 has resulted in a marked decrease in the number of reported cases. With increasing immunization coverage, the global number of measles deaths was estimated to have been reduced to 128 000 in 2021, an 83% decrease compared to 761 000 estimated measles deaths in 2000 *(14)*.

The vaccines have been highly effective at reducing the burden of disease and have led to the elimination of measles and rubella from several countries in the European, Western Pacific and American regions of WHO. However, insufficient overall population immunization coverage can result in a shift of the median age for measles and rubella cases to young adults, which in the case of rubella may result in more CRS cases.

Currently, all Member States of the WHO European Region use measles- and-rubella-containing vaccines in their national immunization programmes. Measles and rubella vaccines in use in the Region are most often combined in different presentations with mumps and sometimes with varicella vaccines.

Rationale for measles and rubella elimination

The elimination and eventual global eradication of measles and rubella are highly desirable goals because the diseases are ubiquitous, affect large numbers of susceptible individuals and can cause serious complications and death. Available evidence indicates that both measles and rubella meet the criteria for diseases that can be eradicated (*15)*.

- There is no animal or environmental reservoir and humans are critical to maintaining transmission.
- Accurate diagnostic tests are available.
- Vaccines and existing vaccination strategies for both diseases are effective and safe *(10,12,16)*.
- Transmission has been interrupted in a large geographic area (e.g. nationwide) for a prolonged period *(17)*.

In 2010, the WHO Strategic Advisory Group of Experts (SAGE) conducted a comprehensive review of the evidence to establish the biological and technical feasibility of measles eradication and concluded that measles can and should be eradicated. It was also noted that use of the combined measles–rubella vaccine and an integrated surveillance system for fever and rash provide an opportunity to accelerate the control of rubella and the prevention of CRS *(18)*. Global measles and rubella eradication are considered biologically feasible and cost-effective *(19)*. Furthermore, strategies and activities for measles and rubella elimination offer multiple opportunities to help achieve broad health systems strengthening goals; and measles cases and outbreaks can serve as a sensitive “tracer”, highlighting immunity gaps and signalling potential inequities in the effectiveness of health-care delivery strategies and systems *(4)*.

Elimination strategies

The elimination of measles and rubella is defined as the interruption of endemic measles and rubella transmission in a defined geographic area such as a country or WHO region for a period of at least 12 months, in the presence of a well-performing surveillance system. Elimination at national or Regional level can be declared after at least 36 months of the absence of endemic measles or rubella in a country or in all countries of the European Region, respectively. WHO identified five core strategies for eliminating measles and rubella (Box 2) in line with those identified in the Global measles and rubella strategic plan 2012–2020 (*20)*.

Successful implementation of these strategies hinge on strategic priorities laid out in the Measles and rubella strategic framework 2021–2030 *(21)*. These priorities include improving ownership of and accountability for measles and rubella goals, addressing immunity gaps, reaching underserved populations by targeted approaches, improving the collection and use of monitoring and surveillance data and ensuring outbreak preparedness for timely detection and effective response.

Box 2.
Core strategies for achieving measles and rubella elimination in the WHO European Region

• Achieve and sustain high vaccination coverage (≥ 95%), with two doses of measles- and rubella-containing vaccine administered through high-quality routine immunization services.

• Provide measles and rubella immunization opportunities covering high-risk groups, including supplementary immunization activities, for all populations susceptible to measles and rubella.

• Strengthen surveillance systems through rigorous case investigation and laboratory confirmation of suspected sporadic cases and outbreaks.

• Build up methodologies and capacities to timely and adequately respond to outbreaks.

• Improve the availability and use of high-quality, evidence-based information for health professionals and the public on the benefits and risks associated with immunization against measles and rubella to build confidence and demand for immunization.

1

Surveillance Guidelines

1.1 Rationale and objectives of surveillance

Surveillance is one of the key strategies to achieving elimination of measles and rubella (Box 2) *(22)*. The key objective of surveillance is to identify areas of measles or rubella virus transmission which may reveal potential immunity gaps in the population. This will guide effective public health responses to achieve elimination of endemic measles and rubella and sustain elimination in post-elimination settings. All countries in the WHO European Region should strive to implement and maintain elimination-standard surveillance. This section provides the standards for surveillance in countries moving towards or maintaining elimination.

Surveillance for CRS is an important adjunct to rubella surveillance. Rubella surveillance cannot capture every case of rubella since it is frequently mild or asymptomatic. CRS is the most severe outcome of rubella, and the prevention of CRS is the primary reason for rubella vaccination. Thus, CRS surveillance is integrally linked with acquired or postnatal rubella surveillance and vaccination coverage monitoring (Box 3). Incorporation of all these activities allows more sensitive monitoring of rubella and generates the quality of surveillance required to document progress towards achieving and maintaining its elimination.

> All countries in the Region should strive to implement and maintain elimination-standard surveillance for measles and rubella.

1.1.1 Measles

The objectives of measles elimination-standard surveillance are:

- detect and confirm cases to document the burden of measles;
- monitor the impact of the vaccination programme, evaluate the adequacy of the programme and modify as needed, ensure proper case management and implement appropriate public health strategies to control further transmission;
- investigate cases to determine the source of infection and conduct contact tracing with the aim of identifying all potential cases and the origin of the virus (i.e. to classify the case as imported, importation-related or endemic);
- identify populations and areas with low coverage and at higher risk of outbreaks that require enhanced vaccination efforts, and determine the reason for each measles case:
    - vaccine was recommended but person did not get it;
    - person was vaccinated according to the recommended schedule but did not develop immunity (vaccine failure);
    - vaccine was not received because it is not normally recommended for this person (e.g. younger than the routine age for vaccine);
- provide documentation supporting the absence of endemic transmission for national and regional verification of the elimination of endemic virus.

1.1.2 Rubella

The objectives of rubella elimination-standard surveillance are aligned with those for measles and have the following additional objectives:

- detect and confirm rubella cases in pregnant women, facilitate proper referrals and document the pregnancy outcome;
- (when feasible) establish appropriate linkage with CRS surveillance including laboratory data.

1.1.3 Congenital rubella syndrome

The main aim of CRS surveillance is to provide data in support of rubella elimination in the Region. The specific objectives of CRS surveillance are:

- detect and isolate affected infants rapidly and ensure proper infection control measures are implemented to prevent further spread of infection;
- provide timely notifications to health-care providers, facilitating the early provision of appropriate medical care;
- document absence of CRS caused by endemic rubella transmission to support verification of rubella elimination.

1.2 Types of surveillance recommended

Box 3.
How CRS surveillance relates to rubella surveillance

CRS surveillance systems are separate from clinical rubella surveillance, and so are addressed in a different section in this document. The surveillance systems for the two manifestations of rubella infection (acquired and congenital) differ substantially in terms of case definitions, age groups of interest and sites for case detection. The two surveillance systems are linked when a pregnant woman is identified who has acquired rubella infection and the pregnancy outcome is followed, including an assessment to determine whether the newborn has CRS. Despite having distinct methodology and approaches, the results of the two surveillance systems often need to be interpreted together, as both are manifestations of the same viral infection and are linked in terms of public health significance and implications for vaccination.

1.2.1 Elimination-standard surveillance for measles and rubella

In elimination-standard surveillance, WHO recommends an integrated approach for surveillance of measles and rubella, functioning in unison to detect, confirm or discard suspected cases (see Box 4). Measles and rubella surveillance must be case-based and achieve all the critical elements of disease surveillance in a timely manner: detection, notification and investigation of suspected measles or rubella cases and outbreaks, and correct classification of cases as confirmed or discarded. The information collected from cases should include vaccination status if possible and indicate whether the case was due to a failure of programme implementation (e.g. should have been vaccinated but was not), due to vaccine failure, or the case occurred in someone for whom vaccination is not recommended. The complete epidemiological data related to the cases and outbreaks are vital to inform actions that reduce morbidity and mortality and prevent further virus transmission *(22)*. Active surveillance in health facilities, such as regular review of clinic logbooks for missed cases, is essential to ensure that no cases are overlooked.

Surveillance should be nationwide with inclusion of all health facilities (all levels, both private and public), with a system for zero reporting (reporting that there were no cases). If desired and resources exist implementing community-based surveillance should be considered (such as notification of cases by community health workers or teachers) in areas that are at risk for measles, during outbreaks and in populations where not all individuals with measles seek care in health facilities. Countries may initially identify a rubella case through testing of serum that was negative for measles and vice versa.

Box 4.
Integration of measles and rubella surveillance

Measles and rubella surveillance should be integrated whenever possible. Both diseases have a similar clinical presentation with a rash illness, and both have regional targets of elimination. As such, both should have similar approaches to surveillance. Laboratory tests for suspected cases of measles or rubella should be performed for both diseases either in parallel or in series, depending on local epidemiology and public health priorities. Many details of measles surveillance would also pertain to rubella surveillance, and vice versa.

1.2.2 Surveillance for CRS

All countries should have a CRS surveillance system that can capture most infants with suspected CRS within the country. The target age group for CRS surveillance is infants < 12 months of age. The recommended minimal surveillance for CRS is sentinel-site and case-based with laboratory confirmation. Since CRS encompasses a constellation of congenital abnormalities that may have other causes, CRS surveillance requires a high level of specificity, and thus laboratory confirmation is critical.

Surveillance systems based on aggregate reporting without laboratory confirmation are inadequate for CRS surveillance. Pregnancy registries can complement CRS surveillance systems but are insufficient for identifying most CRS cases, as acquired rubella infection in a pregnant woman, as in the general population, generally causes a mild illness or the infection is asymptomatic.

Enhanced surveillance for CRS

Countries may also implement or enhance CRS surveillance associated with a case of rubella or an outbreak. The recommendation for enhanced surveillance for cases of CRS is to implement a case-based surveillance system (passive, active or both) that includes all levels of facilities within the country complemented by laboratory confirmation.

Case detection strategies for CRS

A number of useful strategies can be employed in the detection of CRS cases:

- Facility-based surveillance is preferred because infants with the birth defects associated with CRS present to secondary, tertiary or specialty hospitals/sites, and the case definition requires clinical evaluation.
- If conducting sentinel-site CRS surveillance, a programme should be established at selected sentinel hospitals and other sites that capture most infants with suspected CRS. Tertiary care and specialty hospitals, which are most likely to receive infants with cataracts, heart defects and hearing impairment, should be prioritized as sentinel sites for establishing CRS surveillance. Later, surveillance can be expanded to include additional sites that have contact with more of the population.
- In most settings, a combination of passive and active approaches should be employed to increase the likelihood that all CRS cases will be captured by surveillance within the included health facilities. Specialists in ophthalmology, cardiology, ear/nose/throat and paediatrics should be familiarized with the process for reporting and investigating CRS cases.
- During active surveillance visits to a site, a review of medical records (including admission and discharge records) should be conducted in units where infants who have manifestations consistent with CRS are likely to be seen (e.g. neonatal wards, paediatric surgical wards, and eye, cardiac and ear clinics).
- As part of a comprehensive CRS surveillance system, testing and follow-up should be conducted with pregnant women who were detected through fever–rash surveillance, either as suspected measles/rubella cases or identified as potentially exposed to a confirmed rubella case. Rubella identified in pregnancy registries can be used as part of the CRS surveillance

system at the local level. These registries usually contain maternal demographic information, test results, contact information and pregnancy outcomes (delivery status of baby and birth defects). Infants identified as having suspected or confirmed CRS should be included in the CRS surveillance system.

- Clinicians should notify public health authorities of suspected CRS cases immediately.

Further details and more information on other types of CRS surveillance can be found in the publication Introducing rubella vaccine into national immunization programmes: a step-by-step guide *(23)*.

Linkages of CRS surveillance to other surveillance systems

CRS surveillance with laboratory confirmation can be incorporated into existing birth defect surveillance as part of an enhanced birth defect surveillance system, or into other surveillance systems capturing congenital cataracts. An enhanced birth defect surveillance might include expansion of existing surveillance to include ages up to 12 months and key CRS signs (such as congenital cardiac defects) *(24)*. Pregnant women with rubella identified as part of integrated measles–rubella surveillance should be followed up and birth outcomes monitored to identify potential CRS cases.

1.3 Definitions and classifications

1.3.1 Case definitions and final classifications

Case definitions are designed to standardize case identification and reporting across health facilities and various levels of the health system – subnational, national and international – and are specifically intended for surveillance and outbreak investigation purposes. This facilitates identification of outbreaks, aggregation, analysis and interpretation of data, as well as comparison between geographic areas and over time. Case definitions and final classifications of measles and rubella cases for the European Region are listed below. Suspected cases that exhibit clinical features of measles or rubella and are not laboratory-confirmed or are not considered as epidemiologically linked cases should only be classified as clinically compatible cases after an independent review as part of the epidemiological investigation to ensure that the case definition is met.

1.3.2 Measles

Suspected case definition for case finding

A suspected case is one in which a patient presents with fever and maculopapular (non-vesicular) rash, or in whom a health-care worker suspects measles.

We acknowledge that many countries in the European Region use the following clinical description as a suspected measles case: fever, maculopapular (non-vesicular) rash and one or more of the typical measles symptoms present (cough, coryza or conjunctivitis). This more specific definition is acceptable if surveillance systems have sufficient sensitivity to detect every suspected case of measles.

Final case classification

• **Laboratory-confirmed measles:** a suspected case of measles that has been confirmed positive by testing in a proficient laboratory, and for which the possibility of vaccine-associated reaction has been ruled out. (For more information on proficient laboratory and vaccine-associated reaction see 1.3.5 Additional definitions.)

• **Epidemiologically linked measles:** a suspected case of measles that has not been confirmed by a laboratory but was geographically and temporally related with a laboratory-confirmed case or another epidemiologically linked measles case with dates of rash onset occurring 7–23 days apart.

• **Clinically compatible measles:** a suspected case with fever and maculopapular (non-vesicular) rash and one or more of the typical measles symptoms present (cough, coryza or conjunctivitis). There was no adequate clinical specimen taken, and the suspected case was not epidemiologically linked to a laboratory-confirmed case of measles or to a case of another communicable disease. As countries get closer to achieving the interruption of endemic transmission, the majority of measles cases should be confirmed by laboratory testing or by epidemiological linkage.

• **Non-measles discarded case:** a suspected case that has been investigated and discarded as a non-measles (and non-rubella[1]) case must meet one or more of the following criteria:

- Negative results are obtained by laboratory testing in a proficient laboratory on an adequate specimen collected during the proper time period after rash onset (For more information on adequate specimen see 1.5 Specimen collection, processing and transport).
- Epidemiological link is identified to a laboratory-confirmed case or outbreak of another communicable disease that is not measles.
- There is confirmation of another aetiology, regardless of whether it meets the definition of epidemiological linkage.
- The case fails to meet the clinically compatible measles case definition.

See Box 5 for measles case classification in countries post-elimination or close to elimination.

[1] If the case is also negative for rubella, this is a non-measles non-rubella discarded case.

Box 5.
Measles case classification in countries post-elimination or close to elimination

In countries that have eliminated measles or are close to elimination, both positive and negative IgM results should be closely reviewed for each measles case before assigning a final classification. As measles prevalence decreases, the positive predictive value of IgM testing decreases, which means that false-positive IgM results are to be expected. Additional sources of data such as the clinical presentation, epidemiological context (including travel and case history), the timing and quality of specimen collection and further testing are required to confirm or discard a case. The IgM result obtained from a true measles case may be negative if the blood specimen is collected too early or too late in the course of illness (< 4 days and > 28 days). This is especially important in outbreak settings where it is necessary to determine if there is sustained transmission. In outbreak settings, discarded cases should be reviewed within 46 days (i.e. two incubation periods) from the last confirmed measles case to ensure that they are truly negative and transmission has ended.

1.3.3 Rubella

Suspected case definition for case finding

A suspected rubella case is one in which a patient presents with fever and maculopapular (non-vesicular) rash, or in which a health-care worker suspects rubella.

We acknowledge that many countries in the European Region use the following clinical description as a suspected rubella case: fever, maculopapular (non-vesicular) rash and one or more of the typical rubella symptoms present (arthralgia, arthritis or adenopathy). This more specific definition is acceptable if surveillance systems have sufficient sensitivity to detect every suspected case of rubella.

Final case classification

- **Laboratory-confirmed rubella:** a suspected case of rubella that has been confirmed positive by testing in a proficient laboratory. (For more information on proficient laboratory see 1.3.5 Additional definitions.)
- **Epidemiologically linked rubella:** a suspected case of rubella that has not been confirmed by a laboratory but was geographically and temporally related to a laboratory-confirmed case or another epidemiologically linked rubella case with the dates of rash onset occurring 12–23 days apart.

- **Clinically compatible rubella:** a suspected case with maculopapular (non-vesicular) rash and fever (if measured) and symptoms of arthritis/arthralgia or lymphadenopathy or both. There was no adequate clinical specimen taken and the suspected case was not linked epidemiologically to a laboratory-confirmed case of rubella or other communicable disease. In a low-incidence setting, the majority of rubella cases should be confirmed by laboratory or epidemiological linkage.
- **Non-rubella discarded case:** a suspected case that has been investigated and discarded as a non-rubella (and non-measles[2]) case must meet one or more of the following criteria:
    - Negative results are obtained in a proficient laboratory on an adequate specimen collected during the proper time period after rash onset (see Fig. 3). (For more information on adequate specimen see 1.5 Specimen collection, processing and transport.)
    - An epidemiological linkage is identified to a laboratory-confirmed case or outbreak of another communicable disease that is not rubella.
    - There is confirmation of another aetiology, regardless of whether it meets the definition of epidemiological linkage.
    - The case fails to meet the clinically compatible rubella case definition.

See Fig. 3 for a summary of the classification process for measles and rubella cases.

1.3.4 Congenital rubella syndrome

Suspected case definition for surveillance purposes

- Any infant < 12 months of age that presents with any of the following:
    - congenital heart disease;
    - evidence of hearing impairment as indicated by routine screening;
    - one or more of the following eye signs: cataract (white pupil), congenital glaucoma (larger eyeball) or pigmentary retinopathy;
- Any infant < 12 months of age in whom a health worker suspects CRS, even without apparent signs of CRS, including maternal history of suspected or confirmed rubella during pregnancy.

Final case classification

Final classification of CRS cases depends, in part, on identifying group A or group B clinical signs of CRS (see Fig. 4a and 4b).

Group A: cataract(s), congenital glaucoma, pigmentary retinopathy, congenital heart disease (most commonly peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects), hearing impairment.

Group B: purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, jaundice that begins within the first 24 hours after birth.

[2] If the case is also negative for measles, this is a non-measles non-rubella discarded case.

Using these clinical signs, one of the final classifications listed below may be made.

- **Laboratory-confirmed CRS:** a suspected CRS case with at least one sign from group A and meets the laboratory criteria for confirmation of CRS (see 1.6 Laboratory testing).
- **Clinically compatible CRS:** a suspected CRS case without an adequate specimen in which a qualified clinician detects at least two of the complications from group A or one from group A and one from group B.
- **CRI:** an infant who has none of the clinical signs of CRS from group A, but who meets the laboratory criteria for CRS.
- **Discarded:** a suspected CRS case with an adequate specimen not meeting the laboratory-confirmed case definition, or a suspected case without an adequate laboratory specimen and not meeting the clinically compatible case definition.

Fig. 3.
Classification of suspected measles and rubella cases

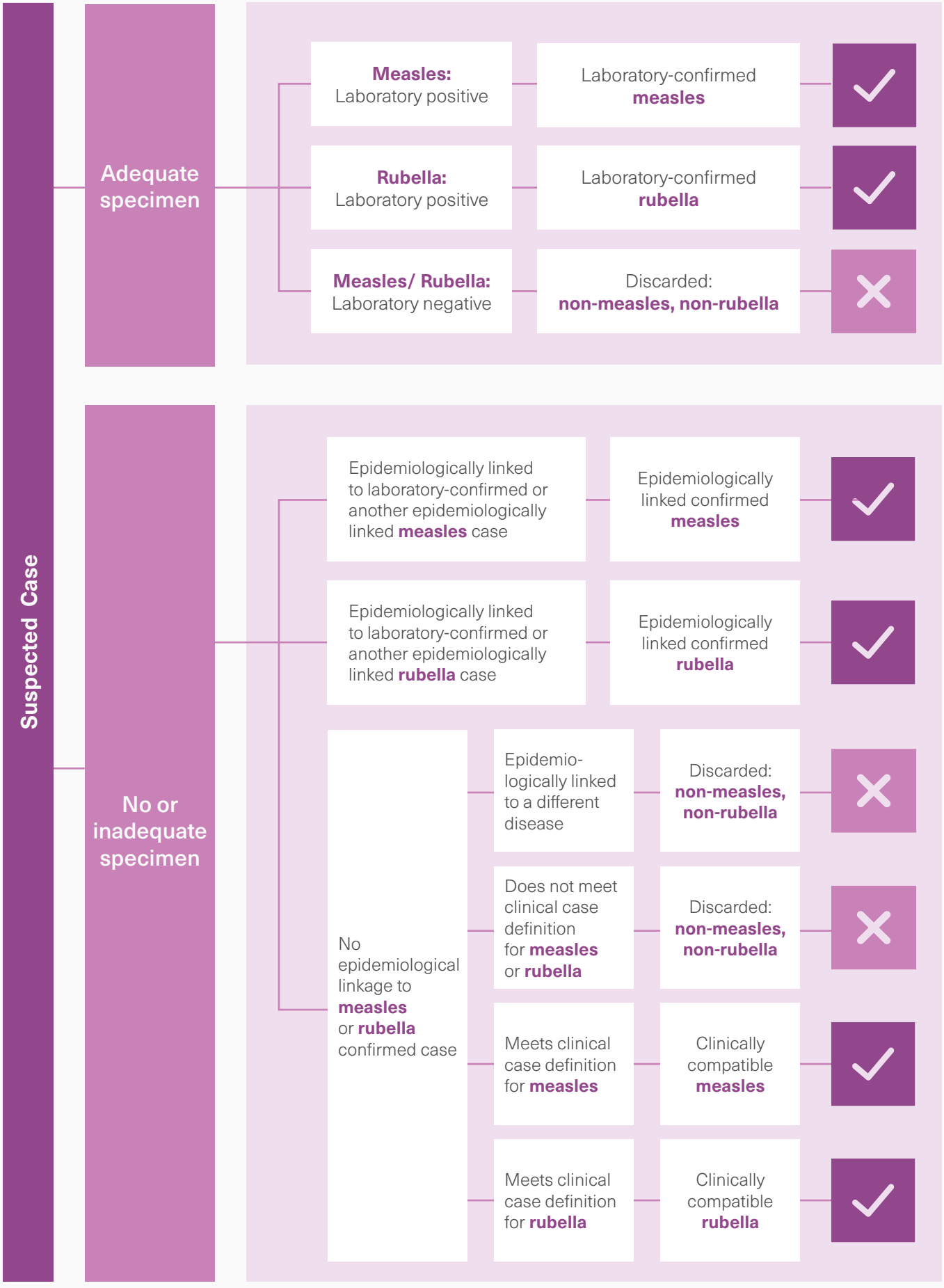
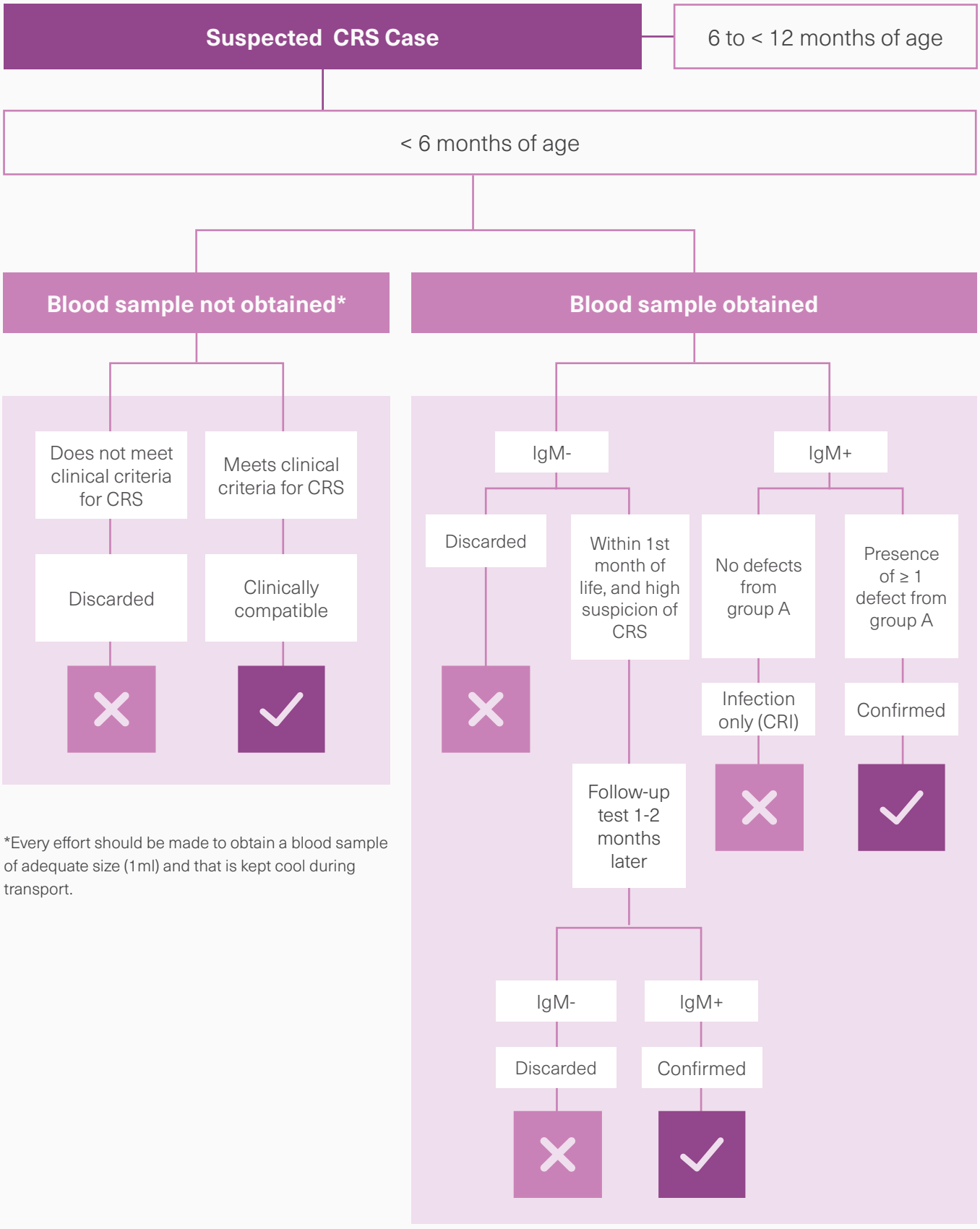
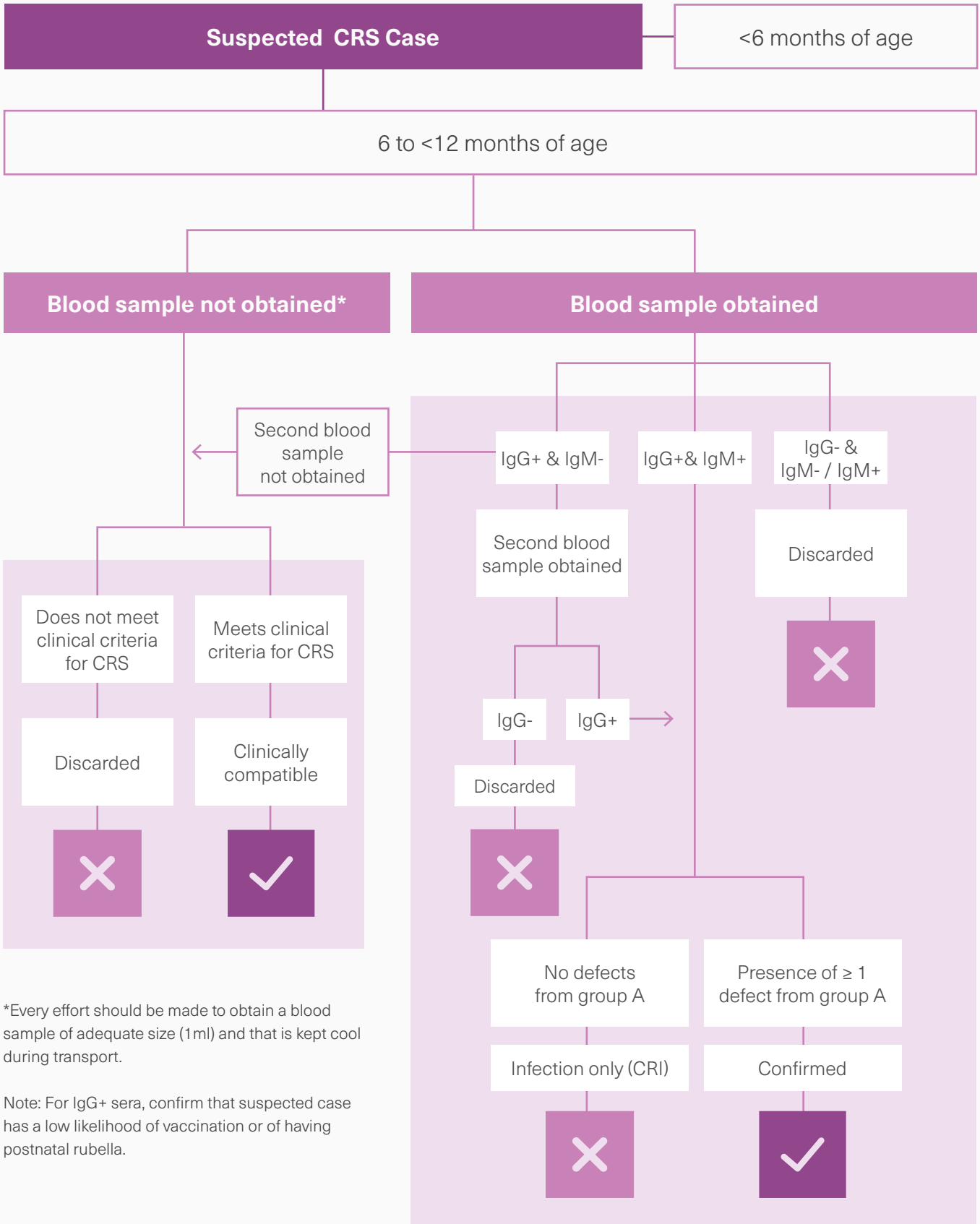


Fig. 4a.
Surveillance classification of suspected CRS case-patients < 6 months of age



*Every effort should be made to obtain a blood sample of adequate size (1ml) and that is kept cool during transport.

Fig. 4b.
Surveillance classification of suspected CRS case-patients ≥ 6 months to < 12 months of age



*Every effort should be made to obtain a blood sample of adequate size (1ml) and that is kept cool during transport.

Note: For IgG+ sera, confirm that suspected case has a low likelihood of vaccination or of having postnatal rubella.

1.3.5 Additional definitions

Endemic measles or rubella case: a laboratory-confirmed or epidemiologically linked case of measles or rubella resulting from endemic transmission of measles or rubella virus.

Endemic CRS case: a confirmed case whose mother had rubella or was exposed to an endemic rubella case during gestation, as supported by epidemiological or genotyping evidence. A chain of rubella virus transmission that is continuous for ≥ 12 months within a country is considered endemic transmission.

Endemic transmission: is defined as a chain of measles or rubella virus transmission that is continuous for ≥ 12 months within a country. To the greatest extent possible, this chain of transmission should be defined based on genotyping evidence along with epidemiological investigation. It is often the situation that discerning a single, continuous chain of transmission from multiple, separate chains of transmission is challenging for measles, given the high rate of infectivity, and mass movements of people. Similarly, cases of rubella that are critical in linking cases in a single chain of transmission are frequently missed due to the mild presentation of many cases.

Re-establishment of endemic transmission: re-establishment of endemic measles or rubella transmission is a situation in which epidemiological and laboratory evidence indicate the presence of a chain of transmission of a virus variant that continues uninterrupted for a period of 12 months or more in a defined geographical area where disease was previously eliminated.

Disease elimination: the interruption of endemic measles or rubella transmission in a defined geographical area such as a country or WHO Region for a period of at least 12 months, in the presence of a well-performing surveillance system.

Verification of elimination: elimination at national or Regional level can be declared after at least 36 months of absence of endemic measles or rubella in a country or in all countries of the European Region, respectively.

Disease eradication: worldwide interruption of measles or rubella transmission in the presence of a verified, well-performing surveillance system.

Genotype: operational taxonomic unit defined on the basis of nucleotide variation between viral sequences. Measles virus genotypes are currently defined on the genetic analysis of the N-450 sequence, which is the most variable coding region of the measles virus genome *(25)*. Rubella virus genotypes are currently defined on genetic analysis of the E1-739 sequence *(26)*.

MeaNS Distinct sequence identifier (DSId): specific identification of each measles sequence variant in the WHO Measles Nucleoltide Surveillance online database (MeaNS).

Named strain (measles only): DSId named in MeaNS with a representative N-450 sequence due to its widespread transmission in multiple countries. This is used to describe clusters and it allows us to describe viral diversity with finer resolution within a single genotype *(25)*.

Proficient measles and rubella laboratory: a proficient laboratory meets the requirements for WHO accreditation and/or has an established quality assurance programme with oversight by a WHO-accredited laboratory, and/or meets requirements for a fully accredited laboratory by a national or international entity with an established quality assurance programme recognized by bodies such as the International Organization for Standardization or certified by the Clinical Laboratory Improvement Amendments *(27)*.

Imported measles or rubella case: a case occurring in an individual (returning citizen or foreign visitor) whose travel dates outside their country of residence are consistent with infection acquired while in another country (7–23 days prior to rash onset for measles; 12–23 days prior to rash onset for rubella) that is supported by epidemiological or virological evidence.

Because the time spent outside of the country may have been synchronous with only a portion of the incubation period (see above) for measles or rubella, it is important to investigate whether the exposure to another measles or rubella case may not have occurred during the days spent in another country or during travel. Cases are classified as imported cases by the geographic location where the case was exposed and infected. When possible, genotyping evidence should be added to the epidemiological investigation in order to accurately classify the case or chain of transmission.

Importation-related measles or rubella case: a locally acquired infection that occurs as part of a chain of transmission originating from an imported case as supported by epidemiological and/or virological evidence. In countries with strong genotyping data, it is possible that a case with no definitive epidemiological link to an imported case or importation-related case may be ultimately classified as importation-related based on compelling genetic evidence that links the case to a contemporaneous chain of transmission involving an imported measles or rubella case. If transmission of measles or rubella from cases related to importation persists for ≥ 12 months within a country, cases are no longer considered importation-related but are classified as endemic.

Imported CRS case: a confirmed case whose mother was exposed to rubella outside of the country during gestation, as supported by epidemiological or genotyping evidence.

Unknown source measles or rubella case: a confirmed case for which no epidemiological or virological link to importation or endemic transmission can be established after a thorough investigation.

Unknown source CRS case: a confirmed case not meeting the above endemic or imported CRS case definitions.

Outbreak: see 2.3.2 Definition of an outbreak.

Measles vaccine-associated reaction: a suspected case of measles that meets all five of the following criteria:

- The patient had a rash illness but did not have cough or other respiratory symptoms related to the rash.
- The rash began 7–14 days after vaccination with a measles-containing vaccine.
- The blood specimen, which was positive for measles IgM, was collected 8–56 days after vaccination.
- A thorough field investigation did not identify any secondary cases.
- Field and laboratory investigations failed to identify other causes.

When laboratory investigation confirms genotype A, it should also be classified as a vaccine-associated reaction.

Acute measles-related death: any death occurring within 30 days of rash onset of a measles case (laboratory-confirmed, epidemiologically linked, clinically compatible) that is related to a complication of measles (such as pneumonia) and is not due to other unrelated causes, e.g. trauma. Rare deaths from post-infectious encephalitis and subacute sclerosing panencephalitis (SSPE) occur months to years after measles infection and would not be detected by surveillance for acute measles illness.

1.4 Case investigation

1.4.1 Measles and rubella

Countries nearing elimination of measles or rubella should investigate all suspected cases and obtain clinical specimens for laboratory testing. All suspected cases should be notified to the public health authorities within 24 hours of identification and investigated within 48 hours of notification.

An investigation should be conducted for each case, with data collected on potential risks of exposure and spread among contacts to identify transmission patterns and interrupt chains of transmission. It is important to ensure that the minimum data elements on the case investigation form are collected (see 1.8 Data collection, reporting and use). The source of infection for measles is an infectious person who interacted with the case 7–23 days before rash onset (for rubella, contact 12–23 days prior to rash onset). Sometimes, however, the source patient cannot be identified, such as when the infection is travel related or infection occurred at a large venue.

Once the case investigation form has been completed and laboratory test results are available, suspected cases should be classified by confirmation status (as laboratory-confirmed, epidemiologically linked, clinically compatible) or discarded, as well as according to the source of infection (imported, importation-related, endemic, unknown).

Although it may occasionally be necessary, the confirmation of a suspected case based on it meeting the definition of a clinically compatible case should be limited and carefully applied. This is especially true for rubella, as there are many other causes of rash that can mimic the mild rash caused by rubella. Additionally, there should be very few confirmed cases of measles or rubella that are classified as unknown source cases.

The source of infection for rubella can be especially difficult to identify because of the mild clinical presentation – an important difference from measles. Because a significant proportion of rubella cases are mild or subclinical, a more extensive investigation is needed to minimize the number of transmission chains with an unknown source of infection. For elimination-standard surveillance, it is imperative to minimize the number of cases confirmed as clinically compatible or classified as having unknown source because these designations suggest that either a substandard investigation was conducted or that surveillance is substandard because a source case was unreported.

1.4.2 Congenital rubella syndrome

Suspected CRS cases should be investigated within 48 hours of detection. A standard case investigation form should be used for investigation of all suspected cases and should include clinical examination for CRS-related signs, especially those conditions that benefit from early intervention. Specimens should be taken for laboratory confirmation of all suspected CRS cases. Pregnancy outcomes should be monitored for pregnant women with suspected or confirmed rubella. For those pregnancies that result in a live birth, the infant should be followed up with appropriate clinical and laboratory evaluation, and placed under droplet and contact precautions to minimize potential spread. After a country has achieved rubella elimination, a single CRS case, where the rubella infection in the mother cannot be traced to an import or import-related rubella case, should lead to intensified rubella and CRS surveillance and an investigation to determine where the mother was exposed and the reason for insufficient immunity.

1.4.3 Considerations for measles, rubella and CRS case surveillance and confirmation

In the interpretation of laboratory results, it is important to be aware of factors that can affect serology results and/or the ability to accurately determine the status of a suspected case. For example, a recent history of vaccination, cross reactivity with other infections or non-specific stimulation of the immune system due to other pathogens must be considered, especially in the context of a sporadic case of measles or rubella. Such situations may produce indeterminate test results, or a positive test result may be obtained for both measles and rubella. In addition, the positive predictive value of IgM is greatly reduced (false-positive results are encountered more frequently) as disease incidence approaches zero in elimination settings. These situations are described in more detail in the WHO Manual for the laboratory-based surveillance of measles, rubella and congenital rubella syndrome *(27)*.

Specifically, for rubella, the procedures of investigating suspected cases who are pregnant (or the evaluation of contacts of rubella cases who are pregnant) will vary by country. However, the follow-up of such cases and contacts should continue through delivery to determine the outcome of the pregnancy, including assessment of the newborn for CRS. For all laboratory-confirmed cases of rubella infection during pregnancy, the patient's name and other relevant information should be entered into a rubella pregnancy registry. Counselling services and medical follow-up of newborns from mothers who were infected with rubella during pregnancy should continue post-delivery.

1.5 Specimen collection, processing and transport

1.5.1 General points for specimen collection

Several different types of specimens can be collected from suspected measles or rubella cases based on the timing of the investigation (see Table 2). Specimens should be collected on first contact with the case; collection should not be delayed until the ideal window for IgM detection, or the case might be lost to follow-up. Transport and storage requirements for measles, rubella and CRS specimens are identical.

An adequate specimen for antibody detection is defined as a blood sample collected within 28 days after rash onset that consists of ≥ 0.5 mL of serum. However, the volume of whole blood to be collected is based on age and is provided in Table 2. In areas where suitable collection devices and processing of alternative samples for antibody testing are available, samples of oral fluid (OF) or of whole blood dried on filter paper can be utilized (see 1.5.4 Details on collection and processing of specimens).

At a minimum, all cases should have a specimen collected for antibody detection (unless they can be epidemiologically linked to a laboratory-confirmed or another epidemiologically linked case). Additionally, if the case is not linked to a known chain of transmission, an appropriate specimen should be collected for viral detection (RT-PCR/genotyping) at first contact. Appropriate specimens to collect for virus detection include throat, nasal or nasopharyngeal (NP) swab, OF, urine or NP aspirates.

In the context of an outbreak, specimens for viral studies should be collected from several individuals (5–10 cases) with rash onset, early in the chain of transmission, and every two months thereafter if transmission continues. Additional samples can be utilized to document transmission (and elimination) of a single genotype (or named strain). Conversely, genetic analysis of viruses collected from subsequent cases may indicate that a separate introduction of a virus occurred during an extended and widespread outbreak.

Laboratory testing and the identification of epidemiological links for case confirmation should be used together in a sustainable way that allows efficient use of laboratory resources. Particularly in endemic settings, epidemiological investigations should be utilized to provide case confirmation through contact tracing to reduce the burden on the laboratory. This is particularly necessary during confirmed outbreaks and in situations in which sample collection and/or transportation is especially difficult, such as during disasters and in remote locations.

In countries that are close to elimination or where elimination has been verified, maximum efforts should be directed towards collection of a serum specimen as well as a specimen for viral detection at first contact, and a follow-up sample if necessary, for every case.

1.5.2 Specimen collection considerations for rubella

Specimens should be collected from every suspected case because the symptoms of rubella are non-specific.

The types of specimens collected for postnatal rubella confirmation are the same as those for measles testing and are given above. However, there are some considerations that need to be considered for specimens collected specifically for laboratory confirmation of rubella infection:

- For rubella, the ideal timing for collection of a follow-up serum sample for IgM retesting is after day five post rash onset (versus after day three for measles). Rubella-specific IgM may be undetectable by EIA in up to 50% of rubella cases with serum collected on the day of rash onset, and a proportion of cases will be IgM negative if collected ≤ 5 days after rash onset. If a rubella IgM-negative result is obtained in specimens taken on or before five days after rash onset, serological testing should be repeated on a specimen collected 6–28 days after rash onset. The initial blood sample should always be collected on first contact with the case.
- Urine samples have been used successfully for both measles and rubella virus detection and isolation. Throat swabs may be superior to urine in terms of sensitivity, particularly for rubella. However, collection of both types of specimens may increase the chances of virus detection.
- To test for suspected rubella encephalitis, a cerebrospinal fluid specimen can be collected.

Table 2.
Specimen types for diagnosis of measles

Type of specimen	Type of test	Volume to be collected	Timing of collection	Storage conditions	Advantages	Disadvantages	Comments
Whole blood/ serum (by venepuncture)	Antibody detection[a] (measles-specific IgM, paired sera to document IgG seroconversion or significant rise in IgG, between acute and convalescent phase sera)	4–7 mL of blood for older children and adults; 1 mL for younger children; 0.5 mL for infants	≤ 28 days post rash onset Paired sera are normally collected 10–20 days apart The interval between the 2 serum samples can be shorter if virus-specific IgG was not detected in the first serum sample	Whole blood: 4–8 °C (never freeze whole blood) for up to 24 hours or for 6 hours at 20–25 °C before the serum is separated from clotted blood through centrifugation Serum should be stored at 4–8 °C until shipment to laboratory, ideally no longer than 7 days	• Most widely collected and tested • Technically simple and standardized • WHO correlate of protection exists	• Sensitivity of the test is lower ≤ 3 days after rash onset[a] • Positive predictive value of IgM in elimination settings is low	Laboratories should report results for IgM within 4 days of receipt of the specimens
Alternative specimen: dried blood spots (whole blood)	Antibody detection[a] (measles-specific IgM, paired sera to document IgG seroconversion or significant rise in IgG)	At least 3 fully filled circles on a filter-paper collection device	≤ 28 days post rash onset	Does not require cold chain Should be dried before storage at low humidity	• Does not require cold chain • Potentially lower transportation cost • Can collect from finger or heel prick • Potential for viral RNA and antibody detection from same sample	• Sensitivity reduced if not dried/stored properly • Increased workload in laboratory • No quality control on extraction process • Possibility that insufficient blood collected in the field • Lower sensitivity for RT-PCR	Preference is for serum to be collected, with DBS reserved for situations where it is hard to collect venous blood (e.g. infants), reverse cold chain cannot be maintained, or where expedited shipping is not possible
	Detection of viral RNA by RT-PCR		Up to 14 days post rash onset if performing virus detection using RT-PCR				
Throat (recommended), nasal, or NP swabs or aspirates[b]	Viral isolation by cell culture	Swab or NP aspirate	Within 5 days after rash onset for viral isolation (cell culture)	4–8 °C	• Superior to OF for virus isolation • Can be more sensitive for confirmation than serum within first 3 days	• Requires cold chain • Should get to laboratory within 48 hours ideally	Both NP and OF samples can be stabilized on FTA cards for transport at ambient temperature. In this case, detection of antibodies is not possible, but viral RNA can be detected by RT-PCR
	Detection of viral RNA by RT-PCR[c]		Up to 14 days post rash onset if performing virus detection using RT-PCR				

Table 2. (continued)

Type of specimen	Type of test	Volume to be collected	Timing of collection	Storage conditions	Advantages	Disadvantages	Comments
Oral fluid (OF)	Antibody detection[a] (measles-specific IgM)	Using a sponge collection device that is rubbed along the gums for > 1 minute to ensure the device is thoroughly wet (~0.5 mL crevicular fluid)	Up to 28 days if antibody testing	Does not require cold chain if < 22 °C ambient temperature and shipped to the laboratory within 24 hours At higher temperatures, the OF samples should be kept at 4–8 °C until the samples can be shipped on cold packs	• Less invasive than blood collection • Does not require cold chain • Potentially lower transportation cost • Viral detection and antibody detection from same sample	• Somewhat less sensitive for antibody detection than serum when collected early • Not suitable for virus isolation (cell culture) • External quality control programmes have not been established • Limited number of EIA test kits validated for OF If stored at room temperature, samples must be shipped to laboratory within 24 hours of collection	Both NP and OF samples can be stabilized on FTA cards for transport at ambient temperature. In this case, detection of antibodies is not possible, but viral RNA can be detected by RT-PCR
	Detection of viral RNA by RT-PCR		Up to 14 days post rash onset if performing virus detection using RT-PCR				
Urine	Viral isolation by cell culture Detection of viral RNA by RT-PCR	Minimum 10 mL (preference first morning void) Larger volumes have a higher chance of detection	Within 5 days after rash onset for viral isolation Up to 14 days post rash onset if performing virus detection using RT-PCR	Stored at 4–8 °C until the urine can be centrifuged Original urine sample should not be frozen prior to centrifugation		• Often difficult to collect, transport and process • Less sensitive than throat swabs • May contain substances that are inhibitory for RT-PCR	

Notes:

a. Antibody detection: adequate samples are those collected within 28 days after onset of rash. However, IgM detection by EIA for measles is more sensitive when collected 4–28 days after the onset of rash. In the first 72 hours after rash onset, a negative result for measles IgM may be obtained from up to 30% of measles cases. A second serum sample may be required for additional testing under the following circumstances:

- Detection of virus-specific RNA by RT-PCR is either unavailable or the results were inconclusive.
- The first serum specimen was collected ≤ 3 days after rash onset and is negative for measles IgM, or is negative in serum collected
  ≤ 5 days for rubella IgM by EIA.
- Repeat testing of the initial serum specimen fails to resolve an equivocal result for IgM.

b. Properly collected serum tested for IgM is still considered by some laboratories as the only adequate specimen to rule out measles. A negative
RT-PCR from a sample taken from the upper respiratory tract is not considered to rule out measles because specimen timing and quality are critical. However, some countries are collecting only upper respiratory tract specimens from infants because of the difficulty of drawing blood. In some countries with very low measles prevalence, these samples can be a significant fraction of the total.

c. Because the virus is more likely to be isolated (and the RNA detection rate is higher) when specimens are collected early, the collection of specimens for virus detection should not be delayed until laboratory confirmation is obtained by antibody detection of a suspected case. Samples for antibody and viral detection should be collected at first contact with a suspected case.

1.5.3 Specimen collection considerations for CRS

Serum specimens

Serum specimens taken from infants for serological testing are the most common specimens used for CRS diagnosis and are collected at first contact during the initial investigation. If possible, 1 mL of blood from infants should be collected, although 0.5 mL can be acceptable in very young infants.

Ideally, both a serum specimen for serological testing and a specimen for viral detection should be collected. As indicated below, additional samples may be needed in infants < 1 month of age or individuals > 6 months of age.

- If an infant is < 1 month of age with a high suspicion of CRS and a negative IgM serology, then a second specimen should be collected after 1 month of age to retest for IgM (IgM levels can be undetectable at age < 1 month).
- For infants ≥ 6 months of age but < 12 months with an initial positive rubella IgG serology, a second serum specimen for IgG should be collected after one month and tested in parallel with the initial serum specimen to assess whether there is a sustained rubella IgG response.

Specimens for viral detection

Specimens for viral detection are also useful for laboratory testing of suspected CRS cases. The best results come from throat swabs, but nasal swabs, urine, serum or dried blood spots (DBS) (in remote locations where serum transport is not possible) may also be used. Depending on the clinical picture, specimens such as cerebrospinal fluid or cataract tissue may be appropriate for rubella virus detection. However, the performance characteristics for rubella virus detection have not been established for these alternative specimen types and a negative result does not necessarily rule out a CRS case. Details on collection of these specimens can be found elsewhere *(28)*.

1.5.4 Details on collection and processing of specimens

Whole blood/serum

Collection of whole blood is done by venepuncture using a sterile, plain collection tube or gel separator tube without additives. Whole blood can be stored at 4–8 °C (whole blood should never be frozen) for up to 24 hours or for 6 hours at 20–25 °C before the serum is separated from the clotted blood through centrifugation. After this time, whole blood must be transported to a facility equipped to separate the serum in order to avoid haemolysis. Serum should be stored at 4–8 °C until shipment, but ideally should not be held at this temperature for longer than seven days. For longer periods, such as when a delay is anticipated in shipping or testing, serum samples must be frozen at -20 °C or below and transported to the testing laboratory on frozen ice packs in a sufficiently insulated container. Cycles of repeated freezing and thawing should be avoided, as this can have detrimental effects on the integrity of IgM antibodies.

Aliquots of important serum specimens should be prepared prior to freezing. As a rule, serum specimens should be shipped to the laboratory as soon as possible, and shipment should not be delayed for the collection of additional specimens.

Whole blood/dried blood spots

Blood can be dried onto filter paper for DBS if venepuncture is not possible, or if a cold chain or economical method to ship serum samples are not available. While venous blood can be collected for DBS, normally DBS are prepared using capillary blood. Blood should be collected by finger- or heel-prick using a sterile lancet, preferably single-use disposable. Collection from a capillary tube (finger- or heel-stick) can be used for DBS. Approximately 3–5 drops of whole blood is required. This amount is sufficient to fill 3–4 of the filter-paper circles, assuming the volume of one drop yields the 50 uL required for each filter paper circle. Blood specimens that have been spotted on filter paper should be allowed to air dry completely. Individual cards should be wrapped in wax paper and placed in a sealable plastic bag with a desiccant pack. DBS should be stored at 4 °C until they can be shipped to the laboratory. It is acceptable to transport DBS at ambient temperatures of up to 42 °C if the sample is delivered to the laboratory within three days.

Oral fluid

An adequate OF sample is one that is collected by gently rubbing along the base of the teeth and gums for at least 1 minute, which should allow the sponge to absorb about 0.5 mL of crevicular fluid. If the daily ambient temperature is below 22 °C, OF samples should be shipped to the laboratory within 24 hours. At higher temperatures, the OF samples should be kept at 4–8 °C until the samples can be shipped to the laboratory on cold packs. The OF samples are not considered a biohazard and can be shipped without special documentation from the site of collection to the laboratory.

Throat (oropharyngeal) swab, NP swab or aspirate, nasal swab

An oropharyngeal swab is the recommended sample for both viral detection and virus isolation for suspected cases. NP swabs will serve as good samples for both virus isolation and detection but are more difficult to collect. NP aspirates and nasal swabs are variations that have been used successfully to detect measles virus. Swabs should be collected using only synthetic fibre swabs with plastic shafts. Calcium alginate swabs or swabs with wooden shafts should not be used as they may contain substances that inactivate viruses and/or inhibit RT-PCR testing. The throat swab is collected by swabbing the posterior pharynx, avoiding the tongue. The NP swab is longer, with a flexible shaft. To collect the NP sample, tilt the patient's head back and insert the swab into the nostril parallel to the palate. The swab should contact the mucosal surface. Swab samples should be placed in sterile tubes containing 2–3 mL of viral transport media (VTM) or phosphate buffered saline (PBS). It is important to prevent the swabs from drying out. The throat and NP swabs may be refrigerated at 2–8 °C for up to 48 hours and shipped on dry ice or frozen ice packs. If arrangements cannot be made for shipment within this timeframe, it is best to preserve the sample at -70 °C. After freezing at -70 °C, the samples should be shipped on dry ice. Freeze/thaw cycles should be avoided. If storage at -70 °C is not available, samples should be stored at -20 °C; water crystal formation may result in loss of viability of the virus, but the integrity of the viral RNA may be maintained and detected by RT-PCR.

Urine

Urine should be collected in a suitable sterile, leak-proof container. The urine sample should be stored at 4–8 °C until the urine can be centrifuged. The original urine sample should not be frozen prior to centrifugation. The unprocessed urine sample may be shipped in a sealed container at 4 °C, but centrifugation within 24 hours of collection is recommended. The urine should be centrifuged at 500 × g (approximately 1500 rpm) for 5–10 minutes, preferably at 4 °C and the supernatant removed. Sterile VTM, tissue culture medium or PBS should be added to the sediment to bring the final volume to 2 mL. If a pellet is not visible in the bottom of the centrifuge tube, all but a small volume (approximately 1 mL) of the supernatant should be removed and mixed with an equal volume of VTM. The processed urine sample should be stored at 4 °C and shipped within 48 hours. Alternatively, the processed urine sample may be frozen at -70 °C in VTM and shipped on dry ice. If storage at -70 °C is not available, samples can be stored at -20 °C; the viability of the virus will be lost, but the integrity of the viral RNA may be maintained and detected by RT-PCR.

Regardless of the specimen type collected, all specimens should arrive at the laboratory within five days of collection, except in the case of samples as noted above.

1.6 Laboratory testing

1.6.1 Laboratory networks

WHO coordinates the Global Measles and Rubella Laboratory Network (GMRLN), a network of over 700 laboratories at national and subnational levels that meet rigorous standards to provide accurate results *(29)*. The WHO Regional Office for Europe coordinates the European Measles and Rubella Laboratory Network *(30)* which is part of the GMRLN. Regional and global reference laboratories can provide specialized serological testing such as avidity testing and neutralization assays as well as virus detection and molecular characterization for laboratories that do not have access to these techniques in their own facilities. It is important to ensure that samples are tested in a WHO-accredited or proficient laboratory, as defined in 1.3.5.

1.6.2 Confirmation methods

Measles

Laboratory confirmation for a suspected measles case can be obtained using the following methods:

- Use of EIA for detection of anti-measles IgM antibody: this has historically been considered the gold standard for laboratory diagnosis. Results of IgM testing should be reported within four days of the specimen's arrival at the laboratory (Fig. 5b and 5c).
- Demonstration of a diagnostically significant increase in titre of IgG antibody between acute and late-acute, or between acute and convalescent-phase serum samples; or a documented seroconversion (IgG negative to IgG positive) (Fig. 5b).
- Virus detection using RT-PCR or by virus isolation in cell culture (Fig. 5a).

Since the procedure for measles testing is the same as that for rubella, it is recommended to also test for rubella.

Rubella

Laboratory confirmation for a suspected rubella case can be obtained using the following methods:

- Use of EIA for detection of anti-rubella IgM antibody: this has historically been considered the gold standard for laboratory diagnosis. Results of IgM testing should be reported within four days of the specimen's arrival at the laboratory (Fig. 5b and 5c).
- Demonstration of a diagnostically significant increase in titre of rubella IgG antibody between acute and late-acute or between acute and convalescent-phase serum samples; or a documented seroconversion (IgG negative to IgG positive) (Fig. 5b).
- Virus detection using RT-PCR or by virus isolation in cell culture (Fig. 5a).

Since the procedure for rubella testing is the same as that for measles, it is recommended to also test for measles

Congenital rubella syndrome

Laboratory confirmation of CRI or CRS in an infant (note appropriate age for the testing) is demonstrated using one of the following methods:

- For infants < 6 months of age, anti-rubella IgM antibody is detected by EIA.
- For infants ≥ 6 months but < 12 months of age, rubella virus is detected by both rubella IgM and IgG antibodies, or demonstration of a sustained rubella IgG antibody level, as determined with serum samples collected at two (or more if needed) time-points at least one month apart in the absence of receipt of rubella vaccine or exposure to wild-type rubella.
- For infants any age < 12 months, rubella virus is detected by virus growth in cell culture or by RT-PCR in an appropriate clinical sample (throat, NP or nasal swabs, blood, urine or cerebrospinal fluid specimens).

Because IgM may not be detectable in some infants with suspected CRS that are tested at < 1 month of age, infants with a negative result for IgM should be retested at 1 month of age or shortly thereafter. Although anti-rubella IgM antibodies may persist for up to one year, about 50% of CRS cases are IgM negative at 6 months of age, depending on test sensitivity. Therefore, the laboratory confirmation of CRS in an infant older than 6 months of age should not depend on the IgM test alone if the IgM result is negative. In such cases, as mentioned, serial samples for IgG testing should be collected at least one month apart and tested in parallel to check for a sustained level of IgG antibody over several months.

1.6.3 Genotype identification

Measles and rubella genotype identification (and the designation of named strains for measles) can aid in understanding the epidemiology of an outbreak or a sporadic case. In addition, it allows mapping of circulating genotypes to inform progress towards elimination of some genotypes. By comparing sequences, the presumption of an epidemiological link between a contemporaneous case and an ongoing chain of transmission can be strengthened or can be disproved. It is recommended that adequate specimens are collected in ≥ 80% of laboratory-confirmed outbreaks for RT-PCR and genetic sequencing so that a genotype can be identified. In some situations, analysis of additional gene targets (extended window) or whole genome sequencing may be considered to assess whether an outbreak is ongoing or the result of a new importation. Molecular analysis (genotyping) of viruses is recommended because the data can aid in tracking transmission, contributing to the epidemiology of measles or rubella as progress is made towards elimination or is maintained in a country. In addition, the surveillance of genotypes provides data that are essential to monitor virus transmission regionally and globally *(25,26)*. Genotyping results should be reported to MeanNS and RubeNS WHO databases within two months of the specimen's arrival at the laboratory (see 3.1.3. B. Molecular epidemiology of measles and rubella viruses).

Genotyping plays a similar role in CRS as it does in rubella virus surveillance, providing information that can potentially indicate an association with an earlier imported rubella case, or suggest an epidemiological link to an earlier outbreak that was not recognized as a source of infection for the mother of the CRS case. In a post-elimination setting, identification of a genotype should be attempted for every CRS case if the case is encountered at < 12 months old (when virus shedding occurs).

1.6.4 Special laboratory considerations

Integrated laboratory testing for measles and rubella

Laboratories can perform testing on specimens from suspected measles or rubella cases using different testing algorithms, depending on initial suspicion based on the epidemiology of the case(s) and available resources. It is recommended that both diseases be ruled out by integrating the testing for measles and rubella. This can be achieved by testing for both diseases simultaneously (if resources are sufficient to take this approach). However, if resources are limited or measles burden is high, measles testing may be completed first, and rubella testing may then be performed on samples that were negative for measles. Conversely, if rubella cases are prevalent, the operation is reversed – rubella testing should be performed first and those samples that are negative for rubella should then be tested for measles.

Timing of specimen collection

Specimens for antibody detection and molecular testing, as appropriate, should be collected at first contact with a suspected case of either measles or rubella. When blood or OF is collected on the day of rash onset (or within a few days after rash onset) and a negative result for IgM is obtained, an additional specimen should be collected. It is extremely important to be aware of the possibility that IgM may be undetectable in samples collected early. Conversely, the ability to detect viral RNA decreases (at different rates depending on the type of virological specimen) with specimens collected further out from symptomatic disease. Therefore, accurate recording of specimen collection and rash onset dates are critical in order to correctly interpret and classify suspected cases of measles and rubella including suspected rubella infection in pregnant women *(27)*.

Laboratory testing for other febrile rash illnesses

In countries that use the fever–rash case definition, additional disease-specific testing can be integrated into the measles/rubella testing algorithm. When determining the proper algorithm at country level, the burden of other febrile-rash diseases, the risk of delayed diagnosis for measles and rubella and availability of resources should be considered. Guidance on determining the proper algorithm is beyond the scope of this document.

Laboratory testing in an elimination setting

In an elimination setting, both positive and negative IgM test results should be critically evaluated. As the prevalence of measles or rubella decreases, the positive predictive value of IgM decreases, making false-positive IgM results a real concern. Epidemiological data and additional tests can strengthen the argument for or against an IgM-positive result representing a true case. For example, a second specimen for IgM testing may need to be collected if the original sample that tested negative for measles IgM was collected less than four days after rash onset (less than six days after rash onset for rubella), to ensure the case is truly negative. Fig. 5a, 5b and 5c illustrate the process for laboratory testing of suspected measles and rubella cases when a country is near or at elimination. Suspected cases in low-incidence settings should be evaluated and classified after taking into consideration all laboratory and epidemiological data *(27)*.

Interpreting laboratory results

In interpreting laboratory results, the following should be kept in mind:

- Upon vaccination, particularly of adults, IgM antibodies may persist for as long as six months after the date of vaccination. Care should be taken when interpreting an IgM positive result in those who have been recently vaccinated *(28)*.
- A positive IgM result may be obtained in either measles or rubella EIA assays due to the presence in the serum of rheumatoid factors (indicating rheumatologic disease), cross-reacting IgM or current infection with other viruses *(27)*.
- IgG peaks between three to five weeks after rash onset, so the timing for collection of paired specimens for antibody testing is very important to document seroconversion or a significant rise in titre. Of course, the possibility of recent vaccination after the onset date

should be ruled out, as well as the presence of maternal antibodies if the case-patient is an infant (possibly present until 9 months of age).

- A negative RT-PCR result alone is not sufficient to discard a suspected case, however it can support other test results, clinical findings and/or epidemiological information that are inconsistent with a true case.
- Avidity testing of IgG and detection of wild-type rubella virus can be used to resolve uncertainties in the serological evaluation of suspected rubella cases.
- IgG determined to be of low avidity is associated with recent primary rubella (or measles) infection. High avidity IgG is associated with prior immune experience with the virus, through natural disease or as a result of vaccination, and is not consistent with a true rubella case. However, measles has been confirmed among symptomatic individuals with high avidity IgG; these cases are described as breakthrough infections.[3]

Rapid diagnostic tests

Rapid diagnostic tests (RDTs) to detect measles- and rubella-specific IgM antibodies have recently been developed as an alternative to EIA. RDTs use lateral flow technology and can be used on serum, capillary blood or OF specimens. The incorporation of the tests into surveillance programmes is currently being piloted prior to developing guidance on its use *(27,31)*.

[3] The term "breakthrough infection" is applied when disease (usually measles) is confirmed even though virus-specific IgG is demonstrated to be of high avidity – indicating prior immune experience with the virus, through natural disease or as a result of vaccination.

Fig. 5a.
Laboratory testing for suspected measles or rubella cases in countries at or near elimination, part 1

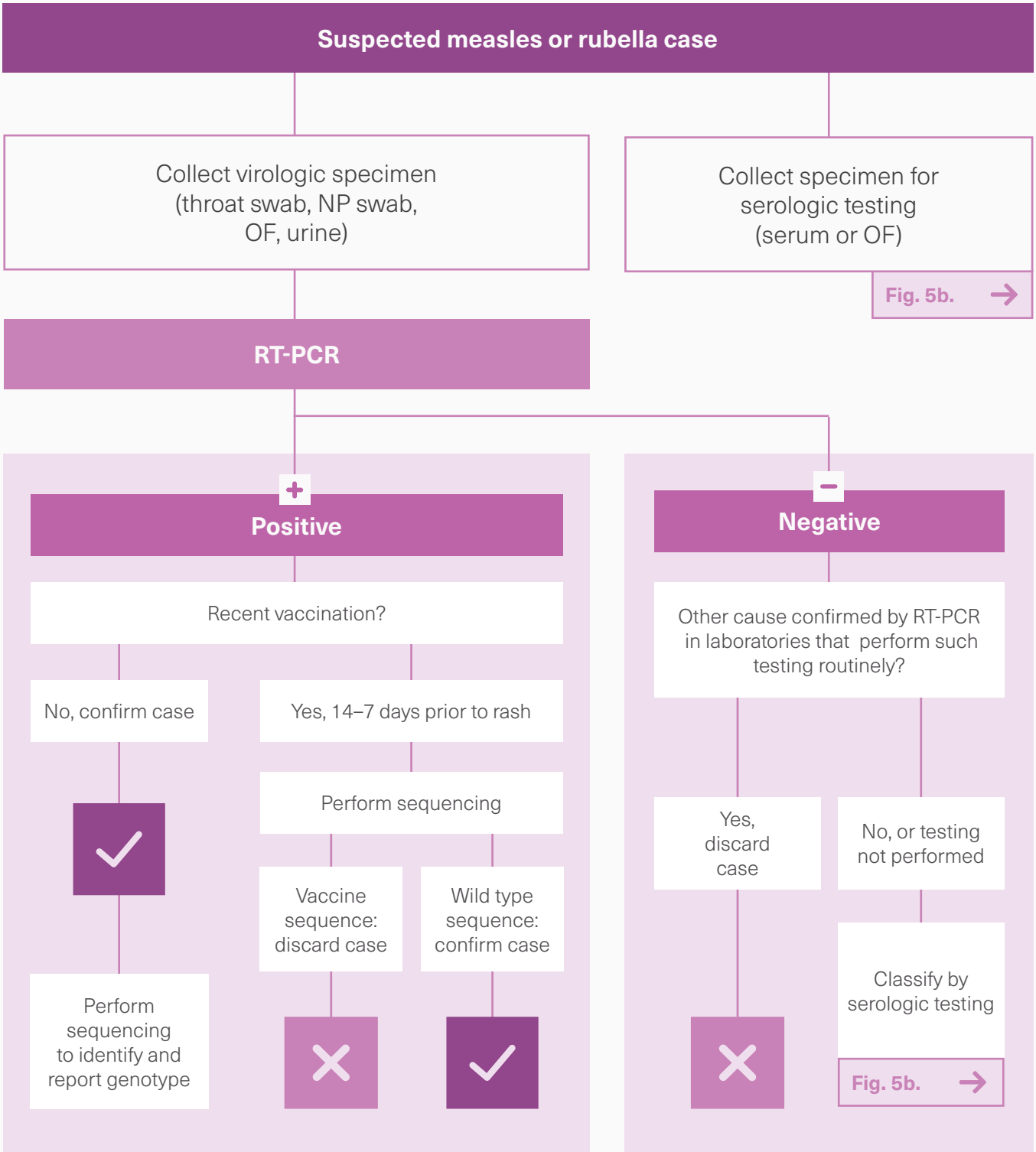


Fig. 5b.

Laboratory testing for suspected measles or rubella cases in countries at or near elimination, part 2 (sample collected at the optimal time window)

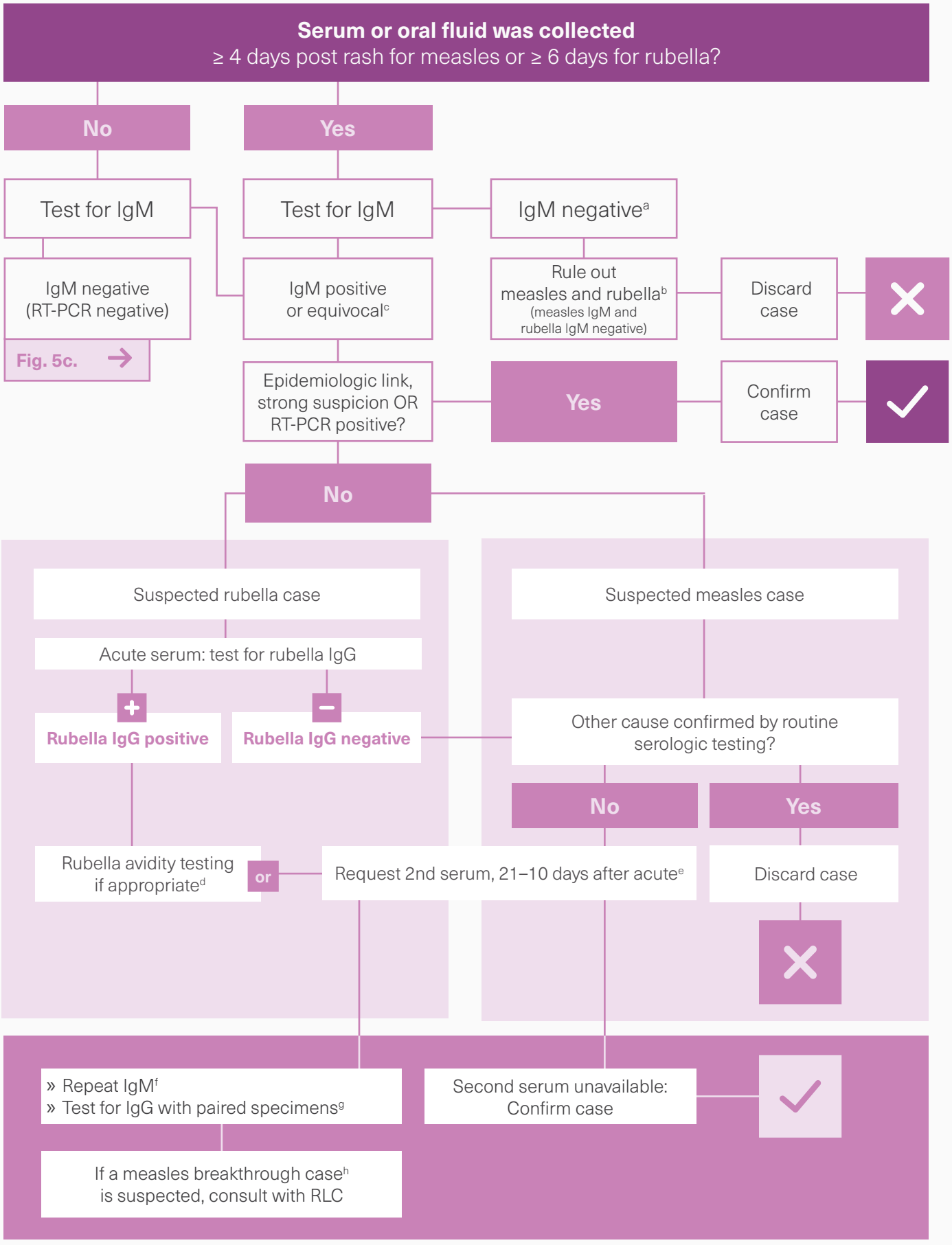


Fig. 5b.

Notes:

a. A measles breakthrough case can have a negative IgM result. If a measles breakthrough case is suspected, consult with the regional laboratory coordinator. Breakthrough cases can be confirmed by RT-PCR, a rise in IgG titer or by measuring high levels of measles neutralizing antibody levels (≥ 40,000 mIU/mL) by plaque reduction neutralization testing.

b. Parallel, or reflex, testing should be performed according to the resources available and regional surveillance recommendations.

c. An equivocal IgM result is obtained after repeat of test. The equivocal or positive IgM result was obtained using a validated assay in an accredited laboratory.

d. A positive IgG result and an equivocal IgM for rubella are inconsistent with primary rubella. If acute serum was IgM positive, rubella avidity testing or evaluation of IgG titers with paired specimens may be necessary to resolve the case.

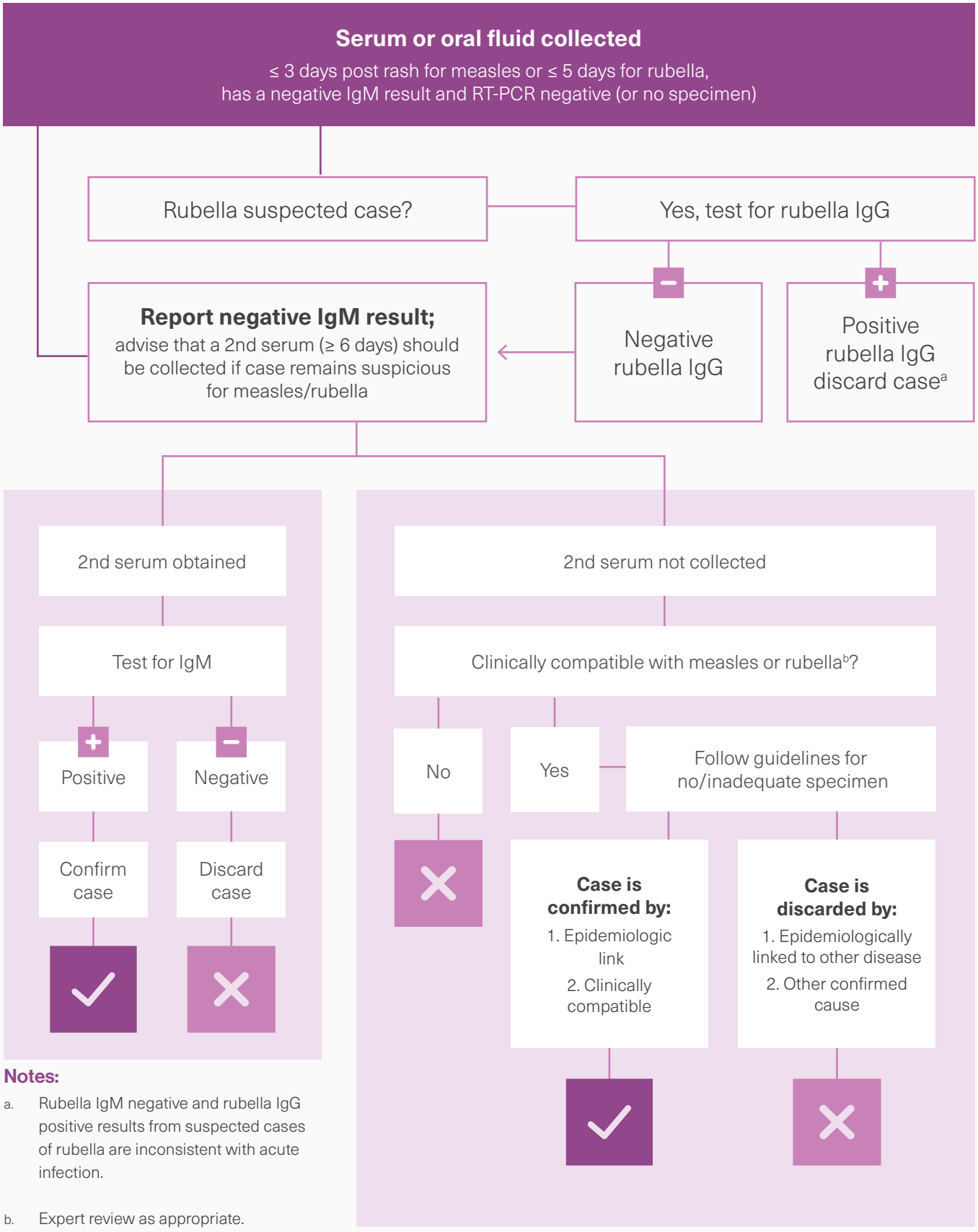
e. If the acute serum was IgG negative, the absence of seroconversion can be demonstrated with a second serum collected ≥ 10 days post rash.

f. In most instances, a suspected case with an equivocal IgM result obtained from acute serum and a positive IgM from the second serum confirms the case. However, an evaluation of IgG titers may be deemed necessary to support the IgM result.

g. IgG should be tested for, if the test is available (by semi-quantitative EIA) using appropriately timed paired specimens, tested together. Seroconversion or demonstration of a diagnostically significant rise confirms the case. Absence of seroconversion (both IgG negative) rules out the case. Note: failure to measure a diagnostically significant rise in titre must be interpreted with caution since the ideal timing for demonstration of a rise in titre can vary among individuals.

h. The rise in IgG titre from a measles breakthrough case is rapid, and remarkably high titres in acute serum are typical. Consultation with the regional laboratory coordinator is recommended to determine if additional testing is warranted and feasible.

Fig. 5c.
Laboratory testing for suspected measles or rubella cases in countries at or near elimination, part 3



Notes:

a. Rubella IgM negative and rubella IgG positive results from suspected cases of rubella are inconsistent with acute infection.

b. Expert review as appropriate.

1.6.5 Laboratory testing for pregnant women exposed to rubella

Although it is not recommended, many pregnant women with no known exposure to rubella are tested for rubella IgM as part of their prenatal care. If rubella IgM is detected (positive test result) from a serological specimen from a pregnant woman in the absence of symptoms and/or she is considered to have a low risk of exposure to rubella (in an area or country without current circulation of rubella) additional laboratory evaluation should be conducted.

For pregnant women with a known exposure to rubella, medical management and decisions may rest on collection and interpretation of laboratory data. Fig. 6 shows the recommended laboratory testing algorithm.

1.7 Special considerations for measles, rubella and CRS surveillance

1.7.1 Measles

Risk assessments

A multitude of factors must be evaluated when assessing the risk of an area for a measles outbreak. The WHO Measles Programmatic Risk Assessment Tool was developed to help national programmes identify areas that are not meeting measles programmatic targets and use the findings to guide and strengthen measles elimination activities and reduce the risk of outbreaks *(32)*. The tool triangulates data from surveillance and the immunization programme to give a more complete map of subnational risk of measles outbreaks. One limitation of the tool is that it focuses primarily on early childhood risk.

Humanitarian emergencies

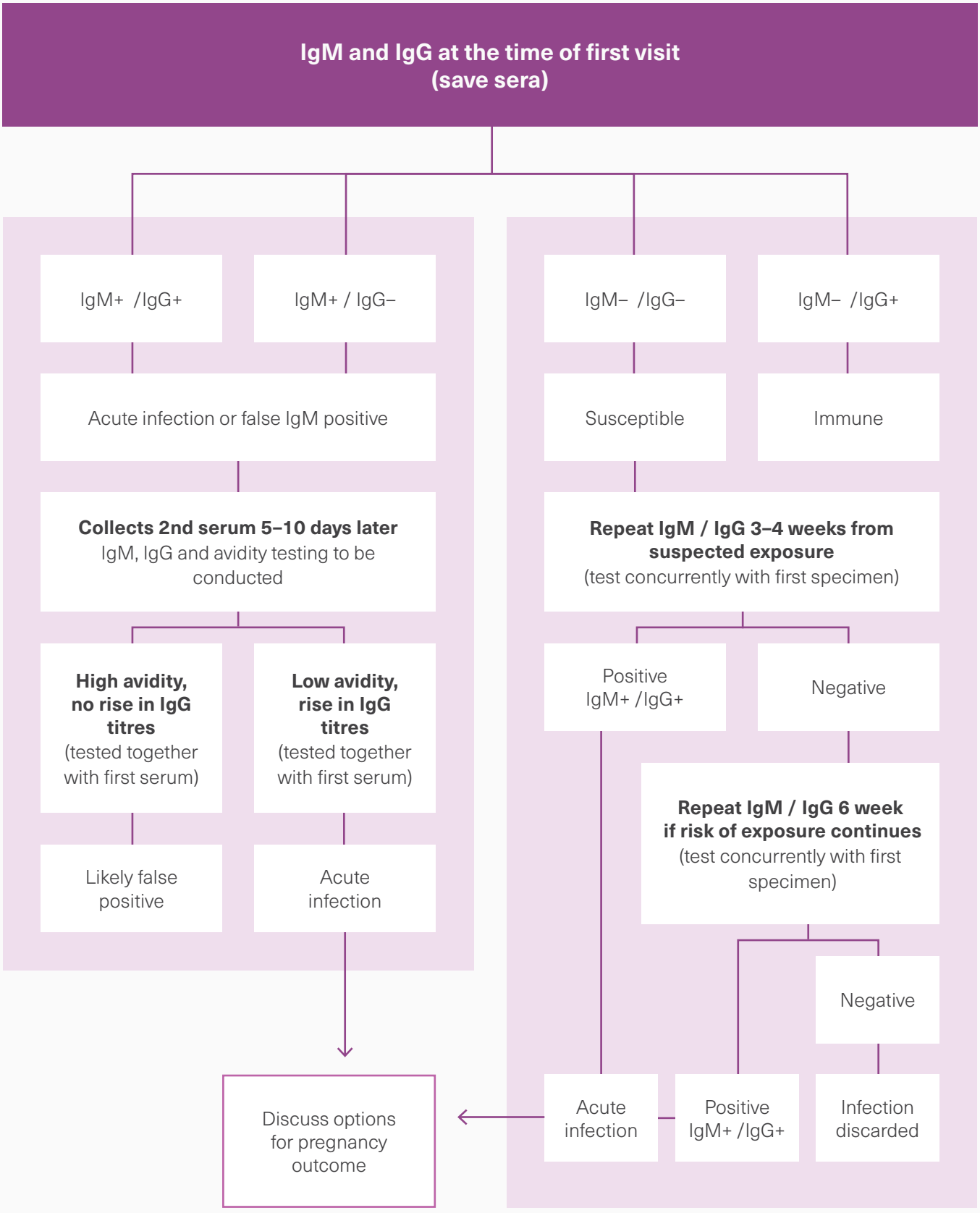
Measles is a highly infectious disease with grave consequences during humanitarian emergencies, especially those emergencies with displaced populations and among the malnourished. In these settings, surveillance must be capable of identifying suspected measles cases and may need to be modified to include, for example, daily reporting and community-based surveillance. Further information is available in Vaccination in acute humanitarian emergencies: a framework for decision making *(33)*.

1.7.2 Measles and rubella

Serosurveys

Serosurveys may be helpful to provide data on population immunity in selected places, to predict the at-risk populations where there is an information gap and provide evidence to encourage political commitment for an appropriate intervention *(34)*.

Fig. 6.
Serological evaluation of pregnant women with known exposure to rubella



Serosurveys are a direct measure that can be of use to vaccine programmes, theoretically indicating the proportion of a population immune to a particular pathogen. Seropositivity, however, is not necessarily the same as protection against a pathogen, as serosurveys usually measure the level of specific IgG detectable in serum or plasma and this does not correlate well with the level of functional, protective antibodies. Results are often reported relative to WHO standards, measured in international units per millilitre (IU/mL), but many of the commonly available assays are not validated against WHO standards and have a wide range of sensitivities and specificities.

Seroprevalence studies are not feasible for all countries or all circumstances, and it may be more appropriate to make use of existing data, for example, by the reanalysis of databases on measles and rubella serological status gained through IgG screening of women of childbearing age, in order to estimate population immunity. Existing serum collections – for example from blood donors, HIV screening of women during prenatal care, nutritional surveys, etc. – can effectively be used and tested for measles and rubella antibodies to estimate population seroprevalence profiles without the need to conduct new surveys.

1.7.3 Congenital rubella syndrome

Medical record review

Retrospective medical record review should be used to monitor the sensitivity of CRS surveillance systems annually. For countries unable to establish or maintain CRS surveillance, retrospective record review can be conducted to identify CRS cases. Reviewing medical records, while not considered surveillance, can inform disease burden estimates or provide baseline data for measuring the impact of vaccine introduction for a country. It can also be used in special circumstances (e.g. in countries with a small population) where it is believed that CRS elimination has already been achieved. However, a limitation of this approach is that retrospectively identified cases usually lack laboratory confirmation, and therefore lack a definitive diagnosis. Further details and more information on other types of CRS surveillance can be found in the publication Introducing rubella vaccine into national immunization programmes: a step-by-step guide *(23)*.

1.8 Data collection, reporting and use

1.8.1 Recommended data elements

Because it is recommended that measles and rubella surveillance be integrated, entry of the required information into databases and data reporting are usually performed together for both diseases. Below is a list of general data elements that can be adapted to case investigation forms for both diseases in national surveillance systems, with rubella-specific data points indicated with * symbol. Data management tools for measles and rubella surveillance (i.e. electronic case-based records, Excel linelists) in countries should be able to capture all core and possibly additional variables in the case investigation form to allow comprehensive analysis.

Measles and rubella

Demographic information

- Name (if confidentiality is a concern omit name as long as a unique identifier exists)
- Unique identifier
- Place of residence (e.g. city, district and province)
- Place of infection (e.g. city, district and province)
- Date of birth (or age if date of birth not available)
- Gender
- Race and/or ethnicity, if appropriate in country setting
- Country of birth

Reporting information

- Place of reporting (for example, county or district)
- Date of notification
- Date of investigation
- Name of clinician who suspects measles (or rubella)

Clinical

- Date of rash onset
- Symptoms
    - Fever
    - Maculopapular rash
    - Cough
    - Conjunctivitis
    - Coryza
    - Lymphadenopathy*
    - Arthralgia or arthritis*
- Severe complications
    - Pneumonia
    - Persistent diarrhoea
    - Encephalitis
    - Thrombocytopenia*
    - Other
- Hospitalizations
    - History of hospitalization in 23 days prior to rash onset?
    - Dates of hospitalization
    - Hospitalized because of this current fever–rash diagnosis?
- Outcome (patient survived or died)
    - Date of death
- For women of childbearing age
    - Number of previous pregnancies*
    - Pregnancy status*
        - Number of weeks gestation at onset of illness*
        - Prior evidence or date of rubella serological immunity, or both*

    - Number and dates of previous pregnancies and location (second administrative level) of these pregnancies*
    - Pregnancy outcome, when available (apparently healthy infant, termination, infant with CRS, etc.)*

Laboratory methods and results

- Type(s) of specimen(s) collected
- Date of specimen(s) collection
- Date specimen(s) sent to laboratory
- Date specimen(s) received in laboratory
- Date of results from laboratory
- Laboratory results (serology, viral detection, genotype)

Vaccination status

- Number of doses of measles-containing vaccine
    - Dates of all doses of vaccine given (if card available)
- Number of doses of rubella-containing vaccine*
    - Dates of all doses of vaccine given (if card available)

Contact tracing

- Persons who came in contact with the case 7–23 days before symptom onset (source of case's infection). Determine if any of them had rash illness with fever
- Persons who came in contact with the case in the four days prior to and four days after rash onset (seven days before and after rash onset for rubella) (potential persons exposed by the case)

Epidemiological data

- Transmission setting (infection acquired at home, health-care setting, day-care, school, workplace, etc.)
- Enrolled in a school/day-care setting?
    - If yes, name of the school
- Visited a health facility in the 7–23 days before symptom onset?
    - If yes, name of the facility
- Travel history in the past 7–23 days?
    - If yes, provide dates and places
- Relationship to outbreak (Is the case part of an outbreak or is it sporadic?)
    - If yes, outbreak ID

Classification

- Final case classification (laboratory-confirmed, epidemiologically linked, clinically compatible, discarded)
- Origin of infection (imported, importation-related, endemic, unknown)

Note: The time period of 7–23 days is used to cover both measles and rubella exposure periods.

Congenital rubella syndrome

Demographic information

- Child
  - Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)
  - Unique case identifier
    - Place of residence (city, district and province)
    - Age/date of birth
    - Gender
    - Age when case detected
  - Race and/or ethnicity, if appropriate in country setting
  - Country of birth
- Mother
  - Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)
  - Age at birth of affected child
  - Country of birth (to aid in determination of mother's rubella vaccination status)

Reporting information

- Place of reporting (e.g. name of health facility, county, district)
- Date of notification
- Date of investigation

Clinical

- Health-care worker suspects CRS?
- Signs and symptoms
  - Cataracts (unilateral, bilateral)
  - Hearing impairment
  - Developmental delay
  - Congenital heart defect (please specify)
  - Congenital glaucoma
  - Pigmentary retinopathy
  - Purpura
  - Radiolucent bone disease
  - Hepatosplenomegaly
  - Meningoencephalitis
  - Microcephaly
  - Jaundice < 24 hours from birth
  - Other
- Outcome (patient survived, died, unknown)
  - Date of death

Laboratory methods and results (performed on infant)

- Types of specimen(s) collected
- Date(s) of specimen(s) collection

- Date(s) specimen(s) sent to laboratory
- Date(s) specimen(s) received in laboratory
- Serology and/or viral detection results for each specimen type
- Genotype
- Follow-up specimen collection number 1: type, date, result
- Follow-up specimen collection number 2: type, date, result

Maternal history

- Gravida (number of pregnancies)
- Para (number of pregnancies carried to viable gestational age)
- History of rubella-like illness during pregnancy?
    - If yes, months (or weeks) of gestation
    - Was rubella diagnosed by a health-care worker at the time of illness?
        - If yes, confirmed by laboratory?
    - Identified as part of pregnancy tracking register?
- Was the mother directly in contact with someone with confirmed rubella during pregnancy?
    - If yes, what month of gestation?
- Vaccination history of mother
    - Number of doses of rubella-containing vaccine given
    - Dates of vaccination

Location and exposure history

- If location of exposure unknown, did the mother travel outside the country of residence during pregnancy? (If yes, list countries visited and month of gestation)

Classification

- Final case classification (laboratory-confirmed CRS, clinically compatible CRS, discarded)
- Origin of infection (imported, endemic, unknown)

1.8.2 Reporting requirements and recommendations

1.8.2.1 Reporting at national level

Measles and rubella

All reported suspected cases should be classified based on epidemiological and laboratory investigations. Case-based data on all suspected cases should be reported and analysed, regardless of final classification, from local to national level, to allow for adequate understanding of disease epidemiology and surveillance performance. Measles and rubella cases should be reported regularly to the next level within the national public health system structures (at least monthly, preferably weekly). Reporting should include zero reporting (reporting to confirm that no suspected cases have been detected during the designated reporting time period). Annexed to this document is an example of a measles and rubella case investigation and reporting form (annex 1) and a measles and rubella outbreak reporting form (annex 2). These are provided for the reader's information, knowing that countries already created similar documents and

databases, mostly incorporating WHO recommendations, and synchronizing procedures in the Region. It is emphasized that in counting cases, the inclusion of clinically confirmed cases among the total cases introduces uncertainty about the rigor with which the surveillance of cases was conducted. In addition, in countries nearing elimination or those having achieved elimination, the accuracy of diagnosis of measles or rubella based solely upon clinically compatible symptoms (Koplik's spots may be an exception for measles) may be quite low.

National surveillance systems should further classify all confirmed cases to determine the proportion of cases attributable to programme failure – that is, cases in persons who should have been vaccinated according to the national schedule but were not. Even in outbreaks this should be strived for, though it might not be feasible due to the large number of cases. A programmatically preventable measles or rubella case is a confirmed case for whom the vaccine was indicated based on the national immunization schedule, but who did not receive the recommended doses. A programmatically non-preventable measles or rubella case is a confirmed case who had been appropriately vaccinated as per the national schedule, or for whom vaccine is not routinely recommended. This distinction can help immunization programmes determine the need to improve delivery of recommended measles- and rubella-containing vaccines or change the national policy, such as adjusting the timing of vaccination doses.

Congenital rubella syndrome

CRS cases should be reported separately from postnatal rubella cases. The clinician should transmit the case notification form or set of core information to the local epidemiologist or public health personnel. After case investigation is completed, case-based data should be transmitted from local levels to higher administrative levels of the surveillance system, including to the national level/ministry of health. Annex 3 provides an example of a CRS case investigation and reporting form.

1.8.2.2 Reporting to WHO

The objectives of reporting to WHO are to:

- provide a standardized, up-to-date and complete picture of the epidemiology of measles and rubella in the Region to indicate the burden they place on population and public health system, and to facilitate response and control measures when such intervention from WHO is needed.
- identify more precisely the geographic areas and populations where actions are needed e.g. low coverage in districts or in particular risk groups.
- ensure timely dissemination of critical and accurate information about infectious diseases among public health professionals.

Reporting data on measles and rubella is in line with regional decisions and agreements at Regional Committee resolutions on measles and rubella elimination with the aim of enabling monitoring of progress towards these goals. All countries should submit monthly case-based data to the Regional Office through the WHO Immunization Information System (WIISE) *(35)*.

Annex 4 shows the standard template for reporting such data to the WHO Regional Office for Europe. To avoid duplication of data reporting, countries belonging to the European Union and European Economic Area provide their data to the regional office through The European Surveillance System (TESSy) of the European Centre for Disease Prevention and Control (ECDC) *(36)*. Complete and accurate data from all suspected cases including laboratory-confirmed, epidemiologically linked, clinically compatible and discarded cases should be included in the reports. In the absence of disease, countries should provide monthly zero reports.

In addition, measles and rubella laboratory data are reported monthly to the WHO Regional Office for Europe as part of WHO measles rubella laboratory accreditation programme. At the time of publication of this document, data is reported mainly as aggregated laboratory indicators and there is no linkage with epidemiological surveillance data. A limited number of laboratories are reporting specimen-based data to the online Measles and Rubella Laboratory Data Management System platform *(37)*. Generalization of specimen-based data reporting is planned as part of WIISE system implementation in the Region. Genotyping data is reported to the WHO MeaNS and RubeNS databases *(38,39)* hosted by the United Kingdom Health Security Agency.

Every year, WHO requests its Member States to submit reports of cases of measles, rubella and CRS through the electronic Joint Reporting Form (eJRF). Measles and rubella are not currently notifiable diseases under the International Health Regulations (IHR) (2005); however, measles outbreaks may be considered as events involving epidemic-prone diseases of special national or regional concern that have demonstrated the ability to cause serious public health impact and to spread rapidly internationally. As such, they may be reported through IHR mechanisms. CRS is also not a currently reportable condition under the IHR.

1.8.3 Recommended data analyses

To understand the epidemiological situation and for the purposes of verification of measles and rubella elimination the following analyses are recommended.

Measles and rubella

- Number of suspected and confirmed cases by age, date of onset (month and year at a minimum, by week in outbreak settings) and geographic area.
- Incidence per million population by 12-month period and geographic area (because of seasonality, it is not appropriate to calculate incidence for shorter periods of time).
- Age-specific, sex-specific and district-specific incidence rates.
- Measles or rubella vaccine status among confirmed and discarded cases by year and geographic area.

- Proportion of confirmed cases by age group and immunization status. Suggested age groups are < 6 months, 6–8 months, 9–11 months, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–44 years, ≥ 45 years, but the age groups should be based on the epidemiology of the disease, vaccination schedule and history of the vaccine programme.
- Proportion of cases by final classification and origin of infection.
- Proportion of complications and death, stratified by age.
- Proportion of cases that are preventable (e.g. age ≥ age of first recommended dose), separated into vaccine failures and programmatic failures; proportion of cases not preventable by vaccination (age below that of first recommended dose).
- For rubella, include the number and proportion of rubella cases in pregnant women by trimester of exposure.

Epidemiological and genomic data can be used to create phylogenetic trees and visual illustrations of the spatial and temporal distribution of cases as well as chains of transmission *(25)*. Examples of such visuals include:

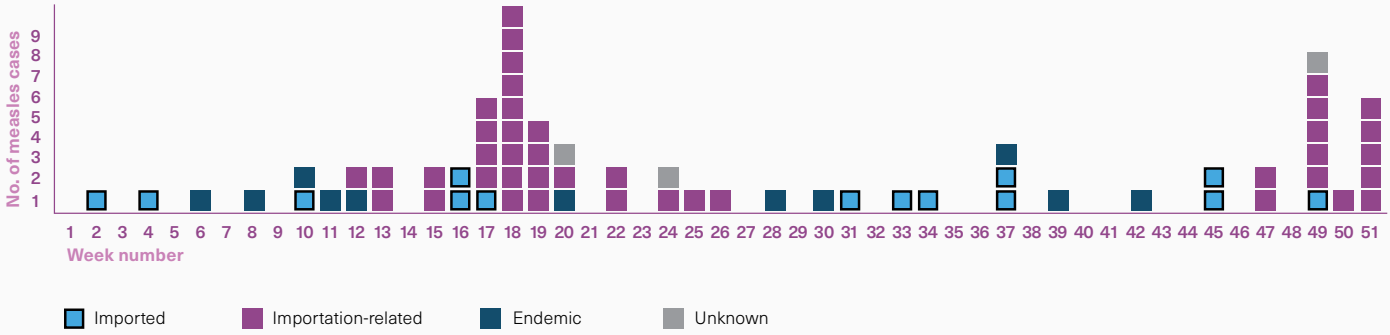
- Epidemic curve showing cases over time by genotype/named strain (Fig. 7).
- Genomic data over time (Fig. 8).
- Maps showing geographical distribution of cases by genotype/sequence variant (Fig. 9).

Congenital rubella syndrome

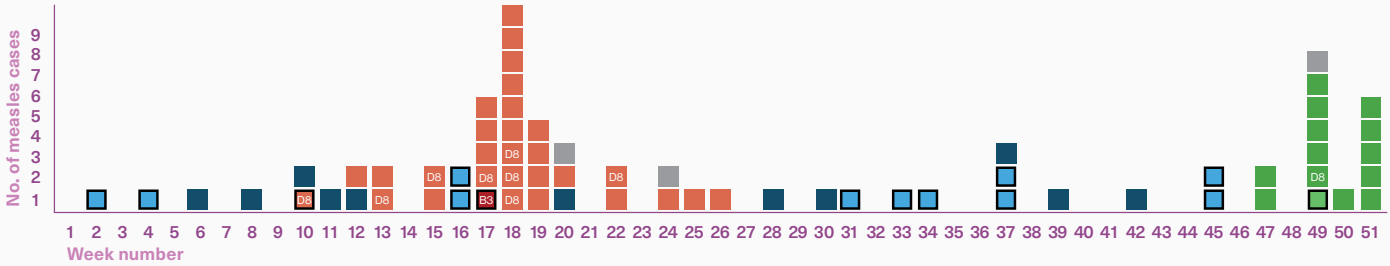
- Final case counts by final case classification, month/year and geographic area (province, district, etc.).
- Confirmed cases by source of infection (import, importation-related, unknown, endemic).
- CRS incidence (number of CRS cases per 1000 live births) by year.
- Clinical characteristics (types of birth defects) and outcome of CRS cases.
- Maternal characteristics including age group, race/ethnicity, country of birth, location of exposure, vaccination status, gravida/para.
- Number of CRS cases with maternal history of rubella-like illness in pregnancy (including month or week of gestation during illness, whether this was clinically compatible or laboratory-confirmed, and whether she was included in a pregnancy registry).
- Proportion of cases clustered or associated with a rubella outbreak.
- Spot maps of confirmed CRS cases by year.
- Age of CRS case at time of diagnosis (< 1 month, 1–5 months, 6–11 months).
- Number of infants diagnosed with CRS with follow-up virological specimens collected to confirm clearance of virus.
- CRS surveillance data should be triangulated with rubella surveillance data. For instance, after a rubella outbreak in women of childbearing age, there may be an increase in CRS cases in the same area in the following months (typically 6–8 months later).

Fig. 7.
Example of an epidemic curve of measles outbreak by source, week of onset and genotype

Example 1



Example 2



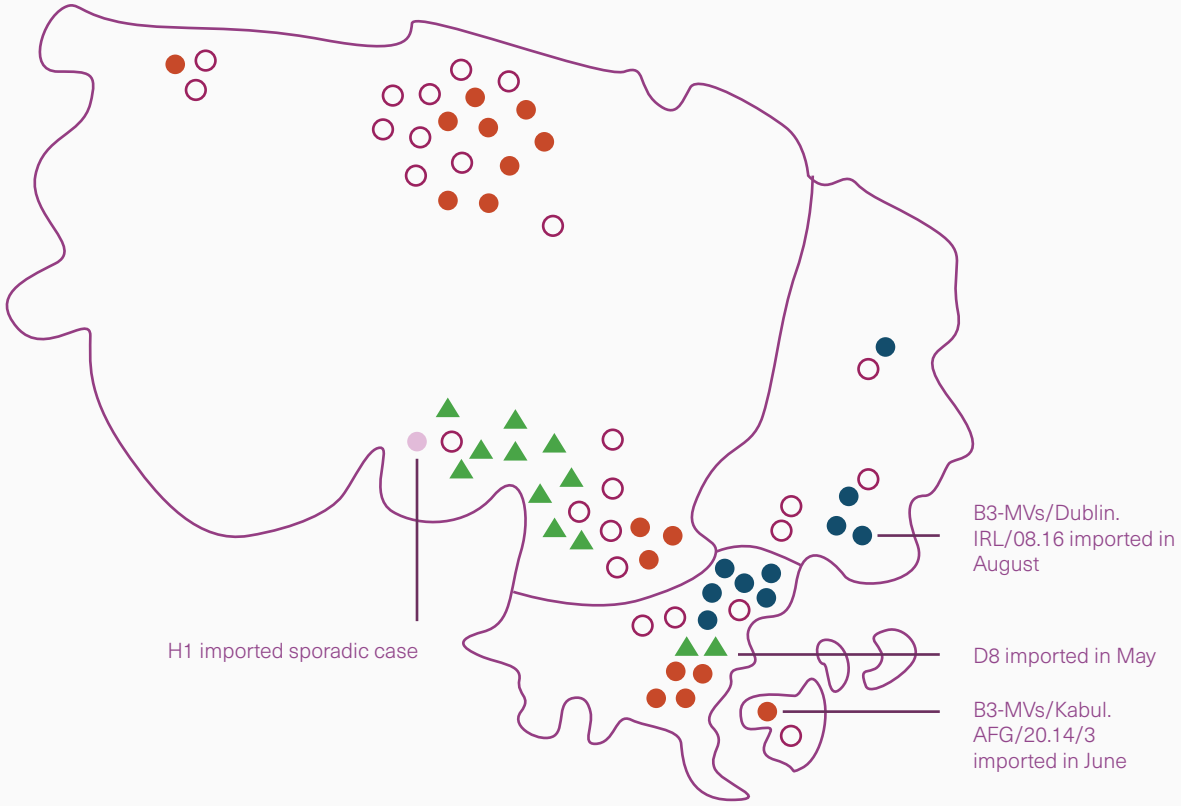
Imported case	History of travel during incubation period but no virological information available
Imported D8 case	History of travel during incubation period and genotype identified as D8
Importation-related D8 case	Case belonging to the same chain of transmission as the imported D8 case above based on epidemiological linkage and virological information
Importation-related case belonging to the first D8 chain of transmission	Case without virological information belonging to the same chain of transmission based on epidemiological linkage to first D8 case/chain of transmission
Importation-related D8 case belonging to a second D8 chain of transmission	No history of travel during incubation period but genotype identified and epidemiologically linked to a case belonging to a second chain of transmission of D8
Imported case epidemiologically linked to the second D8 case	Case without virological information but with a history of travel during incubation period and epidemiologically linked to the D8 case in the second chain of transmission
Importation-related case belonging to the second D8 chain of transmission	Case without virological information belonging to the same chain of transmission based on epidemiological linkage to second D8 case/chain of transmission
Imported B3 case	History of travel during incubation period and genotype identified
Unknown	No data on importation status, no virological information and no epidemiological linkage to another case/chain
Sporadic case not imported and not linked to any case/chain	No history of travel during incubation period, no virological information and no epidemiological linkage to another case/chain

Fig. 8.
Example showing the predominant measles virus sequence variants in Germany by federal state and week of onset.

Variant	2016				2017												Federal State
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
B3-4686		1															Sachsen-Anhalt
		1	14	2	1												Thüringen
				2	2												Rheinland-Pfalz
						1											Hamburg
B3-4751					8	5	1										Sachsen
					2	1											Baden-Württemberg
							1										Sachsen-Anhalt
B3-4299, MVs/ Dublin.IRL/ 08.16					2	1	8		1	1							Baden-Württemberg
						1	1										Saarland
						5	7	16	27	9	5	4					Nordrhein-Westfalen
						1			2								Sachsen
						1					5	2	2				Berlin
							1										Hamburg
			1				1		6				1			6	Bayern
											1	1	1				Brandenburg
												3					Sachsen-Anhalt
												1					Mecklenburg-Vorpommern
											2	7			1		Niedersachsen
													7				Hessen
D4221-8, MVs/ Osaka.JPN/ 29.15					2	4											Hessen
					1												Baden-Württemberg
	1						1	1									Bayern
		1								1			1				Nordrhein-Westfalen
	3										1	1	1				Berlin
													1				Rheinland-Pfalz
D8-2283, MVi/Hulu Langat.MYS/ 26.11			2														Saarland
				1													Brandenburg
					6	6	1										Berlin
						3											Baden-Württemberg
D8-4807						9	12	1									Hessen
						2	1		1								Rheinland-Pfalz
						1	1	1									Nordrhein-Westfalen
								1									Baden-Württemberg

The number of detected cases is given in each field. Sample collection date as of 31st December 2017.

Fig. 9.
Example showing the geographical distribution of measles cases by genotype/variant in a country



- B3-MVs/Dublin.IRL/08.16 (related to June import)
- B3-MVs/Kabul.AFG/20.14/3 (related to August import)
- D8
- H1
- Non-genotyped

This figure shows the distribution of genotyped and non-genotyped measles cases in a fictitious country. In this scenario 4 imported cases where identified belonging to 3 different genotypes: 2 cases were B3 (one imported in June and one in August), 1 case was D8 and one case was H1.

Epidemiological investigation combined with molecular typing of the measles viruses could identify two different N-450 variants of B3 genotype imported on two occasions (one in June and one in August) giving rise to 2 different chains of transmission of the same B3 genotype each with a different named strain: B3-MVs/Dublin.IRL/08.16 and B3-MVs/Kabul.AFG/20.14/3. The B3-MVs/Dublin.IRL/08.16 outbreak imported in August has spread to remote areas of the country.

1.8.4 Using data for decision-making

Regular epidemiological analysis and synthesis of data informed by local knowledge of the context should be conducted in order to capture patterns of disease and identify any immunity gaps. Such analysis will provide insight into the likelihood of future issues requiring similar interventions and indicate whether control or elimination status can be sustained using these methods. The synthesis and interpretation should include an epidemiological description of who is infecting whom, particularly with respect to the source of infection for infants, and where immunity gaps seem to be most evident among birth cohorts or underserved populations. Such a synthesis should be derived from and informed by the analysis of surveillance data. The most important uses of data are the following:

- evaluation of cases and outbreaks to guide immediate action to prevent further transmission;
- identification of the proportion of endemic and imported/importation-related cases;
- description of the predominate transmission patterns (e.g. infection among infants under 12 months of age; hospital- or institution-acquired infections and outbreaks); evaluation of the effectiveness of actions taken to interrupt transmission and reduce future occurrences;
- evaluation of the risk factors for infection, complications and death and the effectiveness of measures taken to eliminate or decrease these risks;
- identification of potential immunity gaps based on risk factors for infection within the affected population; determination of whether such gaps exist among culturally diverse groups or birth cohorts in order to tailor messages, target vaccination efforts and/or adjust the vaccination programme;
- evaluation of the sustainability of progress towards elimination or maintenance of existing disease elimination with current resources and surveillance.

The following specific recommendations apply to analyses of surveillance data for rubella:

- epidemiology should be reviewed, especially age distribution of rubella cases, alongside CRS epidemiology to see if modifications in vaccination strategy should be considered. A shift of rubella infection to older children and young adults can signal an impending risk of CRS if the immunity gap is not filled through enhanced vaccination coverage;
- the risk of exposure among women of childbearing age should be determined, as should the potential burden of CRS-related disabilities that could occur in the affected population;
- because 20–50% of rubella cases are subclinical, analyses of data from rubella surveillance should be complemented with CRS surveillance data to provide a more in-depth understanding of rubella epidemiology in the country.

The following specific recommendations apply to analyses of surveillance data for CRS:

- the burden of CRS prior to rubella vaccine introduction should be documented;
- the impact of rubella vaccine introduction in reducing the incidence of CRS should be monitored;
- the epidemiology of CRS and its burden in the population should be evaluated in order to guide rubella immunization strategies, including the need to address immunity gaps in adolescents and young adults;

- risk factors for CRS should be determined, such as women of childbearing age who may have migrated from a country where rubella vaccine has not yet been introduced or was only recently introduced;
- in conjunction with rubella surveillance data, the accumulated epidemiological evidence (and corresponding genetic data) should be utilized to document the progress towards achieving or maintaining rubella elimination goals.

1.9 Surveillance performance indicators

Measles and rubella surveillance should be evaluated routinely at national and subnational/local levels; these assessments are frequently important in decision-making by national verification committees and the Regional Verification Commission for Measles and Rubella Elimination. It is recommended that countries review their national measles and rubella surveillance system annually as the country approaches, achieves and sustains elimination. Additionally, measles and rubella surveillance should be reviewed within the context of comprehensive vaccine-preventable diseases surveillance reviews, which should be conducted at least every five years.

Tables 3a and 3b list indicators established by WHO, against which the measles and rubella surveillance system can be evaluated to help pinpoint problems and make improvements.

Table 3a. Indicators of the quality of surveillance for measles and rubella

Surveillance attribute	Indicator	Target	How to calculate indicator	Comments
Timeliness of reporting	Percentage of measles or rubella routine surveillance reports[a] submitted to the national level by the deadline[b] (T)	≥ 80%	(A/B) * 100 = T A = number of reports submitted by deadline B = number of expected reports	At each level, reports should be received on or before the requested date.
Completeness of reporting	Percentage of measles or rubella routine surveillance reports[a] submitted to the national level (C)	100%	(D/B) * 100 = C D = number of submitted reports B = number of expected reports	
Timeliness of investigation	Percentage of suspected measles or rubella cases with an adequate investigation[c] initiated within 48 hours of notification (H)	≥ 80%	(F/G) * 100 = H F = number of suspected cases of measles or rubella for which an adequate investigation was initiated within 48 hours of notification G = number of suspected measles or rubella cases	
Origin of infection	Percentage of measles or rubella cases for which origin of infection has been identified (imported, importation-related or endemic) (in %) (O)	≥ 80%	(J/K) * 100 = O J = number of measles or rubella cases for which the origin of infection has been identified (imported, importation-related or endemic) K = number of measles or rubella cases	Unknown origin should be kept to a minimum but will continue to occur even with thorough field investigations. This target might not be achievable in large outbreaks.
Rate of laboratory investigations	Percentage of suspected cases of measles or rubella with adequate specimens[d] collected and tested in a WHO-accredited or proficient laboratory[e] (N)	≥ 80%	M/G * 100 = N M = number of suspected measles or rubella cases with adequate specimens collected and tested in a proficient laboratory G = number of suspected measles or rubella cases	Exclude from the denominator any suspected cases not tested by a laboratory and (a) confirmed by epidemiological linkage, or (b) discarded as non-measles/ non-rubella by epidemiological linkage to a laboratory-confirmed case of another communicable disease or epidemiological linkage to a measles or rubella IgM-negative case.

Table 3a. Continued

Surveillance attribute	Indicator	Target	How to calculate indicator	Comments
Viral characterization	Percentage of laboratory-confirmed outbreaks (chains of transmission) or sporadic cases from which samples were obtained and sequenced in an accredited or proficient laboratory[e] (in %) (V1, V2)	≥ 80% for outbreaks (chains of transmission)	(U1/W1) * 100 = V1 U1 = number of outbreaks (chains of transmission) from which samples were obtained and sequenced in an accredited laboratory W1 = number of outbreaks (chains of transmission) identified	When possible, samples should be collected from at least 5–10 cases early in a chain of transmission and every 2–3 months thereafter if transmission continues, and from all sporadic cases. Ideally all sporadic cases should be genotyped in countries that are approaching elimination or have already achieved elimination.
		≥ 80% for sporadic cases	(U2/W2) * 100 = V2 U2 = number of sporadic cases from which samples were obtained and sequenced in an accredited laboratory W2 = number of sporadic cases identified	
Rate of discarded cases	The rate of suspected measles or rubella cases investigated and discarded as non-measles or non-rubella cases using laboratory testing in an accredited or proficient laboratory[e] and/or epidemiological linkage to another confirmed disease (rate per 100 000 population) (D)	≥ 2/100 000 population	(X/P) * 100 000 = D X = number of suspected cases that have been investigated and discarded as a non-measles or non-rubella case using: (a) laboratory testing in a proficient laboratory or (b) epidemiological linkage to a laboratory-confirmed outbreak of another communicable disease that is neither measles nor rubella in a 12-month period P = national population	
Representativeness of reporting discarded cases	Percentage of subnational administrative units (e.g. province or its administrative equivalent) that report at least 2 discarded non-measles or non-rubella cases per 100 000 population per year (in %) (R)	≥ 80%	(Y/Z) * 100 = R Y = number of subnational administrative units achieving a rate of discarded cases of ≥ 2 per 100 000 population Z = number of subnational administrative units	If the administrative unit has a population < 100 000, the rate should be calculated by combining data over more than 1 year for a given administrative unit to achieve ≥ 100 000 person-years of observation, or neighbouring administrative units can be combined for the purpose of this calculation. Administrative units should include all cases reported from their catchment area, including import and importation-related cases, and cases residing in neighbouring administrative units but reported in this one.

Table 3b. Alternative indicators of the quality of surveillance for measles and rubella

Surveillance attribute	Indicator[f]	Target	How to calculate indicator	Comments
Timeliness of notification	Percentage of measles or rubella routine surveillance reports[g] submitted to the national level within 48 hours of rash onset (in %) (Tn)	≥ 80%	(AA/G) * 100 = Tn AA = number of reports submitted within 48 hours G = number of suspected measles or rubella cases	Alternative to timeliness and completeness indicator
Rate of cases that test negative for measles or rubella IgM	The rate of cases of measles or rubella-like illnesses (whose specimens tested IgM negative in an accredited or proficient laboratory[e] (rate per 100 000 population) (Rn)	≥ 2/100 000 population	(BA/P) * 100 000 = Rn BA = of cases of measles or rubella-like illness tested negative for measles or rubella IgM in a proficient laboratory[e] P = national population	Alternative to rate of discarded cases indicator

Notes:

a. Regular monthly or weekly reports, including "zero" reporting to be submitted by each surveillance reporting unit to national level. This does not refer to laboratory reporting of cases.
b. The deadline to submit data for the previous month or week is to be defined by the country.
c. An adequate investigation includes the collection of at least the following essential data elements from each suspected measles or rubella case: case identifier, age (or date of birth), date of rash onset, date of specimen collection and vaccination status. Countries may wish to collect other data that may be important for epidemiological investigation.
d. A single clinical sample obtained at the first contact with the health-care system at any time within 28 days after rash onset is considered adequate for surveillance purposes.
e. A laboratory that is WHO-accredited and/or has an established quality assurance programme with oversight by a WHO-accredited laboratory (see 1.3.5 Additional definitions - Proficient measles and rubella laboratory).
f. The two indicators in Table 3b should be used by countries that are unable to report standard indicators on timeliness of reporting and/or rate of discarded cases as described in Table 3a.
g. Regular monthly or weekly reports, including "zero" reporting to be submitted by each surveillance reporting unit to national level. This does not refer to laboratory reporting of cases.

1.10 Contact tracing

Rapid initiation of contact tracing is critical to assess the potential for transmission, arrange the appropriate resources to investigate the outbreak and take action to control it. Identification of the source of infection and the setting for transmission will be key in indicating how expansive the investigation will need to be and will also often provide important epidemiological information for designation of the origin of the virus (endemic, imported, importation-related). Contact tracing is particularly important in schools due to the intensity of exposure and the presence of nonimmune children. In health-care settings, measles or rubella infection can be amplified with an elevated risk of infection due the presence of vulnerable, susceptible populations such as the very young, the immunocompromised and patients with underlying conditions or receiving treatment for illnesses that can diminish the immune response.

Implementation of measures to reduce severity of infection, protect susceptible populations and limit transmission should be anticipated and initiated immediately upon evaluation of the transmission setting, and the exposed and potentially exposed contacts. An expanded discussion of preventive measures for susceptible contacts is provided in 2.4.2 Contact management.

1.10.1 Measles

Because measles is highly infectious, contact tracing is essential to quickly determine the source of infection for the measles case, as well as identify those whom the case may have subsequently infected. Any person who had contact with the case during the four days before through the four days after rash onset may have been infected and should be monitored by public health authorities for 23 days from last contact with the confirmed case. A contact is defined as anyone, known or unknown to the measles case, that was potentially exposed to measles virus by sharing an enclosed area or room with the case, including at school, in a health facility waiting room, office or shared transportation for any length of time during the case's infectious period. In addition, measles virus can remain viable in the air or on infected surfaces for up to 2 hours, so transmission can occur to individuals who were not in direct contact with the case. Therefore, in some investigations, contacts of a case include anyone who had been in an area (usually an enclosed environment) within 2 hours of when the infectious case was there.

1.10.2 Rubella

Every effort should be made to conduct case investigations and identify contacts for all suspected cases. Persons who have been in contact with a case of rubella during the infectious period (from seven days before through seven days after the rash onset) should be located and interviewed to determine their past exposure and vaccination status. It is important to note that a CRS case can transmit rubella virus. Transmission of rubella from a CRS case is different from an acquired rubella case in that CRS cases may shed rubella virus for up to 12 months from birth. However, exposure for CRS cases is through physical contact

with the case (touching), while exposure from rubella disease is through airborne transmission. Therefore, in the absence of contact with a known rubella case, contact tracing may include questions regarding close physical contact with infants < 12 months old. Contact tracing is essential to identify the individual who was the source of infection for the rubella case and any additional contacts that were potentially exposed to the virus by the source case or the current case under investigation during their respective infectious periods. Any person who had contact with the rubella case (or contact with a confirmed CRS case) during the infectious period could have been exposed and possibly infected and should be monitored by public health authorities for 23 days from the last contact with the confirmed case.

A contact for a rubella case includes individuals living in the same household or sharing other enclosed environments – such as a classroom or school, health facility waiting room, office or transportation – for any length of time with the case during the case's infectious period. Pregnancy status should be determined for each female contact so that appropriate follow-up can be done. Pregnant contacts should be tested for rubella to rule out infection. Those with evidence of infection should be referred to the health-care provider to follow their pregnancy for further management, and if necessary, public health measures.

1.10.3 Congenital rubella syndrome

Contact tracing is recommended for mothers of infants diagnosed with CRS to identify the source of the rubella virus infection of the mother. Infants with CRS shed rubella virus for long periods (60% for the first four months of life, and potentially infectious up to 12 months of age), and appropriate infection control measures should be applied. It is particularly important that pregnant women who are not rubella-immune avoid exposure to infants with CRS. To prevent further infection with rubella virus and further transmission, protective immunity should be assured among contacts of CRS cases, including health-care workers and family members. Persons in contact with the infant should be immune to rubella either through vaccination or natural infection (serological evidence of immunity). Persons who lack documentation of immunity should be vaccinated except pregnant women; pregnant contacts should be tested as outlined in the rubella section above.

2

Outbreak investigation and response guidelines

The purpose of this section is to provide guidance to European Region Member States to facilitate early detection and a rapid and appropriate response to outbreaks of measles or rubella, with the aim of achieving measles and rubella elimination in the Region.

This section provides guidance on:

- confirming and investigating an outbreak, including intensifying surveillance;
- responding to outbreaks, including immunization activities;
- analysing outbreaks and communicating about the response.

The regional guidelines are aligned with the global WHO documents: Measles outbreaks strategic response plan: 2021–2023 *(40)* and Measles outbreak guide *(41)*, which contain more elaborated explanations on outbreak response in different control/elimination settings and circumstances.

2.1 Rationale for investigating measles and rubella outbreaks

In general, the primary reason for an outbreak investigation and response is to control the outbreak and help prevent future occurrences. The objectives of outbreak investigations are to facilitate rapid implementation of control measures to reduce the extent of disease spread and associated morbidity and mortality, and to ensure that virus transmission is interrupted as soon as possible. As the Region works towards achieving elimination, timely outbreak investigation and response becomes one of the most important measures.

Countries should have in place a detailed outbreak response plan before an outbreak occurs. This plan should include how surge capacity will be managed to provide adequate staff for epidemiological investigations and response, as well as supplies and staffing for an increased volume of laboratory testing. The event of an outbreak would serve as an opportunity to test,

evaluate, and modify the plan, as necessary, after the investigation and response. If this plan is not yet in place, investigation and response of eventual outbreaks should be used as a trigger for development of such a plan.

Secondary goals for outbreak investigation and response in countries of the European Region include:

- monitoring the changing transmission and epidemiology of measles and rubella;
- identifying high-risk population subgroups and geographic areas – immunity gaps that call for targeted immunization strategies;
- assisting in the identification and correction of weaknesses in immunization and surveillance systems;
- raising communities' and health-care professionals' awareness of these diseases and their prevention.

Importations of measles and rubella viruses are common and can lead to outbreaks and even re-establish transmission in areas that had previously successfully interrupted endemic transmission.

2.2 Outbreak investigation

Local risk assessments should be conducted such as rapid community surveys and health facility vaccination record review, in outbreak areas, neighbouring villages, health centre catchment areas, districts and provinces, depending on the extent of the outbreak. This includes ensuring that first and second dose measles and rubella vaccination coverage in the area is sufficiently high (≥ 95%) to prevent disease transmission. Children who are unvaccinated or under-vaccinated should receive vaccines through the routine vaccination programme and, if needed, by supplementary immunization activities. In some settings, it may be important to conduct epidemiological studies, such as case-control/cohort studies, to determine vaccine effectiveness or assess risk factors and transmission patterns. These studies may be required to fully investigate the outbreak, complete the epidemiological synthesis, and decide what action is required.

At a minimum, all outbreak investigations should include an evaluation of which age/birth cohorts are most affected and why the affected individuals and communities are unvaccinated, in order to guide the programme in the future. This can be done after, rather than during the outbreak, when many resources are already stretched. In outbreak settings, it is especially important to explore the possibility of other sources of infection (or chains of transmission) that may not be as easily recognized. Surveillance is often focused on reports from health-care facilities; however, not all cases will seek health care. For this reason, it is important to reach out to all contacts of cases with measles or rubella in the affected communities. Information concerning possible exposures they can recall during the relevant time period may be useful to identify additional individuals with measles or rubella who may be contributing to transmission.

The size and duration of outbreaks may be used by national surveillance systems as an indirect indicator of immunity, immunization coverage, quality of surveillance system and adequacy of response and control measures. The information should be interpreted after a thorough outbreak investigation that includes active case-finding and epidemiological linkage of cases.

2.3 Recommendations for outbreak confirmation and investigation

2.3.1 Establishing an outbreak response team

To enhance capacities and facilitate effective outbreak responses with a timely flow of information, an outbreak response team or working group should be established at the appropriate level depending on the extent of the outbreak and existing structure of the health system. Such teams should consist of stakeholders (public health officials, clinicians, local government officials, community representatives, etc.) with defined roles and responsibilities. The functions of this group will be to plan and coordinate all aspects related to outbreak investigation and response and to ensure adequate communication and feedback. Investigation and response should be initiated as soon as an outbreak is suspected.

The steps described below are recommended for the management of suspected measles and rubella outbreaks, including confirmation, investigation, and response. The order of these steps does not necessarily indicate the chronological order of their implementation. Many of these actions will have to be undertaken concurrently as soon as the outbreak is suspected or confirmed.

2.3.2 Definition of an outbreak

In the WHO European Region, outbreaks of measles and rubella are defined as follows:

- Measles outbreak: two or more laboratory-confirmed cases that are temporally related (with date of rash onset occurring between 7 and 23 days apart) and epidemiologically or virologically linked, or both.
- Rubella outbreak: two or more laboratory-confirmed cases that are temporally related (with date of rash onset occurring between 12 and 23 days[4] apart) and epidemiologically or virologically linked or both.

[4] Extending to 46 days for rubella should be considered, since a generation of cases may be missed.

National health authorities in the European Region should consider one laboratory-confirmed case of measles or rubella with one or more temporally related suspected cases to be a potential outbreak. In elimination settings, where endemic virus transmission is absent, it is highly recommended that countries consider a more sensitive definition of an outbreak, such as the presence of a single laboratory-confirmed case of measles (*42)* or rubella (*43)*, to trigger an aggressive public health investigation and response.

An outbreak of measles or rubella is considered over after there have been no further epidemiologically or virologically linked cases for two incubation periods (46 days) from the date of onset of the last case.

2.3.3 Confirming and characterizing the outbreak

Because measles and rubella viral infections have many symptoms in common with each other, as well as other rash illnesses, all suspected measles or rubella outbreaks should be confirmed by laboratory. For individual case confirmation, laboratory confirmation or epidemiological linkage with a laboratory-confirmed case should be sought. Specimens should be collected not only for laboratory confirmation but also for virus characterization to allow identification of the genotype and the variant and to assist in identifying the origin of the virus (endemic versus imported) in combination with epidemiological information. Once the outbreak has been confirmed as measles or rubella, subsequent cases can be primarily confirmed based on epidemiological linkage to a laboratory-confirmed case.

During an outbreak, laboratory confirmation should be sought for the initial 5–10 cases per district (or equivalent administrative unit). However, laboratory confirmation should be sought for all suspected cases of measles and rubella in pregnant women, even if the outbreak is confirmed and regardless of the background incidence or number of previously confirmed cases. If suspected cases are reported outside the initially affected geographic areas and there is no clear epidemiological linkage with the initial outbreak, the first 5–10 suspected cases in these other districts should also be tested to confirm the cause. If the outbreak continues, another 5–10 suspected cases should be tested every 2–3 months, including virus characterization, to confirm that the illness in question is still measles or rubella and to monitor the implicated virus genotype(s).

In outbreaks when measles and rubella are both circulating, laboratory testing may be required for more cases as establishing reliable epidemiological linkages in a mixed outbreak is difficult and creates challenges for final classification. This situation should be assessed and addressed with specific and appropriate protocols by the national public health system, considering its capacities and resources.

Following laboratory confirmation of initial measles and rubella case(s), emphasis should be given to the epidemiological investigation, aimed at confirmation of new cases by epidemiological linkage with the laboratory-confirmed case. Sometimes a situation may arise

in which some clusters of suspected cases are not confirmed either by laboratory testing or by epidemiological linkage. In such situations, the cases from these clusters, which cannot be discarded, should be classified as clinically compatible and included in the overall case count for the outbreak and incidence calculation.

2.3.4 Intensifying surveillance

Surveillance should be intensified to ascertain the size and geographic extent of the outbreak. Surveillance measures should be primarily directed at identifying cases prospectively. This usually involves implementation of active surveillance (i.e. active case finding), in addition to existing passive surveillance systems. However, the investigation should also include efforts to retrospectively find any cases that preceded the first reported case to help determine the time and circumstances of the beginning of the outbreak and better assess its full extent.

Confirmation of the first measles or rubella case should be followed by official communication from the public health authorities to health-care workers or reporting units of the surveillance system. This notice should emphasize the appropriate surveillance activities, including increasing awareness and intensifying surveillance to detect any suspected cases, and outbreak response measures. Health-care workers and surveillance units that have already reported cases should be reminded to follow up on contacts of the cases. Similar messages should be shared with laboratories, to increase their awareness of the current epidemiological situation and the possible increase in laboratory workload. Regular update reports on measles and rubella outbreaks should also be sent to health-care facilities with in-patient care (e.g. hospitals), to also remind them of the risk of nosocomial spread and the need for triage and implementation of infection prevention measures.

2.3.5 Reporting

Once the outbreak is suspected, the frequency of reporting (cases and zero reporting in the absence of cases) should be increased to at least weekly regardless of frequency of reporting prior to the outbreak. If timely case-based reporting during an outbreak is not feasible because of the large number of cases, case-based data should still be collected and reported as soon as it becomes feasible.

Health workers should be alerted about the outbreak and given instructions on where to report suspected cases. Weekly reporting should continue for the duration of the outbreak and for at least two incubation periods (46 days) after the onset of the last laboratory-confirmed or epidemiologically linked case.

If the number of cases is large, line-listing of case-based data can be used to collect key data elements, and the number of elements required to be collected for each individual case may be reduced. However, at a minimum a unique identifier, name, age, clinical symptoms, date of rash onset, date of specimen collection, vaccination status, travel history and place of residence

should be collected. When possible, an outbreak identifier should also be assigned to all cases associated with an outbreak. More detailed information such as potential sources of infection (medical settings, school settings, etc.) should be collected on a sample of cases to help determine major transmitters and transmission settings.

Collecting detailed data during an outbreak and reporting on it usually entails a significant increase in work burden. Standardization of data reporting and recording in line-lists can help increasing efficiency of data collection, reporting and analysis. Unfortunately, conflicting priorities often do not allow adequate outbreak analysis. Adequate outbreak analyses can provide the reasons giving rise to the outbreaks and lessons to be learnt during outbreak investigation and response. In addition, it is important to have an evaluation of an outbreak response to identify gaps and areas for improvement. An example of a measles and rubella outbreak reporting form is found in annex 2.

2.3.6 Active case finding

Along with increased frequency of reporting, active case finding should be implemented through regular visits by the outbreak response team to health facilities (both public and private) to review medical records. Surveillance should include population groups at high risk of disease transmission and congregate settings, such as day-care centres, schools, universities, military installations and workplaces. For measles, any mass event should be assessed against the risk of further spread and if feasible participants should be alerted and involved in surveillance (e.g. self-reporting). Thorough follow-up investigation of patient contacts, including household residents, classmates, and teachers, may help identify additional cases. A review of available vaccination coverage data and community demographic information can help to determine if there are high-risk groups in the area of the outbreak. Comprehensive epidemiological investigation during outbreaks requires significant human and financial resources. Having adequate protocols and outbreak response guidelines in place may help to facilitate mobilization of existing resources and engagement of additional resources.

2.3.7 Information sharing with neighbouring areas and globally

Neighbouring geographic regions and countries should be notified of any confirmed outbreaks so that they can assess the need for enhanced surveillance and targeted vaccination activities in their territory. Sharing of information with neighbouring countries is important in prevention and response to multi-country outbreaks. In addition, international exchange of health information on significant outbreaks occurring worldwide should be used to heighten surveillance (for cases of measles in particular) and for communication purposes.

2.3.8 Special considerations for rubella outbreak investigations

An increase in CRS cases generally occurs 6–8 months after an outbreak of rubella infection. Detecting an increase in CRS cases can be a signal for wider rubella virus circulation in the population, indicating the possible occurrence of a past or current rubella outbreak. In the case of a rubella outbreak, active CRS surveillance should be established or strengthened in maternity and paediatric hospitals, neonatal intensive care units and among specialists who treat infants with cardiac, hearing or eye problems. Hospitals located in the area where the outbreak is occurring should be prioritized and if not already a sentinel site should be included in surveillance and response activities for the duration of the outbreak.

If a passive surveillance system for CRS is in place, it should be enhanced with active case finding in facilities located in outbreak areas. This can help identify infants with CRS who are shedding live rubella virus and prolonging the outbreak. CRS surveillance should continue for a minimum of nine months after the last rubella case.

During rubella outbreaks, a pregnancy registry should be established, if not already in place, to document all pregnancy outcomes of infected and exposed women. Outcomes include miscarriages, fetal deaths, CRS cases, infants with CRI and unaffected infants.

2.3.9 Conducting case investigations

Efforts should be made to conduct case investigations and identify contacts for all suspected cases of measles and rubella. The case investigation should be initiated immediately (no later than 48 hours) after notification and include collection of demographics, epidemiological, immunization and clinical data about the case. An example of a measles and rubella case investigation form is found in annex 1. Anyone who has been in contact with cases of measles or rubella during the infectious period should be located and interviewed to determine their vaccination status and to offer them immunoglobulin prophylaxis or vaccination, as appropriate. Pregnancy status should be determined for each case and contact so that appropriate follow-up of pregnant women exposed to rubella can be conducted.

In an outbreak situation, cases may occur among recently vaccinated persons if they were infected before or shortly after vaccination. It is important to distinguish between wild virus infections and vaccine reactions. Usually a vaccine reaction (rash/fever) is due to the measles component of the vaccine and there are no respiratory symptoms. Suspected cases of measles or rubella occurring in vaccinated persons 7–14 days after vaccination need to be investigated regarding possible contact with a confirmed case, and where possible, specimens for virus detection should be obtained for genetic testing to discriminate between wild type virus and vaccine virus. If the rash is attributable to vaccine virus as demonstrated by genetic testing, no further investigation is warranted, and the suspected case should be discarded. For further information on criteria to be applied when a vaccine-related rash is suspected from an individual with a positive IgM result (see 1.3.5 Additional definitions – Measles vaccine-associated reaction).

When outbreaks become too large to maintain normal case investigation protocols, contact tracing should be deprioritized and a larger public health response to prevent further transmission should be prioritized.

2.3.10 Ongoing descriptive analysis of the outbreak data

Analysis of outbreak data allows health agencies to guide the outbreak response activities, especially vaccination, and helps to focus the response on groups most in need. To maximize the impact and minimize delays, the analysis should be performed not only at the national, but at district and provincial levels as well. Epidemiological data should be analysed rapidly to identify vulnerable groups with low vaccine coverage and target responsive immunization activities appropriately. The basic analysis should describe cases by person, place and time and include case distribution and incidence over time (for example weekly) and categorize cases by age group, gender, immunization status and geographic area. Any additional information to help identify the most severely affected groups and reasons for their susceptibility should also be reviewed and analysed.

2.3.11 Reporting outbreaks to WHO

All outbreaks of measles and rubella should be reported to the WHO Regional Office for Europe. As measles and rubella elimination is the regional target, timely sharing of information on outbreaks of these diseases with other countries in the European Region, using the Regional Office's mechanisms, is important for promptly enhancing surveillance activities and responding to cross-border transmission. Use of the IHR notification and reporting procedures may become more relevant in the context of international public health concern and measles outbreaks may be increasingly classified as events potentially leading to a public health emergency of international concern.

Member States should provide information about individual cases in the outbreak by submitting the data included in the measles–rubella case investigation forms, collected in accordance with routine surveillance. In addition, countries should provide information describing the outbreak, including data on affected populations and response measures implemented, to WHO using as an example the measles and rubella outbreak report form (annex 2) or any national form used. All classification categories of measles and rubella, including discarded cases, should be reported. The initial notification, using the outbreak report form completed with information available at the time, should be submitted early in the outbreak. When the outbreak is over and the data analysis is completed, an updated final outbreak report form should also be submitted to WHO.

2.4 Recommendations for outbreak response

To enhance capacities and facilitate effective outbreak responses with a timely flow of information, an outbreak response team or working group should be established at the appropriate level depending on the extent of the outbreak and existing structure of the health system. Such teams should consist of stakeholders (public health officials, clinicians, local government officials, community representatives, etc.) with defined roles and responsibilities. The functions of this group will be to plan and coordinate all aspects related to outbreak investigation and response and to ensure adequate communication and feedback. Investigation and response should be initiated as soon as an outbreak is suspected.

The steps described below are recommended for the management of suspected measles and rubella outbreaks, including confirmation, investigation, and response. The order of these steps does not necessarily indicate the chronological order of their implementation. Many of these actions will have to be undertaken concurrently as soon as the outbreak is suspected or confirmed.

2.4.1 Isolation of cases

To minimize transmission of the virus, suspected cases should be isolated immediately upon identification. Isolation should continue through the putative infectious period (four days after the rash onset for measles, seven days after for rubella) or until both measles and rubella are ruled out by laboratory testing. Although isolation and social distancing are important components of outbreak control, they are not sufficient alone for controlling measles and rubella outbreaks and should be used in combination with other measures, such as immunization.

2.4.2 Contact management

Persons who have been exposed to a measles or rubella case during the infectious period (for measles, from four days before rash onset through four days after rash onset; for rubella, seven days before and seven days after rash onset) should be identified and followed up. The investigation should include an assessment of the contact's susceptibility to measles/rubella, overall health status and risk factors for severe illness. Among women of childbearing age, pregnancy status should be assessed.

Persons with no history of laboratory-confirmed measles or rubella, and without immunization records indicating receipt of the age-appropriate number of doses of measles- and rubella-containing vaccine or who do not show serological evidence of immunity (presence of IgG antibodies to measles or rubella) should be considered susceptible. In some countries, persons born prior to a certain time (likely infected prior to vaccine introduction) are considered immune (e.g. in the United States of America, those born before 1957). This determination is usually based on disease epidemiology and the history of the measles and rubella immunization programme in the country. However, if epidemiological investigation of

the ongoing outbreak indicates susceptibility in those age cohorts expected to have immunity from natural disease, adequate interventions should be considered.

Contacts at high risk for severe measles disease (i.e. children aged < 5 years and adults; persons living in crowded conditions; persons with immunosuppression and/or malnutrition and/or vitamin A deficiency) should be evaluated and receive appropriate preventive measures.

Vaccination and use of immunoglobulin

Susceptible contacts, who are age-eligible and have no contraindications to measles- and rubella- containing vaccines, should be vaccinated as soon as possible after being exposed to measles or rubella as doing so may prevent later disease. If indicated, a second dose should be given at least 28 days after the receipt of the first dose of the vaccine. There is no upper age limit for immunization with measles- and rubella-containing vaccines.

Measles

Unvaccinated contacts ≥ 6 months of age who are eligible for vaccination should be vaccinated as a prophylaxis, if possible, within 72 hours of exposure. This can prevent or modify the symptoms of measles infection. Any doses given at an age younger than that recommended for the routine first dose of a measles-containing vaccine (MCV1) at 9–12 months of age, are referred to as MCV0 (zero) and do not count as MCV1. The two MCV doses should still be administered as recommended by the national immunization schedule.

For contacts that have contraindications to measles vaccine, human immunoglobulin may be administered intramuscularly within six days of exposure. This includes pregnant women, infants < 6 months of age and individuals with impaired immune systems. All individuals exposed in settings with prolonged close contact and hence high force of infection (e.g. households, day-care centres, classrooms, etc.) may also be considered for measles immunoglobulin prophylaxis. If administered within six days of exposure, this method of passive immunization can prevent illness or reduce its severity. Current recommendations for dose calculations vary by country, although they are all calculated according to body weight.

Rubella

Vaccination can be given in the first 48 hours after exposure to non-pregnant contacts who have no documented protection against rubella. Administration of immunoglobulin within 72 hours of exposure to rubella might modify or suppress symptoms, and decrease viral shedding and the rate of viraemia in those exposed to infection. However, it does not usually prevent infection and is therefore not recommended for routine post-exposure prophylaxis of rubella. Immunoglobulin may be considered for pregnant women exposed to infection. However, infants with congenital rubella have been born to women who received immunoglobulin shortly after exposure.

2.4.3 Immunization activities in response to an outbreak

Outbreak response immunization (ORI) is indicated for confirmed measles or rubella outbreaks. Immunization efforts in an outbreak setting are aimed at reducing the extent and duration of the outbreak and helping to interrupt transmission by raising population immunity. When deciding on the need for immunization activities, the specific target group(s) and the most appropriate strategies for outbreak response immunization, several considerations are relevant. It is important to consider the results of the assessment of risk of a large-scale outbreak, financial and human resources, vaccine availability, the regulatory framework, and the attitude towards immunization and the disease among potential target groups and health-care workers. The potential impact of the intervention will be greater if implemented early in the outbreak and in settings with a substantial proportion of susceptible individuals, where the risk of widespread transmission is higher.

The type of immunization response should be guided by an assessment of the potential scale of transmission and the populations at risk. An assessment of outbreak risk should occur periodically during periods of low transmission, to guide preparedness. Population susceptibility should be the focus of this assessment, using current and historical data on immunization programme policies and performance, vaccination coverage (by age and sex) by routine and by supplementary immunization activities (SIAs), as well as serological data on population susceptibility (if available). In addition, analysis of disease epidemiology in recent years, population characteristics (size, density and movement), availability of and access to health services and the existence of any special circumstances (e.g. reform of the health system, changes of immunization and surveillance regulations, recent conflict situations or civil disturbances and issues with vaccine acceptance) should be considered. After an outbreak has been detected, evaluation of the outbreak characteristics (age, gender, immunization status of cases, particular subpopulation or territory affected, etc.) provides information on the specific populations and exposures that are main drivers of transmission.

2.4.4 Immunization of susceptible contacts

Immunization of susceptible contacts will be a necessary intervention at a minimum. This may only be sufficient for limiting the spread of the virus in settings with uniformly very high coverage, where the risk of subsequent transmission is low. Usually, this applies to outbreaks following importations into countries/areas which have achieved these high levels of population immunity through successful routine immunization programmes over prolonged periods of time and/or through SIAs, and thus may have interrupted endemic transmission. When considering the decision to limit immunization to susceptible contacts, it is vital to consider that the capacity for strong surveillance and contact follow-up is critical for this approach to be successful.

In most settings, however, it will be necessary to expand outbreak response immunization beyond susceptible contacts. This can be done through selective or non-selective immunization of the most affected and/or at-risk populations. The preferred choice of vaccine formulation in case of either measles or rubella outbreak response immunization is that which includes a combined measles and rubella vaccine.

Selective immunization

Selective immunization of susceptible contacts implies the assessment of immunity of persons from the target group based on disease or vaccination history, and provision of vaccination to persons deemed susceptible (i.e. without a history of disease or proof of an age-appropriate receipt of vaccine for measles and rubella). This strategy should only be used for outbreak control purposes if the risk assessment does not indicate the need for wider, non-selective vaccination response (e.g. with small-scale outbreaks in certain settings – schools, colleges, workplaces, small geographic areas, etc.). The availability of easily accessible and reliable individual immunization records, medical histories are essential for successful implementation of selective immunization. This approach is not recommended for disease transmission involving large geographic areas or occurring in large populations, as conducting assessment of susceptibility on an individual basis is logistically challenging, time-consuming and very costly. It is also not recommended that serological screening be performed to determine individual susceptibility with the purpose of identifying individuals who are eligible for selective immunization during a large and widespread outbreak.

Non-selective immunization

Non-selective immunization refers to the provision of a supplementary dose of the vaccine to all individuals in the target group regardless of previous immunization or disease history. This approach allows immunization of large numbers of people without the need to review individual immunization records and verify disease history. For outbreak response purposes SIAs or ORI are indicated to respond to large-scale outbreaks and have been shown to reduce duration and extent. The necessity and extent of an SIA, as well as the target group implementation strategies should be determined based on the outcome of the risk assessment and the epidemiology of the outbreak, while also considering resource availability. Mass immunization campaigns in a short period of time would be most appropriate for ORI, but this intervention can present many challenges and is not easily accepted and implemented in all countries and societies.

2.4.5 Modifying immunization policies

Outbreak response efforts may also include modifying immunization policies and schedules. For example, in many outbreaks, substantial proportions of cases occur among infants too young to be vaccinated. Young children, particularly infants, are at high-risk of severe illness and death from measles. In the European Region, the first dose of measles- and rubella-containing vaccine is usually not given to infants until 12–18 months of age, depending on the country. Therefore, to ensure earlier protection in an outbreak setting, the recommended age of administration of the first dose of vaccine can be moved up to 9 months of age.

In some circumstances, measles- and rubella-containing vaccines[5] can be given as early as 6 months of age. A dose administered before 12 months of age should not be counted as a valid dose for routine immunization purposes and the routine two doses of measles- and rubella-containing vaccines *(44)* should still be administered to these children, according to the national immunization schedule.

Similarly, if most cases occur among preschool children and the second dose of vaccine is not given until the age of school entry (5–7 years) or even later, the recommended age for the second dose can be moved forward to younger ages, or as early as after a minimum of 28 days following receipt of the first dose.

When outbreaks are affecting adults, public health officials may recommend a vaccine dose for previously unvaccinated or under-vaccinated adults with no history of the disease, if this is not already included in country-specific adult vaccination recommendations or policies.

2.4.6 Strengthening routine immunization

Another key component that should be part of outbreak response activities is strengthening routine immunization. Outbreaks provide an opportunity to identify weaknesses of the immunization programme which may have contributed to the outbreak. The priority territories or groups within the outbreak area should be identified and targeted for corrective measures to ensure timely delivery of high-quality routine immunization services and to achieve high coverage. For example, if a selective approach is to be used in response to an outbreak, immunization activities should target all age cohorts (usually preschool and school age children) with missed or delayed routine doses.

Health staff who are susceptible or without known immunity to measles or rubella should also be vaccinated to prevent possible transmission in health-care settings to high-risk individuals. Efforts should be made to minimize transmission in health-care settings, by ensuring immunity of health workers including public health staff, laboratory staff, medical students and nursing students. In the case of a rubella outbreak, particular emphasis should be given to minimizing transmission to pregnant women.

Infection control practices should be implemented in health-care settings (e.g. isolation of cases through seven days after rash onset).

As part of post-outbreak recovery, an assessment of the immunity profile and gaps should be conducted, and a strategy developed to ensure the achievement and sustainability of measles and rubella elimination goals.

[5] Usually measles/mumps/rubella (MMR), but other presentations are also registered for use in WHO European Region countries like measles/rubella (MR), measles/mumps/rubella/varicella (MMRV) and mono-vaccines for each of the diseases.

2.5 Final analysis of an outbreak

Analysis of an outbreak can provide useful information regarding factors that may have facilitated measles or rubella virus circulation. The investigation may help to identify risk factors for infection and provide information that can be used to refine and improve programmatic aspects for achieving elimination goals.

In addition to ongoing analysis during the outbreak, a final analysis should be performed at the end, and should include the following components as highlighted in the current WHO measles outbreak guide (*41*):

- descriptive analysis of the outbreak including additional information available by the end (e.g. hospitalization rates, severe outcomes, additional case classification);
- characterization of the most affected groups and separate analysis by subgroups, if needed;
- history of the measles and rubella surveillance and immunization programme, policies and performance in the country and in the affected territory or population;
- contributing factors to the outbreak (e.g. vaccine failure versus failure to vaccinate, gaps in immunity, nosocomial transmission, etc.);
- origin of the outbreak and genotype involved (imported virus versus endemic transmission);
- description and evaluation of measures implemented in response to the outbreak;
- surveillance systems' performance, both for routine and strengthened activities, during the outbreak (timeliness, completeness, zero reporting, etc.);
- strengths and weaknesses of the immunization system, based on the analysis of outbreak data and recognized gaps in immunity;
- cost of the outbreak.

A detailed approach to conduct root cause analysis of measles outbreaks is found in the WHO measles outbreak guide (*41*). The findings, which include recommendations on strategies for improving preparedness, surveillance, and immunization coverage as well as identification of specific high-risk areas and populations, should be disseminated as a written report to all stakeholders and partners in order to prevent or mitigate future outbreaks.

Lessons learned from an outbreak response can provide valuable information for updating and improving measles and rubella outbreak response plans.

2.6 Advocacy and communication

Advocacy and communication should be part of early outbreak response activities. Outreach to affected community or population groups helps to ensure effective community involvement, raise public awareness and risk perception, address public concerns and encourage cooperation with public health authorities.

Outreach should be focused on communities or settings identified as most affected or at high risk of transmission. It is most effective when public health agencies form partnerships with local community groups, health-care organizations or organizations with a history of successful community involvement (e.g. nongovernmental organizations).

It is important to identify persons in the community who can serve as liaisons/mediators between public health agencies and the local population (e.g. community groups members, health-care workers who treat unique populations, and community and religious leaders). Liaisons should be informed about the characteristics of the current outbreak and clinical symptoms of measles and rubella, as well as about recommended response measures.

Public health officials should work with community liaisons/mediators to develop targeted education messages and materials that address community members' knowledge, attitudes, practices and beliefs regarding health care. Messages and materials should be widely available to populations. Community mediators could support surveillance activities (e.g. they could have knowledge of individuals that are ill or who have missed immunization activities).

Various means of communication can be used to transmit messages to the community, taking into consideration the appropriate messaging to connect and engage various groups within the larger targeted population. In many outbreaks, involvement of health-care workers in advocacy and communication-related outbreak activities is crucial for ensuring successful implementation of response measures.

Messages conveyed through the outreach should be clear and concise, and tailored to targeted populations. These messages should:

- inform about the existence of an outbreak;
- explain the seriousness of measles and rubella diseases;
- describe signs and symptoms of the diseases;
- encourage persons with symptoms and signs of measles and rubella to seek medical advice as soon as possible;
- inform about the benefits of vaccination against measles and rubella;
- explain control efforts;
- provide information regarding who should receive measles- and rubella-containing vaccines and where they can receive them;
- highlight the importance of the evaluation of pregnant women who have contact with rubella cases.

Partnership between the public health sector and the media is critical for successful implementation of public health activities. Because disease outbreaks are often a focal topic of the media, they can be helpful in informing and updating the public about the outbreak, building public confidence and increasing demand for vaccination. Establishing good relations with media at the beginning of the outbreak is critical for managing the flow of information and preventing misinformation.

3

Framework for the verification of measles and rubella elimination

This section describes in detail the steps to be taken to document and verify that the elimination of measles and rubella has been achieved in the WHO European Region.

This section draws from the latest global guidance *(45)* and replaces previous regional guidance. The regional verification process has been informed by the mechanisms that were put in place previously for the certification of global smallpox *(46)* and poliomyelitis eradication *(47)*.

The process for verifying measles and rubella elimination in the European Region is additionally guided by:

- Regional Committee resolutions on measles and rubella elimination and prevention of rubella infection: EUR/RC55/R7 *(44),* EUR/RC60/R12 *(1)*, EUR/RC64/R5 *(2)*;
- Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome *(27)*.

3.1 Documentation required for regional verification of measles and rubella elimination

As part of the verification process, each country is expected to prepare adequate documentation based on the standardized collection and analysis of essential data. The national verification committee for measles and rubella elimination (NVC) of every country submits their documentation to the European Regional Verification Commission for Measles and Rubella Elimination (RVC) for review and evaluation, and responds to queries from the RVC. The WHO Secretariat facilities the correspondence between the two entities. It may be necessary for the RVC and NVCs to undertake field visits to facilitate a better understanding of the presented documentation.

The RVC will consider the verification of the entire European Region based on the national documentation and the status of measles and rubella elimination in the countries. The verification of elimination of endemic transmission of measles and rubella viruses may occur at different times – as such the two might be verified separately.

3.1.1 Basic principles

Ongoing process. To achieve verification of the elimination of endemic transmission of measles and rubella viruses at the regional level, all countries must achieve elimination at the national level – elimination is a national-level process. It is expected that countries will continue to submit the necessary data and documentation for a period of at least three years after regional elimination has been declared.

Evidence-based. The verification process is based on evidence documented by each country to show that interruption of endemic transmission of measles and/or rubella has been achieved at the national level. A standardized format is used to facilitate the collection, interpretation, analysis and visualization of data. The format adopted by the WHO European Region is known as the Annual Status Update (ASU). Some countries may find it difficult to provide all the evidence required to document elimination; alternative and complementary information and data can be used as evidence to verify elimination at the RVC's discretion. The RVC may request clarifications and/or additional data or documents to finalize their conclusions and recommendations. The RVC should attempt to balance standardization against the necessary flexibility to accommodate differences in national health systems.

Detailed information on the epidemiology of measles and rubella and population immunity, supported by information related to molecular epidemiology, quality of surveillance and accountability comprise the key components for standardized verification of the interruption of endemic measles and rubella virus transmission. These components are interrelated; therefore, it is necessary to provide data that are valid, complete, representative and consistent across the different information sources.

Measurable. A set of surveillance performance indicators and two markers (disease incidence and vaccination coverage) are used to make a reliable conclusion regarding achievement of the objectives. Once a country nears the targets suggestive of elimination, an in-depth review is recommended to investigate whether it has indeed achieved elimination.

Independent. Independent external panels of leading experts are engaged in the formal verification process at regional and national levels (see section 3.2 Structure and function of the NVCs and RVC for verification of measles and rubella elimination). Participation in the panels is voluntary and no salary or consultant fees of any kind is paid.

3.1.2 Essential criteria and components supporting elimination

There are two essential criteria which must be met to verify elimination:

- Detailed epidemiology and laboratory-supported documentation of the sustained interruption of endemic measles or rubella virus transmission for at least 36 months after the last known endemic case;

- A high-quality, laboratory-supported surveillance system with adequate sensitivity and specificity to detect, notify and investigate suspected cases and outbreaks in a timely manner, classify cases by source (i.e. imported or importation-related) and as confirmed or discarded, and provide sufficient information for a country to undertake appropriate public health actions to curtail further transmission.

The essential criteria are to be supported by evidence-based information that allows the RVC to determine whether a country or the Region as a whole has achieved elimination. This information presented in lines of evidence (also referred to as components) should be compiled, analysed and validated by NVCs and submitted to the RVC on an annual basis.

3.1.3 Lines of evidence to support the criteria

In determining whether a country or the whole WHO European Region has achieved elimination, the RVC should consider the following lines of evidence, which should be sufficient to ensure a comprehensive assessment of past programme performance and capacity to sustain elimination.

A. Epidemiology of measles, rubella and CRS

An analysis of epidemiological data from a high-quality surveillance system can confirm whether and when endemic virus transmission has been interrupted. All the available current and past epidemiological data should be provided, with a description of how the data were collected.

- Countries should provide the case definitions used and a description of their case classification system; ideally, countries should adhere to the standard case definitions and case classification system described by WHO. As a country nears elimination, all potential false-negative and false-positive cases should be critically reviewed.
- Efforts should be made to identify the source (origin) of each case (endemic, imported, importation-related or unknown). An "unknown source" classification is assigned only after a thorough investigation has failed to identify the source. Understanding the source of maternal rubella infection for CRS cases is important for verifying rubella elimination.
- Analyses should include the pre- and post-interruption epidemiological periods in order to support the timeframe identified for the interruption of endemic virus transmission. Analyses should also include the annual disease incidence rate and case numbers by final case classification, temporal and spatial characteristics, seasonality and the vaccination status and demographic characteristics of confirmed cases. For rubella, countries should assess its epidemiology, stratified by age groups and sex, to identify any susceptibility in older age groups and particularly women of childbearing age.
- For outbreaks, a description of the epidemiology (e.g. by person, time and place) and detailed outbreak investigation reports should be included.

Countries and regions that have eliminated measles or rubella characteristically have few confirmed cases of disease overall, consisting of imported cases with limited or no disease spread and small outbreaks of limited duration.

B. Molecular epidemiology of measles and rubella viruses

Molecular epidemiology should be analysed to document viral transmission patterns and the duration of the circulation of viruses of specific lineages. It is used in documenting interruption of endemic virus transmission in conjunction with standard epidemiological data *(25,27)*. The viruses detected in a country may change over time as the transmission of specific genotypes or lineages are interrupted and new genotypes or lineages are imported.

As the genetic diversity of measles has decreased over time, genotype identification alone is generally inadequate to confirm whether endemic virus has been eliminated. Thus, NVCs and RVCs should evaluate the circulation of measles virus lineages within a genotype, which provides greater resolution in tracking transmission patterns. Reporting sequence data to MeaNs and RubeNs databases allows in-depth analyses of molecular epidemiology for sequences obtained from measles and rubella viruses *(25)*.

Each measles sequence variant is specifically identified with a MeaNS distinct sequence identifier (DSId). The variants identified from measles cases associated with widespread circulation and/or those of important epidemiological significance are designated as "named strains" and a list of these are provided in MeaNS *(25, 48)*. The documentation of measles chains of transmission and sporadic cases using MeaNS DSIds (and named strains where applicable), improves the understanding of the measles virus molecular epidemiology and allows its graphic representation in NVC annual reports and the use of phylogenetic trees as needed. The rubella sequence database is less extensive; however, the number of circulating genotypes of rubella virus is also decreasing, and a system for designating lineages has been described.

Before elimination, genetic characterization of measles and rubella virus is used to identify endemic genotypes and lineages, track importations and distinguish between transmission chains. Elimination requires interruption of endemic lineages for ≥ 12 months. Molecular epidemiology is a powerful means of excluding putative linkages between cases. The circulation of imported lineages for < 12 months is compatible with elimination.

Ideally, genetic information should be obtained from all chains of transmission and made available by accredited laboratories of the WHO European Measles and Rubella Laboratory Network *(29)* for review by the NVC and RVC. The completeness of virological surveillance and the availability of genetic information from viruses collected during the pre-elimination phase varies by country. If data are not available, the RVC and NVC should advocate for improved virological surveillance to provide a baseline snapshot of viruses that are in circulation.

New methods for genetic characterization of measles and rubella viruses are being developed, which should allow better resolution of distinct lineages over time *(25)*. The Global Measles and Rubella Laboratory Network is developing a plan to introduce these methods into surveillance.

Molecular epidemiology is an important component of measles and rubella surveillance. While genetic information makes a valuable contribution to understanding outbreaks and transmission patterns, the information does not stand alone and must be carefully reviewed in unison with clinical and epidemiological information. National laboratories have an essential role in contributing to the preparation of the ASU by providing reliable molecular data and guiding the NVC in its interpretation.

C. Quality of surveillance for measles, rubella and CRS

Epidemiological analysis requires good quality data that can only be acquired through a high-quality surveillance system with an integrated laboratory component for detecting and confirming cases. At a minimum, surveillance must result in detection, notification and investigation of suspected cases and outbreaks in a timely manner, with accurate case classification. The quality of a surveillance system can be assessed by determining whether it meets WHO-defined indicators (Tables 3 a and b).

Laboratory information that is ultimately provided to the RVC by NVCs should originate from proficient laboratories (see 1.3.5 Additional definitions). The laboratories in the WHO European Measles and Rubella Laboratory Network should fully engage in the national verification process by contributing to and critically reviewing the annual country report and providing technical guidance and feedback to the NVC *(27)*.

If a country's surveillance system cannot provide data on the WHO-recommended indicators or if the indicators are not met, supplementary data should be provided to allow assessment of the quality of surveillance. Examples of supplementary data include the median time elapsed until case notification, the number of generations of cases before notification to public health authorities and findings from active and retrospective case searches. In addition, a review of dedicated surveillance sentinel sites and the results of active searches for cases during outbreak field investigation should be considered in high-risk communities, areas with high arboviral disease activity, silent areas, areas in which the surveillance indicators are not measured and areas with low vaccination coverage. If few cases are identified in this manner, then the claim that surveillance is performing well is supported. For countries with a significant private health-care sector, additional evidence should be submitted to demonstrate that cases identified in the private sector are included in national surveillance data. Findings from any recent evaluation of surveillance quality should be provided, with assessments of the quality of the laboratories that conduct testing.

D. Population immunity against measles and rubella

To achieve and maintain elimination, high levels of population immunity are required:

- For measles, assuming that most people born before the introduction of the measles vaccine have naturally acquired immunity, it is sufficient to document immunity for each cohort born since the introduction of the vaccine in the national programme by reviewing the characteristics of cases and vaccination coverage.
- For rubella, the following data can be reviewed to determine population immunity:
    - the frequency and size of rubella outbreaks and the population groups affected, both before and after rubella vaccine introduction;

- the country's vaccination strategy (including the private sector), with an analysis of the population groups that were not vaccinated (e.g. males, unvaccinated birth cohorts);
- representative serosurveys, if available.

To assess vaccination coverage, countries should review and analyse routine and supplementary vaccination data and coverage surveys, when available, at the first, second and third administrative levels, depending on the size of the country. This information will allow estimation of population immunity (vaccination coverage multiplied by vaccine effectiveness) for each cohort. Any mass population movements need to be factored in, as this can affect population immunity. Where relevant, evidence of the immunity of underserved, migrant, refugee and health-care worker groups should be provided. Countries should include other data, such as the results of well-conducted seroprevalence studies, if available.

E. Sustainability of achievements

Once achieved, elimination of endemic virus transmission must be maintained. It is critical that countries have political commitment, good programme management and planning, and favourable economic and legal environments to ensure a robust national immunization programme. These components will help ensure the maintenance of strong surveillance and laboratory systems. Measures and activities that reflect a commitment to sustain elimination of measles and rubella include:

- ensuring adequate funding in the national budget to sustain elimination of measles and rubella;
- conducting risk assessments, and periodic review of outbreak preparedness and response plans;
- setting policy initiatives to ensure high vaccination coverage is maintained and evaluated confirmed by periodic evaluation;
- providing clear and detailed plans for sustained funding for vaccine procurement and programme operation.

3.1.4 Special considerations

Countries with small populations

Countries with populations of < 500 000 inhabitants are unlikely to have sustained endemic transmission due to exhaustion of host availability (natural virus extinction). Outbreaks can still occur, but transmission is highly unlikely to last longer than 12 months. In addition, the population and birth cohort size are so small that minor fluctuations in the number of children vaccinated may have a dramatic effect on coverage. Surveillance performance indicators, such as a discard rate of 2 per 100 000 population, may not be achieved annually. Therefore, to verify elimination of measles and rubella, NVCs and the RVC should be provided with sufficient evidence that population immunity is high, and that the surveillance system can detect cases quickly.

Rubella

While the above criteria and evidence are applicable for both measles and rubella, it is imperative in confirming rubella elimination that there is a focus on the immunity of women of childbearing age. As 20–50% of rubella cases are subclinical, surveillance is more difficult than that of measles. In an elimination setting, the primary purpose of rubella surveillance is to detect as many cases as possible, confirm them by laboratory testing and identify outbreaks.

Additionally, WHO recommends integrating measles and rubella surveillance, using the same definitions of suspected cases and case classification by laboratory testing. Thus, if a country has mandatory measles surveillance and laboratory testing of suspected measles cases, then testing for rubella will be included, as it has a de-facto laboratory-based rubella surveillance system. To verify rubella elimination, a laboratory-based surveillance system for rubella integrated with a high-quality measles surveillance system (e.g. fever/rash) is acceptable.

CRS surveillance is complementary to rubella surveillance in providing evidence that rubella has been eliminated; there should be no CRS cases associated with endemic transmission after rubella elimination.

3.2 Structure and function of the NVCs and RVC

The NVCs and the RVC have the function of reviewing progress towards elimination in accordance with the standard process described above. The RVC works in close collaboration with the Regional Office and reports to the WHO Regional Director for Europe. It provides periodic updates to and coordinates technical and policy issues with the European Technical Group of Experts on Immunization (ETAGE).

Both the NVCs and the RVC are external, independent entities whose members should not be involved in the managerial or operational aspects of immunization programmes in their respective countries (e.g. in the day-to-day management of national immunization or surveillance activities, in the country or countries for which they are reviewing data), although they may serve on the NVC or RVC secretariat. Neither should their members be involved in the surveillance or laboratory-related components of elimination activities, nor have any direct responsibility in connection with achieving elimination goals at regional or national levels.

It is expected that the NVC and RVC members will be senior scientists, experienced physicians or university staff committed to the verification process. They apply a rigorous and scientific approach to assessing the evidence and present their judgments frankly and objectively. All conflicts of interest are identified and declared.

3.2.1 National verification committees

An NVC should be established in every country to conduct annual reviews of progress towards or achievement or maintenance of elimination. NVCs should submit their reports to the RVC and respond to queries from them. NVCs help countries to document progress towards elimination by advising on the collection, analysis and validation of national data, reaching a conclusion on achievement of elimination and providing the necessary documentation in support of their conclusion. The contribution of national measles and rubella laboratories is critical for consistent interpretation and display of laboratory data. NVCs do not have the authority to verify elimination. NVCs in large or federalized countries may consider collecting reports from subnational areas to facilitate interpretation of data and making field visits to identify barriers to achieving elimination. The NVC may also wish to collaborate with other NVCs in forming subregional verification committees responsible for the verification process of the countries participating in them. One such example in the Region is that of the Nordic Verification Committee *(49)*.

Mission

NVCs will develop and monitor the documentation and verification process in their respective countries. They will be responsible for establishing, reviewing and monitoring verification activities at the national level, following standardized operational procedures and preparing national reports for the Regional Office. NVCs will advocate for strengthening measles and rubella elimination programmes by promoting the documentation and verification process, encouraging their national authorities to implement appropriate strategies and monitoring progress towards elimination goals.

Membership

Members of an NVC will be external, independent individuals who are not involved in the managerial or operational aspects of their national immunization programme. In addition, they may not be involved in surveillance- including laboratory-related components or have any direct responsibility in connection with achievement of the elimination goals at national level. It is suggested that each NVC will comprise a maximum of five members: a chairperson, a secretary, and two to three additional members. They will include recognized specialists from various fields (clinicians, laboratory experts, epidemiologists, etc.), who will participate on a voluntary basis. Members of NVCs will be designated by ministers of health in their countries in accordance with official national procedures. Where appropriate, and if approved by the respective ministers of health, NVCs may include members from other countries, for example, members of NVCs in neighbouring countries or officials from international public health agencies.

Functions

The functions of NVCs are to:

- conduct and preside over at least two meetings annually, as required by elimination activities;

- prepare plans of action for the documentation and verification of measles and rubella elimination in the countries – defining responsibilities, products, resources and timelines for the activities, in collaboration with national immunization and surveillance programmes and (on technical matters) the Regional Office and the RVC;
- present the national plans of action to the respective health authorities and RVC;
- compile and analyse the information received from national immunization and surveillance programmes for verification of measles and rubella elimination and CRS prevention, in accordance with the established criteria and procedures;
- propose alternative solutions if the available country data are insufficient or inconsistent;
- advise national surveillance, laboratory and immunization teams on activities related to the process of documenting and verifying the interruption of endemic measles and rubella virus transmission in the countries;
- conduct field visits in selected areas of the countries, if necessary, to monitor progress and verify data analyses;
- participate in RVC work sessions and visits to the countries at different stages of the documentation process;
- prepare and submit annual country reports to national health authorities, which will officially present the documentation to a WHO country office or directly to the Secretariat if there is no WHO country office in the Member State.

3.2.2 Regional Verification Commission

The RVC is responsible for conducting an annual review of all reports from countries that submit them. The RVC verifies achievement of measles and/or rubella elimination in each country and eventually in the WHO European Region.

Mission

The RVC will evaluate the documentation submitted by NVCs with a view to verifying the elimination of measles and rubella at regional level (i.e. that all Member States have been free from transmission of endemic measles and rubella virus for at least 36 consecutive months). Individual RVC members will be assigned to groups of Member States to conduct field visits, monitor progress and verify data analyses, in close consultation with the Regional Office, which will act as the Secretariat.

Membership

The RVC is made up of experts, including epidemiologists, clinicians, virologists and molecular biologists. It includes a chairperson, a vice-chairperson and a maximum of eight additional members, all of whom are independent of the managerial and operational aspects of elimination activities.

Functions

The function of the RVC is to:

- conduct at least one meeting annually;
- define internal procedures and the responsibilities of its members in supervising the documentation and verification process;
- advise NVCs on the process for collecting and analysing data to verify elimination in the countries;
- analyse annual reports submitted by NVCs;
- review and apply the criteria, parameters and procedures for documenting and verifying the achievement of elimination in the Region, in consultation with Member States and ETAGE;
- prepare and submit annual reports to the Regional Director, with feedback to Member States;
- conduct field visits in the countries, if necessary, to monitor progress and verify data analyses, in close consultation with the Secretariat (Regional Office);
- when appropriate, declare the regional interruption of measles and rubella transmission.

3.3 Documentation process

The Regional Office provides NVCs and its secretariat (national public health authorities) with all the necessary information related to the concepts and methods of developing each component of the documentation process, as well as the relevant criteria and practical guidelines and forms. The documentation process includes the identification and validation of data and their sources, both official and unofficial. This information should be consistent with that originating from monthly and annual reports provided by national surveillance systems. NVCs annually analyse all collected data from immunization and surveillance systems and complete the ASU before submitting it to the Regional Office through the national health authorities.

Each country should have in place a plan of action for implementation of the documentation process to be endorsed by its national health authorities. The plan should include the activities necessary for collecting and integrating the required data, and define the responsible parties, as well as products, resources and timelines. The epidemiological surveillance and immunization teams should collect and submit all the required data to the NVC, in accordance with WHO Regional Office for Europe guidance.

At its annual meetings, the RVC reviews and validates the ASU of every country. Based on the evidence provided and in line with the definitions described in section 3.1 Documentation required for regional verification of measles and rubella elimination, the RVC will determine the status of each country as:

- interrupted endemic transmission (the absence of endemic cases for at least 12 months);
- endemic transmission (documentation of endemic transmission or lack of evidence showing interruption);
- re-established endemic transmission.

The review and evaluation of ASUs will continue for each country until the RVC has confirmed that, according to the established criteria, endemic measles and/or rubella transmission have been interrupted in all Member States of the Region for at least 36 months. It is only then that the RVC can declare regional elimination.

Annexes

Annex 1

Measles and rubella case investigation and reporting form

Example for consideration by the national surveillance systems

Case ID: _____ Region: _____ District: _____

Date of notification: ___ / ___ / ___ Date of investigation: ___ / ___ / ___ Date of report: ___ / ___ / ___

Initial clinical diagnosis:

1. Clinical measles ☐ 2. Clinical rubella ☐ 3. Rash and fever ☐ 9. Unknown ☐

Outbreak-related:

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

A. Personal data and immunization status (* to WHO provide unique Case ID, not name and address)

Name: _____

Gender:

1. Male ☐ 2. Female ☐ 9. Unknown ☐

Date of birth: ___ / ___ / ___ if not available, age in years ___ if younger than a year, age in months ___

Address*: _____

For female cases

Is case pregnant?

1. Yes ☐ 2. No ☐ 9. Unknown ☐ **If yes**, gestation age: _____ weeks

Vaccination status

Measles:

1. Yes ☐ 2. No ☐ 9. Unknown ☐ **If yes**, no. of doses ___

Source of vaccination status:

Medical record ☐ Parent or guardian ☐ Last vaccination date: ___ / ___ / ___

Rubella:

1. Yes ☐ 2. No ☐ 9. Unknown ☐ **If yes**, no. of doses ___

Source of vaccination status:

Medical record ☐ Parent or guardian ☐ Last vaccination date: ___ / ___ / ___

B. Clinical information

Maculopapular rash

1. Yes ☐ 2. No ☐ 3. Unknown ☐ Date of rash onset: ___ / ___ / ___

Duration of rash (days): _____

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

Hospitalized:

1. Yes ☐ 2. No ☐ 3. Unknown ☐ Name of hospital: _____

Clinical outcome:

1. Dead ☐ date of death: ___ / ___ / ___ 2. Survived ☐ 3. Lost to follow-up/unknown ☐

Cause of death: _____

C. Epidemiological investigation - possible source of infection and contacts

Did the patient have contact with confirmed case of measles or rubella (within 7–23 days) prior to rash onset?

1. Yes ☐ 2. No ☐ 3. Unknown ☐

If yes: With whom (case ID/name): _____

Where (country/address): _____

When (dates): _____

Were there confirmed cases of measles and/or rubella reported in the area prior to this case?

1. Measles ☐ 2. Rubella ☐ 3. Both ☐ 4. No ☐ 5. Unknown ☐

Did the patient travel within 7–23 days before onset of rash?

1. Yes ☐ 2. No ☐ 3. Unknown ☐

If yes: Where (country/address): _____

When (dates): _____

Travel details: _____

Is the case epidemiologically linked to imported confirmed case?

1. Yes ☐ 2. No ☐ 3. Unknown ☐

If yes: To which case (ID/name): _____
From where (country/address): _____
When exposed (dates): _____

Was the case in contact with a pregnant woman since development of the symptoms?

1. Yes ☐ 2. No ☐ 3. Unknown ☐

If yes, please provide name and address:

_____

Other contacts _____

_____

_____

D. Laboratory investigation

Specimen collected

1. Yes ☐ 2. No ☐ 3. Unknown ☐

If yes, type of specimen:

Serum ☐ Oral fluid ☐ Nasopharyngeal swab ☐ Dry blood spot ☐

Urine ☐ EDTA whole blood ☐ Other ☐

Type and date of specimen collection: ( ) ___ / ___ / ___

Date specimen sent to lab: ___ / ___ / ___

Type and date of specimen collection: ( ) ___ / ___ / ___

Date specimen sent to lab: ___ / ___ / ___

Measles IgM:

Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐

Date of first validated result: ___ / ___ / ___

Rubella IgM:

Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐

Date of first validated result: ___ / ___ / ___

Measles virus detection:

Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐

Genotype: _____

Rubella virus detection:

Not tested ☐ Positive ☐ Negative ☐ In process ☐ Indeterminate ☐

Genotype: _____

E. Final classification disease

CLASSIFIED AS MEASLES OR RUBELLA

Measles, laboratory-confirmed
Measles, epidemiologically linked
Measles, clinically compatible
Rubella, laboratory-confirmed
Rubella, epidemiologically linked
Rubella, clinically compatible

DISCARDED

Discarded, Measles
Discarded, Rubella
Discarded, Measles and Rubella

VACCINE-RELATED

Measles, vaccine-related
Rubella, vaccine-related

F. Final classification origin

Origin of infection (for purposes of verification):

Imported ☐ Importation-related ☐ Endemic ☐ Unknown ☐

Comments _____

Annex 2

Measles and rubella outbreak reporting form

Example for consideration by the national surveillance systems. Countries can use their own forms and report outbreaks to the technical team at the WHO Regional Office for Europe (eumeasles@who.int).

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. of laboratory-confirmed measles cases	
1st subnational administrative level		No. of suspected cases - Total		No. of laboratory-confirmed rubella cases	
2nd subnational administrative level		No. of deaths		Genotype	
Date of rash onset of first case		No. of encephalitis cases		Additional info:	
Date of rash onset last case		No. of hospitalized cases			
Outbreak notification date		No. pregnant women		No. women of childbearing age	
Current outbreak status		**Reporting:** (Name and contact detail of the person reporting this outbreak)		**Date:** (Date of submission of this report, relevant administrative information)	
Outbreak end date					
Importation (Y/N)					
If yes, from which country					

Epidemiological summary of confirmed cases in outbreak

	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								
Vaccinated, with unspecified number of doses								
Vaccination status unknown								
Total								

Description of the outbreak

Measures taken to prevent/control further spread of outbreak

Spread in other regions of country				
Territory/place/city	1st/2nd admin level	Date of first case	Total cases	Epidemiological data and comments

Annex 3

Congenital rubella syndrome case investigation and reporting form

Example of a basic set of data for consideration by the national surveillance systems.

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 (* to WHO provide unique Case ID, not name and address)

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

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

Address: _____

_____

_____

Place infant delivered: _____ Name of mother: _____

B. Clinical signs and symptoms

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

Group A (please complete all)

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: _____

If dead, cause of death: _____

Autopsy conducted:

Yes ☐ No ☐ Unknown ☐

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, give date: ___ / ___ / ___

Coryza:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

Cough:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

Maculopapular rash:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

Lymph nodes swollen:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

Arthralgia/arthritis:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

Other complications:

Yes ☐ No ☐ Unknown ☐ If yes, give date: ___ / ___ / ___

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

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

Was the mother during pregnancy exposed to person of any age with maculopapular (e.g. not vesicular) rash illness with fever

Yes ☐ No ☐ Unknown ☐ **If yes,** when (date): ____ / ____ / ____

Month of pregnancy: _____ Describe where: _____

D. Infant/child laboratory investigations

Specimen collected: Yes ☐ No ☐ Unknown ☐

If yes, please describe:

Serum ☐ Throat swab ☐ Urine ☐ Cerebrospinal fluid ☐

Other: _____

Date of specimen collection: ____ / ____ / ____ Date specimen sent: ____ / ____ / ____

Rubella IgM:

Not tested ☐ Positive ☐ Negative ☐ In process ☐ Equivocal/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 ☐ Yes ☐ No ☐ In process ☐

Rubella RT-PCR:

Not done ☐ Positive ☐ Negative ☐ In process ☐

Genotype: _____

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

E. Final classification

CRS ☐ Discarded ☐ If discarded, please specify: _____

_____

Case classified as:

Laboratory-confirmed ☐ Epidemiologically linked ☐ Clinically-compatible ☐

Origin of infection:

Imported ☐ Importation-related ☐ Endemic ☐ Unknown ☐

Date of final classification: ____ / ____ / ____

Investigator: _____

Annex 4

Standard template to report monthly measles and rubella case-based data to the WHO Regional Office for Europe

Field Description	Data format or values	Mandatory variable	Explanatory notes
Unique EpID or CaseID for a measles or rubella case	Free text (max. 50 characters)	Yes	
Name of the 1st sub-national administrative area/unit where the case was first detected.	Free text (max. 450 characters)	Yes	The geographical location should correspond to the place where the case was first detected by a health facility or health worker. For correct determination of "1st subnational administrative unit": nation is considered as the 0 (zero) administrative level
Name of the 2nd sub-national administrative area/unit where the case was first detected	Free text (max. 450 characters)	No	The geographical location should correspond to the place where the case was first detected by a health facility or health worker. For correct determination of "2nd subnational administrative unit": nation is considered as the 0 (zero) administrative level
Gender	• Male • Female • Other • Unknown	Yes	
Date of Birth	DD/MM/YYYY	Yes (Conditional)	To be reported only if age in years or age in months are missing.

Field Description	Data format or values	Mandatory variable	Explanatory notes
Age at rash onset (in years)	Positive integer values	Yes (Conditional)	To be reported only if date of birth is missing This is a mandatory variable. The value will be automatically calculated if date of birth is reported (calculated as date of rash onset minus data of birth), otherwise it has to be reported as numeric value
Age at rash onset (in months for children <1 year old)	Positive integer values	Yes (Conditional)	To be reported only if date of birth is missing. If date of birth is reported, the value is automatically calculated. Age in month is not mandatory but it should be reported as it provides key information for tailoring vaccination schedule and outbreak response
Date of rash onset	DD/MM/YYYY	Yes	
Number of measles vaccines received (vaccination card or by verbal history)	Positive integer values	No	Indicate the number of measles vaccine doses received Indicate: - 0 = if the case did not receive any dose - 888 = when there is information that the case was vaccinated but the exact number of doses is not known - 999 = when there is no information on doses of measles vaccine received

Field Description	Data format or values	Mandatory variable	Explanatory notes
Date of last measles vaccination	DD/MM/YYYY	No	Leave this blank if the case is unvaccinated or date of last vaccination is unknown
Number of rubella vaccines received (vaccination card or by verbal history)	Positive integer values	No	Indicate the number of rubella vaccine doses received Indicate: - 0 if the case did not receive any dose - 888 = when there is information that the case was vaccinated but the exact number of doses is not known - 999 = when there is no information on doses of rubella vaccine received
Date of last rubella vaccination	DD/MM/YYYY	No	Leave this blank if the case is unvaccinated or date of last vaccination is unknown
Date when case is first reported or notified to public health authorities.	DD/MM/YYYY	No	
Date of epidemiologic investigation of case by public health authorities.	DD/MM/YYYY	No	

Field Description	Data format or values	Mandatory variable	Explanatory notes
Fever	- Yes - No - Unknown	No	
Cough	- Yes - No - Unknown	No	
Coryza	- Yes - No - Unknown	No	
Conjunctivitis	- Yes - No - Unknown	No	
Lymphadenopathy	- Yes - No - Unknown	No	
Arthritis or Arthralgia	- Yes - No - Unknown	No	
Outcome	- Dead - Alive - Unknown	No	
Hospitalized because of current fever-rash diagnosis	- Yes - No - Unknown	No	
Origin of Infection	- Imported - Importation-related (locally acquired) - Endemic (locally acquired) - Unknown	No	The origin of infection should be determined based on epidemiological and laboratory investigations. This variable is used to support the process of verification of measles and rubella elimination.

Field Description	Data format or values	Mandatory variable	Explanatory notes
Outbreak related	- Yes - No - Unknown	No	
Outbreak ID	Free text (max. 50 characters)	No	
Complications	- Yes - No - Unknown	No	
Encephalitis	- Yes - No - Unknown	No	
Pneumonia	- Yes - No - Unknown	No	
Diarrhoea	- Yes - No - Unknown	No	
Other complications	- Yes - No - Unknown	No	
If 'Yes', specify other complications	Free text (max. 450 characters)	No	

Field Description	Data format or values	Mandatory variable	Explanatory notes
Final classification	- Pending - Discarded, Measles - Discarded, Rubella - Discarded, Measles and Rubella - Measles laboratory-confirmed - Measles epidemiologically linked - Measles clinically compatible - Measles vaccine-related - Rubella laboratory-confirmed - Rubella epidemiologically linked - Rubella clinically compatible - Rubella vaccine-related	No	
Date of specimen collected	DD/MM/YYYY	No	Multiple specimens could be collected at different times during the case investigation. Report only the date when 1st specimen collection was made (that could include collection of one or multiple specimen types). This variable will be used to monitor timeliness and adequacy of laboratory investigation (i.e. time from diseases onset, adequate type of specimen).
Type of specimen(s) collected	- Serum - Throat (oropharyngeal) swab - Oral fluid - Nasopharyngeal swab - Dry blood spot - Urine - EDTA whole blood - Other specimen - Multiple specimens	No	Indicate the type of specimen(s) that was (were) collected as 1st laboratory investigation of the case

Field Description	Data format or values	Mandatory variable	Explanatory notes
If 'Multiple specimens', please specify	Free text (max. 450 characters)	No	Use this field to provide additional information if multiple specimens were collected either at the same time or at different time periods. Information may include the rationale for collecting multiple specimens, the timing of specimen collection, etc. N.B. Details on the laboratory investigation will be obtained through the laboratory surveillance database. Epidemiology and laboratory surveillance databases would be connected using CaseID or EpiID.
Date of laboratory results available	DD/MM/YYYY	No	Indicate the date that results were obtained for the specimen(s) that was (were) collected as 1st laboratory investigation of the case.
Measles IgM result	- Not tested - Positive - Negative - In process - Equivocal	No	Considering that multiple results could be available, report the IgM result that was used as main reference to determine the "Final classification". For example, if two specimens were tested at different periods, the first with equivocal and the second with positive results, report the positive result.

Field Description	Data format or values	Mandatory variable	Explanatory notes
Rubella IgM result	- Not tested - Positive - Negative - In process - Equivocal	No	Considering that multiple results could be available, report the IgM result that was used as main reference to determine the "Final classification". For example, if two specimens were tested at different periods, the first with equivocal and the second with positive results, report the positive result.
Measles virus detection (RT-PCR) result.	- Not tested - Positive - Negative - In process	No	Considering that multiple results could be available, report the RT-PCR result that was used as main reference to determine the "Final classification".
Rubella virus detection (RT-PCR) result.	- Not tested - Positive - Negative - In process	No	Considering that multiple results could be available, report the RT-PCR result that was used as main reference to determine the "Final classification".
Comments: any additional notes or findings relevant to case investigation.	Free text (max. 4000 characters)	No	

Note: Additional variables (see 1.8.1 Recommended data elements) could be reported to the WHO Regional Office for Europe but will not be analyzed routinely. They could be used in case of in-depth analysis for specific reasons, such as technical support, verification process and outbreak response.

General rules

- For the unique EpID or CaseID use a unique code (one number = one case) for all types of cases (suspected, clinical, epidemiologically linked and laboratory confirmed).
- It is preferable that all suspected cases are tested for both measles and rubella.
- Data must flow according to the timeline – e.g. date of rash cannot be before date of birth.

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