WHO Vaccine-Preventable Diseases Surveillance Standards

Rubella
Rubella is an acute viral disease traditionally affecting susceptible children and young adults. Its public health importance is due mainly to the teratogenic potential of the virus, causing harm to an embryo or fetus. The incubation period of rubella is 14 days, with a range of 12–23 days. Apart from the congenital infection, rubella is a mild self-limiting illness that usually occurs during childhood. 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 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 one to three days, starts on the face and neck before progressing down the body. Joint symptoms (arthritis, arthralgias), 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 have been reported as high as 1/500 and 1/1600 (1). Rubella infection occurring just before conception and during early pregnancy often results in miscarriage, fetal or early infant death, or multi-organ congenital defects known as congenital rubella syndrome (CRS). CRS risk is unrelated to severity of symptoms in the mother. Surveillance for CRS is discussed in a different chapter.

Rubella-containing vaccines (RCV) are live attenuated virus vaccines, most often combined with measles and sometimes mumps and varicella vaccines (MR, MMR, MMRV). The vaccine has been highly effective at reducing the burden of disease, and has led to the elimination of rubella and CRS from several Western Pacific and European countries as well as all countries in the Americas. As of 2017, three WHO regions have rubella elimination goals (2).

**DISEASE AND VACCINE CHARACTERISTICS**

**Rubella**

**Clinical**

- **Infectivity**
  - Exposure period
  - Infectious period
  - Prodrome: 1–5 days
  - Lymphadenopathy: 1–3 days
  - Rash: 1–3 days

**Laboratory**

- Adequate sample collection
- PCR (max viral shedding)
- IgM (optimal sensitivity)

**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 lab specimen/diagnostics, bars represent the range of days in which that particular test would be positive.
GLOBAL OR REGIONAL LEVEL
The key global objective of rubella surveillance is to measure progress towards elimination, and to document elimination, in five of six WHO regions by 2020.

NATIONAL OR LOCAL LEVEL
The objectives of rubella surveillance at these levels are to:
- detect and confirm cases to document the burden of rubella in countries that have not introduced RCV
- detect and confirm cases to monitor the impact of the vaccination programme, and implement additional vaccination strategies as appropriate
- detect and confirm rubella infection in pregnant women, facilitate proper referrals and document the pregnancy outcome
- investigate cases to determine the source and factors related to transmission
- identify high-risk populations and areas
- verify the absence of endemic rubella cases to document achievements of national targets, such as elimination of endemic virus
- model the expected CRS incidence in a population based on rubella incidence.

**BOX 1**  
**Integration of rubella and measles surveillance**

Integrate rubella and measles surveillance, whenever possible. Both diseases present similarly clinically with a rash illness, and both have regional targets for elimination. As such, both have similar approaches to surveillance. Laboratory test suspected cases of measles and rubella either in parallel or in series, depending on local epidemiology and public health priorities. This chapter specifically addresses rubella surveillance, although many details would also pertain to measles surveillance. See the Measles chapter for additional information about measles.

**BOX 2**  
**How CRS surveillance relates to rubella surveillance**

CRS surveillance systems are separate from clinical rubella surveillance, and so are addressed in a different chapter in these surveillance standards. The surveillance systems for the two manifestations of rubella infection (acquired or 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 see if 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.
Rubella

TYPES OF SURVEILLANCE RECOMMENDED

MINIMAL SURVEILLANCE
Because rubella surveillance should be integrated with measles, and all countries should be conducting elimination-standard surveillance for measles, WHO recommends elimination-standard surveillance for rubella simultaneously. Rubella surveillance should be case-based. Surveillance should be a system that can, in a timely manner, detect, notify and investigate suspected cases and outbreaks, correctly classify them as confirmed or discarded, and inform actions that reduce morbidity and mortality and prevent further virus transmission (2). Surveillance should be national with inclusion of all health facilities (both private and public), with a system for zero reporting (reporting that there were no cases). Countries may initially identify rubella cases through testing of sera that were negative for measles.

LINKAGES TO OTHER SURVEILLANCE
Surveillance for rubella should be done together with measles, as mentioned previously. Additionally, given the broad suspected case detection definition discussed below, other rash-causing diseases, like dengue, can be integrated into this surveillance system.

CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE DEFINITION FOR CASE FINDING
A suspected rubella case is a patient with fever and maculopapular (non-vesicular) rash, or in whom a healthcare worker suspects rubella. A healthcare worker should suspect rubella when a patient presents with the following: fever, maculopapular rash and cervical, suboccipital or postauricular adenopathy or arthralgia/arthritis.

FINAL CASE CLASSIFICATION (FIGURE 2)

Laboratory-confirmed rubella case:
A suspected case of rubella that has been confirmed positive by testing in a proficient laboratory. A proficient laboratory is one that is WHO accredited or has established a recognized quality assurance programme, such as International Organization for Standards (ISO) or Clinical Laboratory Improvement Amendments (CLIA) certification (3).

Epidemiologically linked rubella case:
A suspected case of rubella that has been confirmed by a laboratory, but was geographically and temporally related, with dates of rash onset occurring 12–23 days apart from a laboratory-confirmed case or another epidemiologically linked rubella case.

Clinically compatible case:
A suspected case with maculopapular (non-vesicular) rash and fever (if measured) and at least one of arthritis/arthralgia or lymphadenopathy, but no adequate clinical specimen was taken and the case has not been linked epidemiologically to a laboratory-confirmed case of rubella or other communicable disease.

In a low incidence setting, the vast majority of rubella cases should be confirmed by laboratory or epidemiological linkage. Clinically compatible cases are highly unlikely to be rubella when the country is at or near elimination.

Non-rubella discarded case:
A suspected case that has been investigated and discarded as a non-rubella (and non-measles) when any of the following are true:

» negative laboratory testing in a proficient laboratory on an adequate specimen collected during the proper time period after rash onset (see Figure 1)

» epidemiological linkage to a laboratory-confirmed outbreak of another communicable disease that is not rubella

» confirmation of another etiology, regardless of whether it meets the definition of epidemiological linkage

» failure to meet the clinically compatible rubella case definition.

If the case is also negative for measles, this is a non-measles non-rubella discarded case.
Classification of suspected measles and rubella cases

- **SUSPECTED CASE**
  - **ADEQUATE SPECIMEN**
    - **MEASLES:** LABORATORY POSITIVE
      - **LABORATORY-CONFIRMED MEASLES**
    - **RUBELLA:** LABORATORY POSITIVE
      - **LABORATORY-CONFIRMED RUBELLA**
    - **MEASLES/ RUBELLA:** LABORATORY NEGATIVE
      - **DISCARDED: NON-MEASLES, NON-RUBELLA**
  - **NO OR INADEQUATE SPECIMEN**
    - **EPIDEMIOLOGICALLY LINKED TO LABORATORY-CONFIRMED OR ANOTHER EPIDEMIOLOGICALLY LINKED MEASLES CASE**
      - **EPIDEMIOLOGICALLY LINKED MEASLES**
    - **EPIDEMIOLOGICALLY LINKED TO LABORATORY-CONFIRMED OR ANOTHER EPIDEMIOLOGICALLY LINKED RUBELLA CASE**
      - **EPIDEMIOLOGICALLY LINKED RUBELLA**
    - **NO EPIDEMIOLOGICALLY LINKAGE TO MEASLES OR RUBELLA CONFIRMED CASE**
      - **DISCARDED: NON-MEASLES, NON-RUBELLA**
      - **DOES NOT MEET CLINICAL CASE DEFINITION FOR MEASLES OR RUBELLA**
      - **MEETS CLINICALLY COMPATIBLE CASE DEFINITION FOR MEASLES**
      - **MEETS CLINICALLY COMPATIBLE CASE DEFINITION FOR RUBELLA**
      - **CLINICALLY COMPATIBLE MEASLES**
      - **CLINICALLY COMPATIBLE RUBELLA**
OTHER DEFINITIONS

- **Endemic rubella case:** Confirmed cases of rubella resulting from endemic transmission of rubella. Endemic transmission is defined as a chain of 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 case that chains of transmission are unclear for rubella because of the mild presentation of many cases.

- **Imported rubella case:** A returning traveler or visitor exposed to rubella outside the country during all or part of the 12–23 days prior to rash onset and supported by epidemiological or virological evidence. For cases that were outside the country for only a part of the 12–23 day interval prior to rash onset, conduct additional investigation of whether the exposure to another rubella case likely occurred outside or within the country to determine the source of infection and whether the case can be considered imported. Imported cases are defined by the place where the case was infected, not the country of residence or origin of the case. When possible, add genotyping evidence, particularly new subtyping methods, to epidemiological investigation in order to better define the chain of transmission.

- **Importation-related rubella case:** A locally acquired infection that occurs as part of a chain of transmission originating from an imported case as supported by epidemiological or virological evidence. If transmission of rubella from cases related to importation persists for 12 months or more within a country, cases are no longer considered importation-related but endemic.

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

CASE INVESTIGATION

All suspected rubella cases should be notified within 24 hours of identification and investigated within 48 hours of notification. A case investigation should be conducted on each case, with data collected on potential risks of exposure and spread among contacts to identify transmission patterns and interrupt chains of transmission. The source of infection for rubella is an infectious person who interacted with the case 12–23 days before rash onset.

Once the case investigation form has been completed and laboratory test results are available, suspected cases should be classified both by confirmation status (laboratory-confirmed, epidemiologically linked, clinically compatible, discarded) and by source of infection (imported, importation-related, endemic, unknown). As few cases as possible should be classified as clinically compatible because there are many other causes of rash that may mimic rubella infection. An important difference from measles is that the source of a rubella case can be difficult to identify because of the mild presentation of rubella. A significant proportion of rubella cases are subclinical, so a more extensive investigation is needed to minimize the number of transmission chains with an unknown source of infection.

The investigation of suspected cases who are pregnant women (or the evaluation of contacts who are pregnant) will vary by country. However, follow up of pregnant cases and pregnant contacts until the end of the pregnancy 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 register. Counselling and medical follow-up must be assured.
Collect specimens on every suspected case because the symptoms of rubella are non-specific. Several different types of specimens can be collected from suspected rubella cases based on the timing of investigation (Table 1) (3). Collect specimens on first contact with the case; do not wait for the ideal window or the case might be lost to follow up. An adequate specimen for antibody detection is defined as a sample collected within 28 days after rash onset that consists of ≥ 0.5mL of sera; the volume of whole blood to be collected is based on age. In some regions where suitable testing is available, you may also use a sample of oral fluid or dried blood on a filter paper (≥ 3 fully filled circles).

At a minimum, all cases should have a sample collected for antibody detection (unless they can be epidemiologically linked to a laboratory-confirmed or another epidemiologically linked case). If the case is not part of a known chain of transmission, collect a sample for viral isolation (genotyping) from 5–10 cases early in the chain of transmission and every two months thereafter if transmission continues. Use laboratory testing and epidemiologic linkage for case confirmation together in a sustainable way that allows maximization of laboratory resources. Particularly in endemic settings, epidemiologic linkage should be prioritized during case investigations for routine case confirmation, during confirmed outbreaks, and in times and places where sample collection or transportation is extremely difficult, such as during disasters and remote locations.

In countries that are close to elimination or have been verified, make an attempt to collect from each case a serum specimen and a viral isolation specimen (throat, nasal, or nasopharyngeal swab; oral fluid, urine, or nasopharyngeal aspirates) at the correct time.

The specimens collected for rubella testing are the same as for measles testing, primarily serum specimens for serological testing; naso-/oro-pharyngeal or throat swab; and oral fluid, urine or nasopharyngeal aspirates for virus detection and isolation.

Specimen collection considerations for rubella vary from that for measles in the following ways.

- The follow-up serum sample for IgM testing should be collected after day five post rash onset for rubella IgM re-testing (versus after day three for measles). Samples should still be collected on first contact with the case.
- Urine samples have been used successfully for both measles and rubella virus detection and isolation, but urine is considered to be a less sensitive sample compared to throat swabs for rubella.
- From patients with suspected rubella encephalitis, cerebrospinal fluid (CSF) samples can be collected for testing.

**STORAGE AND TRANSPORT**

Transport and storage requirements for rubella are identical to the requirements for measles specimens.

- **Whole blood/serum.** Collection of whole blood is done by venipuncture using a sterile, plain collection tube or gel separator tube without additives. Whole blood can be stored at 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 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 4–8°C 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. Avoid cycles of repeated freezing and thawing, 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 general
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.

Blood can be dried onto filter paper (dried blood spots, or DBS) if venipuncture 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. Collect blood by finger or heel-prick using a sterile lancet, preferably a single-use disposable lancet. Allow blood specimens that have been spotted on filter paper to air dry completely. Wrap individual cards in wax paper and place them 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 up to 42°C if the sample is delivered to the laboratory within three days.

Oral fluid (OF). An adequate OF sample is one that is collected by gently rubbing along the base of the teeth and gums for at least one 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.

Nasopharyngeal (NP), nasal or oropharyngeal (OP) swabs. An oropharyngeal (throat) 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 rubella virus. Swabs should be collected using only synthetic fiber swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden shafts as they may contain substances that inactivate viruses or inhibit polymerase chain reaction (PCR) testing.

The throat swab is collected by swabbing the posterior pharynx, avoiding the tongue. The NP swab has a flexible shaft. Tilt the patient’s head back and insert the swab into the nostril parallel to the palate. The swab should contact the mucosal surface. Place the sample 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 ice/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 are shipped on dry ice. Avoid freeze/thaw cycles. If storage at -70°C is not available, store samples at -20°C; viral viability will be lost, but the integrity of the viral RNA may be maintained and detected by reverse transcription-polymerase chain reaction (RT-PCR).

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

Regardless of specimen type collected, all specimens should arrive to the lab within five days of collection, except in the case of oral fluids as noted above.
### Specimen types for diagnosis of rubella (and measles)

<table>
<thead>
<tr>
<th>TYPE OF SPECIMEN</th>
<th>TYPE OF TEST</th>
<th>VOLUME TO BE COLLECTED</th>
<th>TIMING OF COLLECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOLE BLOOD/ SERUM (BY VENIPUNCTURE)</td>
<td>Antibody detection* (rubella specific IgM, paired sera to document IgG seroconversion or significant rise in IgG between acute and convalescent phase sera)</td>
<td>Volume of 4–7 mL of blood for older children and adults; 1 mL for younger children; 0.5mL from infants</td>
<td>≤ 28 days after rash onset. Paired sera are normally collected 10–20 days apart. The interval between the two serum samples can be shorter if virus-specific IgG was not detected in the first serum sample.</td>
</tr>
<tr>
<td>ALTERNATIVE SPECIMEN: DRIED BLOOD SPOTS (DBS) (WHOLE BLOOD)</td>
<td>Antibody detection* (rubella specific IgM, paired sera to document IgG seroconversion or significant rise in IgG) Detection of viral RNA by RT-PCR</td>
<td>At least 3 fully filled circles on a filter-paper collection device</td>
<td>≤ 28 days after rash onset</td>
</tr>
<tr>
<td>THROAT (RECOMMENDED), NASAL, OR NASOPHARYNGEAL (NP) SWABS OR NASOPHARYNGEAL ASPIRATES**</td>
<td>Viral isolation by cell culture Detection of viral RNA by RT-PCR***</td>
<td>Swab or NP aspirate</td>
<td>Within 5 days after rash onset for viral isolation (cell culture). Up to 14 days after rash onset if performing virus detection using RT-PCR.</td>
</tr>
<tr>
<td>ORAL FLUID (OF)</td>
<td>Antibody detection* (rubella specific IgM) Detection of viral RNA by RT-PCR</td>
<td>Using a sponge collection device that is rubbed along the gums for &gt; 1 minute to ensure the device is thoroughly wet (~0.5 mL crevicular fluid)</td>
<td>Up to 14 days after rash onset if performing virus detection using RT-PCR. Up to 28 days if antibody testing.</td>
</tr>
<tr>
<td>URINE</td>
<td>Viral isolation by cell culture Detection of viral RNA by RT-PCR</td>
<td>Minimum 10 mL (preference first morning void). Larger volumes have a higher chance of detection.</td>
<td>Within 5 days after rash onset for viral isolation. Up to 14 days after rash onset if performing virus detection using RT-PCR.</td>
</tr>
</tbody>
</table>

* Antibody detection. Adequate samples are those collected within 28 days after onset of rash. However, IgM detection by ELISA for rubella is more sensitive when collected 6–28 days after the onset of rash. 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 ELISA
- Repeat testing of the initial serum specimen fails to resolve an equivocal result for IgM.
TABLE 1 CONTINUATION: SPECIMEN TYPES FOR DIAGNOSIS OF RUBELLA (AND MEASLES)

<table>
<thead>
<tr>
<th>STORAGE CONDITIONS</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 4–8°C until shipment to laboratory, ideally no longer than 7 days.</td>
<td>* Most widely collected and tested, technically simple and standardized * WHO correlate of protection exists</td>
<td>* Sensitivity of the test is lower ≤ 3 days after rash onset* * Positive predictive value of IgM in elimination settings is low</td>
<td>Laboratories should report results for IgM within 4 days of receipt of the specimens.</td>
</tr>
<tr>
<td>Does not require cold chain. Should be dried before storage at low humidity.</td>
<td>* Does not require cold chain * Potentially lower transportation cost * Can collect from finger or heel prick * Potential for viral RNA isolation and antibody detection from same sample</td>
<td>* Sensitivity reduced if not dried/stored properly * Increased workload in laboratory * No quality control on extraction process * Insufficient blood collected in field * Lower sensitivity for RT-PCR</td>
<td>Preference is for serum to be collected, with DBS reserved for situations where it’s hard to collect venous blood (e.g. infants), reverse cold chain cannot be maintained, or where expedited shipping is not possible.</td>
</tr>
<tr>
<td>4–8°C</td>
<td>* Superior to oral fluid for virus isolation * Can be more sensitive for confirmation than serum within first 3 days</td>
<td>* Requires cold chain * Should get to lab within 48 hours ideally</td>
<td>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.</td>
</tr>
<tr>
<td>Does not require cold chain if &lt; 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.</td>
<td>* Less invasive than blood collection * Does not require cold chain * Potentially lower transportation cost * Viral detection and antibody detection from same sample</td>
<td>* 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, need to ship samples to lab within 24 hours of collection</td>
<td>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.</td>
</tr>
<tr>
<td>Stored at 4–8°C until the urine can be centrifuged. Original urine sample should not be frozen prior to centrifugation.</td>
<td>* Often difficult to collect, transport and process * Less sensitive than throat swabs * May contain substances that are inhibitory for RT-PCR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** Properly collected serum tested for IgM is still considered by some labs as the only adequate specimen to rule out rubella. A negative RT-PCR from the upper respiratory tract is not considered to rule out rubella 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 rubella prevalence, these samples can be a significant fraction of the total.

***Virus detection (by cell culture or RT-PCR). Because virus is more likely to be isolated (and RNA detection rate is higher) when specimens are collected early, the collection of specimens for virus detection should not be delayed until laboratory confirmation by antibody detection of a suspected case is obtained. Samples for antibody and viral detection should be collected at first contact with a suspected case.
CONFIRMATION METHODS
Laboratory case confirmation for rubella can yield the following testing results:

- detection of anti-rubella IgM by enzyme immunoassay (EIA). Results of IgM should be reported within four days of the specimen's arrival to the laboratory.
- a diagnostically significant titer change in IgG antibody level in acute or convalescent sera, or documented seroconversion (IgG negative to IgG positive)
- positive RT-PCR or viral isolation in cell culture.

GENOTYPE TESTING
Rubella genotype testing can help to identify the chain of transmission to which the case belongs. It is recommended that at least 80% of laboratory-confirmed chains of transmission have their genotype determined. Molecular typing is recommended because it can provide useful information to track the epidemiology of rubella in a country that has eliminated rubella, and provides monitoring data on rubella virus transmission globally. By comparing virus sequences obtained from new case-patients with other virus sequences, the origin of particular virus types can be tracked.

Results from genotyping samples should be reported within two months of the specimen's arrival to the laboratory.

SPECIAL LABORATORY CONSIDERATIONS

- Sera should be collected as early as possible after onset of illness. However, rubella-specific IgM may be undetectable by EIA in up to 50% of rubella cases with serum samples collected on the day of rash onset, and a proportion of cases will be negative if collected ≤ 5 days after rash onset. For a rubella IgM-negative result in specimens taken on or before five days after rash onset, repeat serologic testing on a specimen collected after five days after rash onset. This is extremely important to confirm cases who are pregnant and in countries that have eliminated rubella.
- Upon vaccination, particularly of adults, IgM antibodies may persist 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 (4).

- False-positive serum rubella IgM tests may occur due to the presence of rheumatoid factors (indicating rheumatologic disease), cross-reacting IgM or infection with other viruses (5).
- IgG peaks between three to five weeks after rash onset, so timing of paired sera is very important to document seroconversion. IgG is most valuable in a suspected case who does not have any exposures or vaccination after the onset date and no maternal antibody (at about nine months). IgG positivity is then confirmatory.
- RT-PCR negative samples should not be used to discard a suspected case.
- Avidity testing and detection of wild-type rubella virus can be used to resolve uncertainties in the serologic evaluation of suspected cases. Low avidity is associated with recent primary rubella infection; high avidity is associated with past infection or reinfection.
- Laboratory testing for measles. Laboratories can perform testing on samples of suspected measles or rubella cases using different testing algorithms, depending on the local epidemiology and available resources. When possible, it is best to integrate the testing of measles and rubella. If resources are sufficient or both diseases occur at a similar prevalence, do measles and rubella testing in parallel, with all samples being tested simultaneously for both diseases. If resources are limited or measles burden is high, do serial testing in which measles testing is done first, followed by rubella testing on samples that are negative for measles. If rubella burden is higher than measles, do the rubella testing first followed by measles testing on samples that test negative for rubella.

- Laboratory testing for other febrile rash illnesses. In countries that use the fever-rash case definition and have a high burden of other fever-rash diseases (such as dengue, Zika and Chikungunya), additional testing can be integrated into the measles-rubella testing algorithm. Weigh the burden of disease and the risk of delayed diagnosis when determining the proper algorithm.
Laboratory testing in an elimination setting. In an elimination setting, critically evaluate both positive and negative IgM testing results. False positives become more likely as the positive predictive value of IgM testing decreases as rubella prevalence decreases. Epidemiological data can strengthen the argument for or against an IgM-positive result representing a true case. A second sample may need to be collected if the original sample that tested negative for rubella was collected ≤ 5 days after rash onset, to ensure they are truly negative. Figures 3a, 3b and 3c demonstrate the process for laboratory testing for suspected measles and rubella cases in elimination settings. Suspected cases in low incidence settings should be evaluated and classified after taking into consideration all laboratory and epidemiological data.

Laboratory networks. WHO coordinates the Global Measles and Rubella Laboratory Network (GMRLN), which is a network of over 700 labs at national and subnational laboratories that meet rigorous standards to provide accurate results (6). Regional and global reference laboratories can provide specialized testing (such as affinity testing) and viral isolation with molecular techniques to those countries that are unable to do this in their own laboratories. Ensure that samples are tested in a WHO accredited or proficient laboratory, or in laboratories with quality assurance support from national labs in GMRLN. If this is not possible, then use a laboratory that has an established recognized quality assurance programme such as ISO 15189 or ISO 17025 accreditation, or CLIA certification.

**FIGURE 3a** Laboratory testing for suspected measles or rubella case in an elimination setting, part I

<table>
<thead>
<tr>
<th>SUSPECTED MEASLES OR RUBELLA CASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLLECT VIROLOGIC SPECIMEN (throat swab, NP swab, oral fluid, urine)</td>
</tr>
<tr>
<td>RT-PCR</td>
</tr>
<tr>
<td>POSITIVE</td>
</tr>
<tr>
<td>RECENT VACCINATION?</td>
</tr>
<tr>
<td>NO, CONFIRM CASE</td>
</tr>
<tr>
<td>YES, 7-14 DAYS PRIOR TO RASH</td>
</tr>
<tr>
<td>PERFORM SEQUENCING to identify and report genotype</td>
</tr>
<tr>
<td>VACCINE SEQUENCE: DISCARD CASE</td>
</tr>
<tr>
<td>WILD TYPE SEQUENCE: CONFIRM CASE</td>
</tr>
<tr>
<td>NEGATIVE</td>
</tr>
<tr>
<td>COLLECT SPECIMEN FOR SEROLOGIC TESTING (serum or oral fluid)</td>
</tr>
<tr>
<td>OTHER CAUSE CONFIRMED by RT-PCR in laboratories that perform such testing routinely?</td>
</tr>
<tr>
<td>YES, DISCARD CASE</td>
</tr>
<tr>
<td>NO, OR TESTING NOT PERFORMED</td>
</tr>
<tr>
<td>CLASSIFY BY SEROLOGIC TESTING</td>
</tr>
</tbody>
</table>
Laboratory testing for suspected measles or rubella case in an elimination setting, part II

**Figure 3b**

**Serum or oral fluid was collected**

- ≥ 4 days post rash for **Measles** or ≥ 6 days for **Rubella**?

**No**

- **Test for IgM**

  - **IgM negative (RT-PCR negative)**

  - **Test for IgM**

    - **IgM positive or equivocal**

    - **Epidemiologic link, strong suspicion or RT-PCR positive?**

    - **Yes**

      - **CONFIRM CASE**

    - **No**

      - **Rule out Rubella**

        - **Measles IgM negative**

        - **Yes**

          - **DISCARD CASE**

        - **No**

          - **SECOND SERUM UNAVAILABLE: CONFIRM CASE**

**Yes**

- **Confirm Case**

**Suspected Rubella Case**

- **Acute serum: Test for Rubella IgG**

  - **Rubella IgG positive**

  - **Rubella IgG negative**

  - **Rubella avidity testing if appropriate**

  - **Repeat IgM**

  - **Test for IgG with paired specimens**

  - **If measles reinfection is suspected, consult with RLC**

**Suspected Measles Case**

- **Other cause confirmed by routine serologic testing?**

  - **No**

    - **Discard case**

  - **Yes**

    - **REQUEST 2nd serum, 21-10 days after acute**

- **Second serum unavailable: confirm case**

**Notes for Figure 3b:**

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

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

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

4. 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.

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

6. 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.

7. Test for IgG if test is available (by semi-quantitative ELA) 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 titer must be interpreted with caution since the ideal timing for demonstration of a rise in titer can vary among individuals.

8. The rise in IgG titer from a measles reinfection case is rapid and remarkably high titer in acute serum are typical. Consultation with the regional laboratory coordinator is recommended to determine if additional testing is warranted and feasible.
FIGURE 3c

Laboratory testing for suspected measles or rubella case in an elimination setting, part III

SERUM OR ORAL FLUID, COLLECTED
≤ 3 days post rash for MEASLES or ≤ 5 days for RUBELLA, has a negative IgM result and RT-PCR negative (or no specimen)

RUBELLA SUSPECTED CASE?

YES, TEST FOR RUBELLA IgG

NEGATIVE RUBELLA IgG

POSITIVE RUBELLA IgG DISCARD CASE

REPORT NEGATIVE IgM RESULT; advise that a 2nd serum (≥ 6 days) should be collected if case remains suspicious for M/R

2ND SERUM OBTAINED

TEST FOR IgM

NEGATIVE

CONFIRM CASE

POSITIVE

DISCARD CASE

2ND SERUM NOT COLLECTED

CLINICALLY COMPATIBLE WITH MEASLES OR RUBELLA?*

NO

YES

DISCARD CASE

FOLLOW GUIDELINES FOR NO/INADEQUATE SPECIMEN

CASE IS CONFIRMED BY:
1) Epidemiologic link
2) Clinically compatible

CASE IS DISCARDED BY:
1) Epidemiologically linked to other disease
2) Other confirmed cause

*Expert review as appropriate
LABORATORY TESTING IN PREGNANT WOMEN

For pregnant women exposed to rubella, medical management and decisions may rest on collection and interpretation of laboratory data. Figure 4 shows recommended laboratory testing algorithm (7).

Particular care should be taken when rubella IgM is detected in a pregnant woman with no history of illness or contact with a rubella-like illness. 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 test results are IgM-positive for persons who have no or low risk of exposure to rubella, additional laboratory evaluation should be conducted (see Figure 4).
Because it is recommended that measles and rubella surveillance be integrated, the case investigation forms, databases and data reporting are usually done together for both diseases. Below is a list of general data elements for both diseases, with rubella-specific data points indicated by *.

**RECOMMENDED DATA ELEMENTS**

**Demographic information**
- Name (in some settings, if confidentiality is a concern, the name can be omitted so long as a unique identifier exists)
- Unique identifier
- Place of residence (city, district, and province)
- Place of infection (at least to third administrative level, if known)
- Date of birth (or age if date of birth not available)
- Sex
- Race and/or ethnicity, if appropriate in country setting
- Country of birth

**Reporting source**
- 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 diarrhea
    - 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 pregnancies (including current one if pregnant)*
- Pregnancy status*
  - Number of weeks gestation at onset of illness*
  - Prior evidence or date of rubella serologic immunity, or both*
  - Number and dates of previous pregnancies and location (second administrative level or country) of these pregnancies*
  - Pregnancy outcome, when available (normal infant, termination, infant with congenital rubella syndrome, 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 seven days prior to and seven days after rash onset (potential persons exposed by the case)

Epidemiological data

» Transmission setting (infection acquired at home, healthcare setting, daycare, school, workplace, etc.)

» Enrolled in a school?
  • If enrolled, 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?

» Relationship to outbreak (Is the case part of an outbreak or is it sporadic?)

Classification

» Final case classification (laboratory-confirmed, epidemiologically-linked, clinically compatible, discarded)

» Source (import, importation-related, unknown, endemic)

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

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Report and analyse case-based data on all suspected cases, regardless of final classification, from local to national level, to allow for adequate epidemiological analysis. Report rubella cases regularly to the next level of the programme within the Ministry of Health (at least monthly, preferably weekly). Reporting should include zero reports (reporting even when no suspected cases have been detected during the designated reporting time period).

Suspected cases of rubella (laboratory-confirmed, epidemiologically linked, clinically compatible and discarded cases) should be submitted to WHO, via country and regional offices, at least monthly. This includes zero reporting. Every WHO Member State uses the Joint Reporting Form (JRF) to report rubella annually. Rubella is not currently reportable under IHR (2005).

RECOMMENDED DATA ANALYSES

» Number of suspected and confirmed cases by age, sex, date of onset (month and year at a minimum, by week in outbreak setting) 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

» 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 base the age groups on the epidemiology of the disease, vaccination schedule and history of the vaccine programme.

» Rubella vaccine status among confirmed and discarded cases by year and geographic area

» Epidemiologic curve showing cases over time by genotype/named strain
Rubella

Proportion of cases by final classification and source
Maps of cases
Proportion of complications and death, stratified by age
Number and proportion of cases in pregnant women by trimester of exposure
Data summaries for endemic and imported virus genotype and lineage characterization

Using data for decision-making
- Confirm cases and outbreaks to take appropriate action to prevent further transmission.
- Determine risk factors for infection and susceptibility gaps in population in order to target vaccination efforts.
- Review epidemiology, especially age distribution, alongside CRS epidemiology to see if change in vaccination strategy should be considered. Shifting of rubella infection to older children and adults can signal an impending CRS problem if the immunity gap is not filled through enhanced vaccination coverage.
- Determine the extent of exposure among pregnant women, as well as the risk and magnitude of possible poor pregnancy outcomes in affected population.
- Characterize transmission patterns and effectiveness of methods to interrupt transmission (for example, nosocomial).
- Verify elimination and sustainability of elimination.
- Because 20–50% of rubella cases are subclinical, analysis 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.

Note about counting rubella cases: Total confirmed rubella cases are the sum of laboratory-confirmed cases, epidemiologically linked cases and clinically compatible cases. However, when disease incidence is very low or a country has achieved or nears rubella elimination, the positive predictive value of the clinically compatible case definition is low and most are likely not rubella. Therefore, in eliminated and near-eliminated settings, total cases are the sum of laboratory-confirmed and epidemiologically linked cases, with the number of clinically compatible cases provided separately. Imported cases should be included in a country’s total case count, unless the source country accepts the cases as part of their case count. Imported cases should be included in analysis but can be analysed separately.

Surveillance performance indicators
Rubella surveillance should be evaluated routinely at national and subnational/local levels, and is frequently important in decision-making by national and regional verification commissions. It is recommended that countries review their national rubella surveillance system annually as the country approaches, achieves and sustains elimination. WHO has established criteria against which rubella (and measles) surveillance should be evaluated (Table 2). Additionally, rubella surveillance should be reviewed within the context of comprehensive VPD surveillance reviews, which should be conducted at least every five years.

Table 2 is a list of indicators against which the rubella surveillance system can be evaluated in order to help pinpoint problems and make improvements.
### Table 2: Indicators of the quality of surveillance for rubella (and measles)

<table>
<thead>
<tr>
<th>Surveillance Attribute</th>
<th>Indicator</th>
<th>Target</th>
<th>How to Calculate (Numerator / Denominator)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timeliness of Reporting</strong></td>
<td>Percentage of surveillance units reporting on time, even in the absence of cases</td>
<td>≥ 80%</td>
<td># of surveillance units in the country reporting by the deadline / # of surveillance units in the country x 100</td>
<td>At each level, reports should be received on or before the requested date.</td>
</tr>
</tbody>
</table>
| **Timeliness and Completeness of Investigation** | Percentage of all suspected measles and rubella cases that have had an adequate investigation initiated within 48 hours of notification | ≥ 80%                                       | # of suspected cases of measles or rubella for which an adequate investigation was initiated within 48 hours of notification / # of suspected measles and rubella cases x 100 | Note 1: An adequate investigation includes collection of all the following data elements from each suspected measles or rubella case: name or identifiers, place of residence, place of infection (at least to district level), age (or date of birth), sex, date of rash onset, date of specimen collection, measles-rubella vaccination status, date of all measles-rubella or measles-mumps-rubella vaccination, date of notification, date of investigation and travel history.  
Note 2: Some variables may not be required for cases that are confirmed by epidemiological linkage (for example, date of specimen collection). |
<p>| <strong>Sensitivity</strong> | Reporting rate of discarded non-measles non-rubella cases at the national level | ≥ 2/100,000 population per 12 months | # suspected cases that have been investigated and discarded as a non-measles and 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 / national population x 100,000 |                                                                                                                                           |</p>
<table>
<thead>
<tr>
<th>SURVEILLANCE ATTRIBUTE</th>
<th>INDICATOR</th>
<th>TARGET</th>
<th>HOW TO CALCULATE (NUMERATOR / DENOMINATOR)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOURCE CLASSIFICATION</strong></td>
<td>Percentage of confirmed cases for which source of transmission is classified as endemic, import or importation-related.</td>
<td>≥ 80%</td>
<td># confirmed cases in which the source can be classified as endemic, import, or importation-related / total number of confirmed cases x100</td>
<td>Unknown source 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</td>
</tr>
<tr>
<td><strong>REPRESENTATIVENESS</strong></td>
<td>Percentage of subnational administrative units (at the province level or its administrative equivalent) reporting at least 2 discarded non-measles non-rubella cases per 100,000 population per year</td>
<td>≥ 80%</td>
<td># of subnational units achieving ≥ 2 per 100,000 population discard rate / # of subnational units x 100</td>
<td><strong>Note 1:</strong> If the administrative unit has a population &lt;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 neighboring administrative units can be combined for the purpose of this calculation. <strong>Note 2:</strong> Administrative units should include all cases reported from their catchment area, including import and importation-related cases, and cases residing in neighboring administrative units but reported in this one.</td>
</tr>
<tr>
<td><strong>SPECIMEN COLLECTION AND TESTING ADEQUACY</strong></td>
<td>Percentage of suspected cases with adequate specimens for detecting acute measles or rubella infection collected and tested in a proficient laboratory</td>
<td>≥ 80%</td>
<td># of suspected cases with an adequate specimen tested in a proficient lab / # of suspected cases - # of suspected cases of measles or rubella that are not tested by a laboratory and are (a) confirmed as measles or rubella by epidemiological linkage or (b) discarded as non-measles and non-rubella by epidemiological linkage to another laboratory-confirmed communicable disease case x 100</td>
<td><strong>Note 1:</strong> Adequate specimens are: a blood sample by venipuncture in a sterile tube with a volume of at least 1 mL for older children and adults and 0.5 mL for infants and younger children; a dried blood sample, at least 3 fully filled circles on a filter-paper collection device; an oral fluid sample using a sponge collection device that is rubbed along the gums for &gt; 1 minute to ensure the device is thoroughly wet; a properly collected upper respiratory tract specimen for RT-PCR. Adequate samples for antibody detection are those collected within 28 days after onset of rash, and for RT-PCR within 5 days of rash onset. <strong>Note 2:</strong> A proficient laboratory is one that is WHO accredited or has established a recognized quality assurance programme (such as the International Organization for Standards (ISO) or Clinical Laboratory Improvement Amendments (CLIA) certified).</td>
</tr>
</tbody>
</table>
Rubella is usually a mild, self-limiting disease that does not require specific treatment. Patients with rubella should have contact isolation precautions put in place for seven days after they develop a rash. Particular emphasis should be placed on preventing exposure to pregnant women. Cases of CRS are managed differently, as discussed in the CRS surveillance chapter.

<table>
<thead>
<tr>
<th>SURVEILLANCE ATTRIBUTE</th>
<th>INDICATOR</th>
<th>TARGET</th>
<th>HOW TO CALCULATE (NUMERATOR / DENOMINATOR)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIRAL DETECTION</strong></td>
<td>Percentage of laboratory-confirmed outbreaks with samples adequate for detecting rubella virus collected and tested in an accredited laboratory</td>
<td>≥ 80%</td>
<td># of outbreaks for which adequate samples have been submitted for viral detection / # of outbreaks identified x 100</td>
<td>Where 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. For virus isolation, adequate throat or urine samples are those collected within 5 days after rash onset. For virus detection using molecular techniques, adequate throat samples are those collected up to 14 days after onset of rash, and adequate oral fluid samples are those collected up to 21 days after onset of rash.</td>
</tr>
<tr>
<td><strong>TIMELINESS OF SPECIMEN TRANSPORT</strong></td>
<td>Percentage of specimens received at the laboratory within 5 days of collection</td>
<td>≥ 80%</td>
<td># of specimens received within 5 days of collection by laboratory / # of specimens x 100</td>
<td>Indicator only applies to public laboratories.</td>
</tr>
<tr>
<td><strong>TIMELINESS OF REPORTING LABORATORY RESULTS</strong></td>
<td>Percentage of IgM results reported to national public health authorities by the laboratory within 4 days of specimen receipt</td>
<td>≥ 80%</td>
<td># of IgM test results reported within 4 days of specimen receipt / # of specimens received by lab x 100</td>
<td>Indicator only applies to public laboratories.</td>
</tr>
</tbody>
</table>
Rubella

CONTACT TRACING AND MANAGEMENT

Make every effort to conduct case investigations and identify contacts for all suspected cases. Persons who have been in contact with cases of rubella during their infectious period (between 7 days before and 7 days after the rash onset) should be located and interviewed to determine their past exposure and vaccination status. It is important to note that CRS cases themselves can transmit rubella virus. Contacts of CRS cases are different from contacts of acquired rubella as CRS cases may shed rubella virus for up to 12 months from birth. However, exposure for CRS cases is through contact with the case (touching), while exposure from rubella disease is through airborne transmission. Therefore, cases should also be asked about exposure to potential CRS cases.

Because of its infectious nature, contact tracing is essential to determine both the source of infection for the rubella case (endemic vs. imported/importation-related), as well as identify those whom the case may have subsequently infected. Any person who had contact with the rubella case in the 7 days before rash onset to 7 days after rash onset (or contact with a confirmed CRS case) have been exposed and possibly infected, and should be monitored by public health authorities for 23 days from last contact with the confirmed case. Contact for acquired rubella refers to sharing the same air space, usually an enclosed area, (for example, living in the same household or being in the same room, school, health facility waiting room, office or transport) for any length of time with a case during the case’s infectious period. Contact tracing is particularly important in schools due to the intensity of exposure and the presence of non-immune children. In healthcare settings, rubella can also be amplified, with an elevated risk due the presence of vulnerable, susceptible populations (such as the very young, immunocompromised and patients with underlying illnesses) as well as hospitalized CRS cases.

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 and to confirm seroprotection. Pregnant contacts who have evidence of infection should be followed throughout the pregnancy. Currently, there is limited evidence demonstrating that post-exposure prophylaxis is efficacious. Immunoglobulin is generally not recommended for routine post-exposure prophylaxis of rubella, even when high titer anti-rubella immunoglobulin is available. Vaccination can be given in the first 48 hours after exposure to non-pregnant contacts who have no documented protection against rubella.
SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN OUTBREAK
A single laboratory-confirmed case should trigger an aggressive public health investigation and response in an elimination setting. An outbreak is defined as two or more laboratory-confirmed cases which are temporally related (with dates of rash onset occurring 12–23 days apart) and epidemiologically or virologically linked.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

Enhance surveillance. Routine passive surveillance should be enhanced during an outbreak (for example, increasing awareness and messaging to clinicians and laboratories). Active surveillance should be established, including laboratory confirmation of cases that are identified by regular visits and record review at health facilities (both public and private, and other settings). 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. Establish intensified surveillance in neighbouring villages, districts and possibly provinces in response to laboratory-confirmed cases or outbreaks to detect and minimize the spread of the outbreak. If the number of cases is large, line listing can be used for collecting the key data elements.

Increased frequency of reporting. During an outbreak, reporting should be at least weekly after the initial report. If timely case-based reporting during an outbreak is not feasible because of the large number of cases, case-based data should still be collected and entered into the database as soon as it becomes feasible. Health workers should be alerted about the rubella outbreak and given instructions on where to report suspected cases. Weekly reporting, including zero reporting in the absence of cases, should continue for the duration of the outbreak and for at least two incubation periods after the onset of the last laboratory-confirmed or epidemiologically linked case. Rubella outbreaks should be reported to WHO through country and regional offices.

Changes to laboratory testing. During an outbreak, laboratory confirmation should be sought for the initial 5–10 cases in a given district (or equivalent administrative unit). In addition to collecting specimens for antibody detection, laboratory confirmation should include obtaining specimens for virus characterization in order to identify the involved strain and its potential origin (endemic versus imported). Once the outbreak is confirmed, subsequent cases can be primarily confirmed based on epidemiological linkage to a laboratory-confirmed case. However, laboratory confirmation should be sought for all suspected cases in pregnant women. If suspected cases are reported outside the initially affected geographic area and there is no clear epidemiological linkage with the initial outbreak, the first 5–10 suspected cases in these other areas should also be tested to confirm the cause. If the outbreak continues, another 5–10 suspected cases should be tested every two months. Following laboratory confirmation of initial rubella case(s), emphasis should be given to epidemiological investigation aimed at confirmation of new cases by epidemiological linkage with the confirmed case. Each outbreak should have a sample collected for genotyping.

CRS surveillance. Establish or strengthen active CRS surveillance in maternity hospitals, paediatric hospitals, neonatal intensive care units and amongst specialists who treat infants with cardiac, hearing or eye problems. Prioritize hospitals located in the area where the outbreak is occurring. Establish a pregnancy registry to document all pregnancy outcomes. These may include abortions (spontaneous and therapeutic), fetal deaths, CRS cases and infants with congenital rubella infection. As mortality of children with CRS can be elevated for up to 2 years of age, CRS surveillance should continue for one to two years after the last rubella case.

Though very rare, concomitant outbreaks of measles and rubella have been known to occur. It is important in these settings to conduct good epidemiological and laboratory investigations according to national guidelines. Appropriate investigations will ensure that appropriate response activities are implemented including case management, vaccination response, and infection control practices.
PUBLIC HEALTH RESPONSE

Outbreak response immunization is indicated for confirmed rubella outbreaks, specifically where the vaccine has been introduced. The extent of the vaccination response will depend on the epidemiological picture. For sporadic cases and very small outbreaks of fewer than 10 cases in geographically limited (same village) or low-risk areas, it may be sufficient to do selective immunization of contacts (excluding pregnant women) in the immediate area of the outbreak (involved and surrounding villages). Health staff without known immunity to rubella should also be vaccinated, and routine immunization services should be reinforced. For larger outbreaks or when the risk assessment indicates there are large areas that are at risk, consider doing a non-selective approach targeting larger areas, with the target age group determined by disease epidemiology and population immunity profiles.

Efforts should be made to minimize transmission in healthcare settings, with particular emphasis on pregnant women, by ensuring immunity of health workers including public health staff, laboratory staff, medical students and nursing students. Implement infection control practices in healthcare settings (isolation of cases up to seven days after rash onset.)

SPECIAL CONSIDERATIONS FOR RUBELLA SURVEILLANCE

As rubella control progresses towards elimination, the sensitivity and specificity of surveillance systems should increase. If resources permit, periodic seroprevalence surveys could be used to supplement the surveillance data to identify immunity gaps in a population. These surveys could include collection of samples from women attending antenatal clinics. Monitoring changes in age-specific and sex-specific seroprevalence provides data for identifying modifications that may need to be made to the immunization strategy.
REFERENCES CITED


ADDITIONAL REFERENCES


