Infectious Disease Epidemiology Section
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MEASLES

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Measles is an acute viral illness caused by a Morbillivirus (RNA virus with envelope), included in the Paramyxovirus family. Other Morbillivirus are the cattle rinderpest virus (likely parent virus) and the canine distemper virus.

Wild-type measles viruses have been divided into eight distinct genetic groups (clades) according to the nucleotide sequences of their hemagglutinin and nucleoprotein genes, with approximately 7% nucleotide variability between the most distantly related viruses. There are eight lineages or clades designated A through H, which are further subdivided into 21 genotypes.

Epidemiology

Before the introduction of measles vaccine in 1963, practically all children became infected by four years of age. Since then, measles incidence decreased drastically. In recent years, outbreaks of measles have been small, with less than 20 cases reported. Recent outbreaks do not have a predominant setting but typically involve people who are exposed to imported measles cases and who are unvaccinated or have received only one dose of measles vaccine. The current surveillance data indicate that measles virus transmission in the 'Region of the Americas' (World Health Organization (WHO) has been reduced in 2002 to historically low levels and possibly interrupted.

The Global Burden of Disease 2000 Study estimated that measles resulted in 777,000 deaths worldwide in 2000, of which 452,000 (58%) deaths were in the 'African Region' of the WHO.

Humans are the only known hosts of measles. The measles virus does not persist in the host except in a few cases, particularly the patients with Subacute Sclerosing Panencephalitis (SSPE). Patients with SSPE are not contagious.

Aerosols are the most important mode of transmission. Measles is transmitted by direct contact with infectious droplets or, less commonly, by airborne spread. The most infectious stage of the disease is associated with sneezing and coughing (late prodromal phase). The mucosal cells of the respiratory tract are the main source of disseminated virus. Infected cells produce viruses for several days before dying. There is no good estimate for the amount of viruses put out in droplets, but judging from the difficulties in isolating the virus, the concentration must be low. On development of antibodies, virus excretion is rapidly curtailed. By the time the rash appears, viral excretion starts to decrease. The urine remains infectious for several days but this is not a usual route of transmission.

Once the virus has been cleared within a few days from the onset of the rash, it does not reappear.

Other direct modes of transmission may occur.

The virus is very labile in the environment. In a very favorable liquid environment, its infectivity is halved in two hours. It is rapidly inactivated on a dry surface, therefore it cannot be transmitted by fomites. It is inactivated easily at pH5 therefore cannot infect through the GI tract. In aerosols, it was found to be most stable when the humidity is less than 40% or greater than 80% which may explain the seasonal

transmission: in winter, people congregate more often in confined places which are heated with having a humidity of less than 40%. In Sahelian Africa, measles epidemics occur during the hot dry season.

Portal of entry: The virus may enter through the lower respiratory tract (most susceptible) and the nose but, not through the buccal mucosa or the eye.

Communicability Patients are contagious from one to two days before the onset of symptoms (three to five days before the rash) to four days after the appearance of the rash. Immunocompromised patients who may have prolonged excretion of the virus in respiratory sections, can be contagious for the duration of the illness.

Measles is one of the most contagious diseases spread by the airborne or droplet route. Secondary attack rates among susceptible individuals in households are commonly around 75%. A significant proportion of measles have been linked to transmission in medical facilities (inpatients and outpatients). In an outbreak reported in Oklahoma (Istre, 1987*), 45% of cases were linked to exposure in medical offices or waiting rooms. A study of measles cases reported to the Centers for Disease Control and Prevention (CDC) from 1980 to 1984, identified 241 cases (1% of all reported cases) that were related to exposure in medical facilities (Davis, 1986**). In one outbreak, (Bloch, 1985***) a 12 year-old boy was examined in a physician's suite on the second day of the rash. The boy was coughing vigorously. He was quickly led to the examining room where he stayed for one hour. After examination, he was escorted out rapidly. There was no contact with other patients in the waiting room. Four patients who were examined subsequently in the same examining room became infected; one of them had gone into the examining room one hour after the index case. Three additional patients who had been in a different waiting room also became infected, thus proving airborne transmission over long distances through recirculated air.

Maternal antibodies are transferred to the newborn. Mothers who have been immunized have approximately half the antibody titers of naturally infected mothers.

Older children are exposed to larger populations and are therefore more exposed; an infant is only exposed to his immediate family (few siblings); a toddler going to a child-care center may be exposed to ten to 30 children; an elementary school child may be exposed to a few hundred others; a high school child may be exposed to a few thousand classmates. If older age groups are not well-protected against measles, there is a marked increase in the age at which measles occur.

The incubation period is generally eight to 12 days from exposure to onset of symptoms; the average interval from exposure to appear of the rash is 14 days. The interval tends to be shorter among children and longer among adults (21 days).

** Istre GR et al, 1987. Measles spread in medical settings: An important focus of disease transmission? Pediatrics 79: 356-358.*
*** Davis RM et al, 1986. Transmission of measles in medical settings: 1980 through 1984. JAMA 255: 1295-1298.*
**** Bloch AB et al 1985. Measles outbreak in a pediatric practice: Airborne transmission in an office setting. Pediatrics 75: 676-683.*

Clinical Description

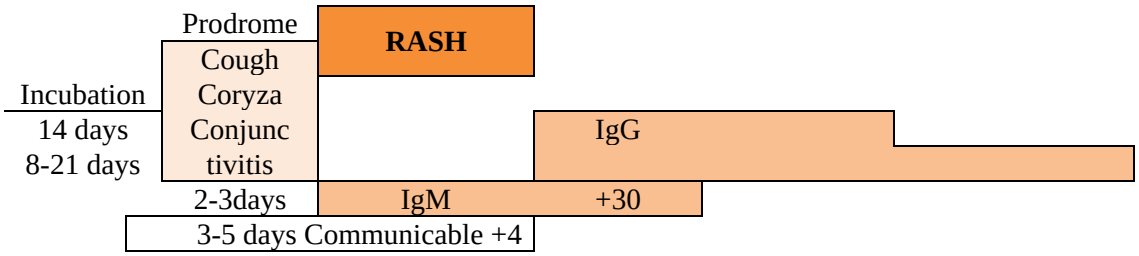
Measles is characterized by a prodrome of fever and malaise, cough, coryza and conjunctivitis, followed by a maculopapular rash. Measles is usually a mild or moderately severe illness. However, measles can result in residual neurological impairment from encephalitis in approximately five to ten cases per 10,000 reported cases and in death in approximately one to three cases per 1,000 reported cases. Pneumonia complicates 6% of measles in the United States; 19% of cases are hospitalized.

Typical measles
Measles is an acute disease characterized by fever, cough, coryza, conjunctivitis, an erythematous maculopapular rash and a pathognomonic enanthem (Koplik spots). The catarrhal syndrome is very prominent in measles. (The Koplik are very useful for the diagnosis because they are not seen in other rash illnesses. They do not appear in all cases. There are no enlarged nodes as in rubella.)

Clinical Case Definition

An illness characterized by all the following:

- a generalized maculopapular rash lasting greater than or equal to three days
- a temperature greater than or equal to 101.0°F (greater than or equal to 38.3°C)
- cough, coryza, or conjunctivitis
- linked epidemiologically to a confirmed case



Complications such as otitis media, bronchopneumonia, laryngotracheobronchitis (croup), and diarrhea occur more commonly in young children.

The clinical diagnosis of measles has a very poor positive predictive value (<1%) because of its low incidence rate. It should always be laboratory confirmed.

Atypical measles

1-Killed vaccine: Killed vaccine were used during the 1960s. After a few years, vaccine protection waned and such individuals when exposed, experienced an hemorrhagic form of measles with pneumonia.

2-Immunocompromised individuals: In immunocompromised individuals, measles is associated with a giant cell pneumonia and severe respiratory distress. No rash appears. The mortality is 40%.

Mortality: The age-specific mortality rate is highest during the first six months, declines for the first five years, and then is followed by an slow increase until age 60 years (where mortality rate is similar to infants).

Death, predominantly due to respiratory and neurologic complications, occurs in one to two of every 1000 cases. Case fatality rates are increased in immunocompromised children, including those with leukemia and HIV infection; sometimes the characteristic rash does not develop in these patients.

Encephalitis: Abnormal encephalographic patterns are usual in measles. It appears that some minor cerebral involvement is usual. Acute encephalitis, occurs in approximately one of every 2,000 cases. Encephalitis occurs six to 15 days after the rash.

Subacute sclerosing panencephalitis (SSPE): SSPE, a rare degenerative central nervous system disease is a result of a persistent measles virus infection that develops years after the original infection. Its frequency is 1:100,000 to 1:300,000 cases of measles. It is characterized by a slow onset of mental deterioration and progresses in a few years to coma and death. It is accompanied by high titers of antibodies in the blood and CSF (high ratio CSF:Blood 320:1). Measles viral antigen and genome are demonstrable in the lesions but no viable virions.

Laboratory Criteria for Diagnosis

In order of preference:

- Detection of measles-virus-specific nucleic acid by polymerase chain reaction, or
- Isolation of measles virus from a clinical specimen, or
- Positive serologic test for measles immunoglobulin M antibody, or

- Significant rise in serum measles immunoglobulin G antibody level between acute- and convalescent-phase specimens, by any standard serologic assay

Case Classification

Suspected: any febrile illness accompanied by rash

Probable: a case that meets the clinical case definition, has noncontributory or no serologic or virologic testing and is not epidemiologically linked to a confirmed case

Confirmed: a case that is laboratory-confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed case. A laboratory-confirmed case does not need to meet the clinical case definition.

Laboratory Tests

Because measles is an extremely rare disease in the United States, clinical evidence is not sufficient to confirm a case of measles. Many clinicians have never seen a case of measles and most patients who present with measles-like illness today, do not have measles. Because measles is such a highly contagious disease, with the potential for explosive spread following importation of the virus, it is critical to rapidly identify the few measles cases that do occur. For these reasons, it is crucial to use laboratory diagnosis to confirm the measles cases among the thousands of patients with suspected measles.

Because measles is so rare, even with the excellent laboratory tests available, there will be some false positive results. (The positive predictive value [PPV] of a test is the proportion of people with positive results who actually have the disease). The PPV decreases when the disease becomes rare.) Some false positive results are expected and it is preferable to misclassify as measles a few cases that are not actually measles than to miss cases that are measles.

To minimize the problem of false positive laboratory results, it is important to restrict case investigation and laboratory tests to patients most likely to have measles, those with fever and generalized maculopapular rash. Testing for measles in patients with no rash, no fever, a vesicular rash, or a rash limited to the diaper area leads to an increase of false positive results.

Virus Detection or Isolation

Nucleic Acid Amplification

Detection of the measles virus by reverse transcription polymerase chain reaction (RT-PCR) in clinical specimens is the preferred test to confirm a case of measles. This test is highly sensitive as long as specimens are obtained within ten days of the rash onset and stored under proper conditions. False negatives can occur, however, if the specimens are mishandled.

Virus Culture

The measles virus can also be isolated from a culture of nasopharyngeal swabs or aspirates, throat swabs, urine, or heparinized blood. While a positive culture is confirmatory of a measles case, it is not recommended for routine laboratory diagnosis because it can take weeks to perform. Isolation of measles virus is technically difficult and is generally performed in research laboratories.

Collection site

Measles virus is present in urine, nasopharyngeal aspirates, heparinized blood, or throat swabs. These specimens should be collected as soon as measles is suspected and should be shipped to the state public

health laboratory or the CDC, at the direction of the state health department. PCR and virus culture are most effective if specimens are obtained within three days of the appearance of the rash. However, samples can be taken up to ten days afterward. Testing both respiratory and urine samples increases the likelihood of detecting the virus.

- **Throat swab**- vigorously swab tonsillar areas and posterior nasopharynx with a viral culturette. Use tongue blade to depress tongue to prevent contamination of swab with saliva. Place swab into a Viral Transport medium (VTM).
- **Urine specimen**- Collect 10 to 40 mL of urine in a sterile 50 mL centrifuge tube or a urine specimen container. First-morning voided specimens are preferred because they generally contain a higher concentration of viral cells. However, any urine collection is adequate. Have patient void directly in container, collecting from the first part of the urine stream if possible.
- **Nasal or nasopharyngeal swab**- Use sterile swabs to swab the nasal passage or the nasopharynx with either a viral culture swab or culturette. Do no use special (e.g., aneaerobic) media. Place swab into VTM.

All specimens should be stored at 4º C and delivered to the lab within 48 hours. Caution should be taken to avoid exposing specimens to heat, as the virus is highly sensitive.

In addition to confirming a case of measles, viral culture and RT-PCR are both extremely important for molecular epidemiologic surveillance to help determine:

1) the origin of the virus
2) which viral strains are circulating in the United States
3) whether these viral strains have become endemic in the United States

This information is helpful in tracing the transmission of the virus, and can be used to compare different strains from different locations and years.

Serologic testing

Serologic testing for antibodies to measles is widely available and commonly used. However, it results in many false positives, so it should not be the sole confirmation of diagnosis. Generally, in a previously susceptible person exposed to either vaccine-related or wild-type measles virus:

- The IgM response starts first around the time of rash onset and is transient, persisting one to two months. The response may take as long as four days after the rash appears.
- The IgG response starts more slowly, at about seven days after rash onset, but typically persists for a lifetime.

Evidence of acute measles infection can be supported by detecting IgM antibody to measles in a single serum specimen. Detecting a rise in the titer of IgG antibody in two serum specimens drawn roughly two weeks apart is not a practical way of confirming measles because of the two-week delay between blood collection. Therefore, this test is rarely used to confirm diagnosis. Uninfected persons are IgM negative and will either be IgG negative or IgG positive depending upon their previous infection or vaccination histories.

Recommendations for serologic testing for measles:

- An enzyme immunoassay (EIA) test for IgM antibody to measles in a single serum specimen, drawn at the first contact with the suspected measles case, is not as useful as the RT-PCR test but can be used as supportive evidence for a confirmed case.
- A single specimen test for IgG is the most commonly used test for immunity to measles because IgG antibody is long lasting.
- Testing for IgG along with IgM is recommended for suspected measles cases.
- When a patient with suspected measles has been recently vaccinated (six to 45 days prior to testing) neither IgM nor IgG antibody responses can distinguish measles disease from the response to

vaccination. After immunization, 2% are IgM positive at one week, 75% at one month, and 10% are still positive after two months.

Tests for IgM antibody

Although there are multiple possible methods for testing for IgM antibody, EIAs are the most consistently accurate tests and are therefore the recommended method. There are two formats for IgM tests.

The first and most widely available is the indirect format. IgM tests based on the indirect format require a specific step to remove IgG antibodies. Problems with removal of IgG antibodies can lead to false positive tests or, less commonly, false negative results. Tests that are negative in the first 72 hours after rash onset should be repeated; serum should be obtained for repeat testing 72 hours after rash onset. IgM is detectable for at least 30 days after rash onset and frequently longer.

The second format, **IgM capture**, does not require the removal of IgG antibodies. The CDC has developed a capture IgM test for measles and has trained personnel from every state public health laboratory. This is the preferred reference test for measles. One direct-capture IgM EIA is commercially available.

EIA tests for measles are often positive on the day of rash onset. However, in the first 72 hours after rash onset, up to 30% of tests for IgM may give false negative results. Tests that are negative in the first 72 hours after rash onset should be repeated; serum should be obtained for repeat testing 72 hours after rash onset. IgM is detectable for at least 28 days after rash onset and frequently longer

IgM tests commonly result in false positives, so additional tests should always be performed. With the elimination of measles in the United States, the positive predictive value of a serologic test has become extremely low. False positive IgM results for measles may be due to the presence of rheumatoid factor in serum specimens. Serum specimens from patients with other rash illness, such as parvovirus B19, rubella, and roseola have been observed to result in false positive reactions in some IgM tests for measles.
False positive tests may be suspected when:

- Thorough surveillance reveals no source or spread cases
- The case does not meet the clinical case definition
- The IgG result is positive within seven days of rash onset
- Subject is adequately immunized

In these situations, confirmatory tests may be done at the state public health laboratory or by the CDC. IgM results by tests other than EIA can be validated with EIA tests. Indirect EIA tests may be validated with capture EIA tests. RT-PCR can help to differentiate actual positives and false positives.

Tests for IgG antibody

Because tests for IgG require two serum specimens and because a confirmed diagnosis cannot be made until the second specimen is obtained, IgG tests are not practical. However, if the IgM tests remain inconclusive, a second (convalescent) serum specimen, collected 14 to 30 days after the first (acute) specimen, can be used to test for an increase in the IgG titer. These tests can be performed in the state laboratory or by the CDC.

A variety of tests for IgG antibodies to measles are available and include EIA, hemagglutination inhibition, indirect fluorescent antibody tests and plaque reduction neutralization. Complement fixation, although widely used in the past, is no longer recommended. The gold standard test for serologic evidence of recent measles virus infection is the plaque reduction neutralization test of IgG in acute and convalescent paired sera.

IgG testing for laboratory confirmation of measles requires the demonstration of a rise in the titer of antibody against measles. The tests for IgG antibody should be conducted on both acute and convalescent specimens at the same time; the same type of test should be used on both specimens. The specific criteria for documenting an increase in titer depend on the test. EIA values are not titers and increases in EIA values do not directly correspond to titer rises.

The state laboratory now has the capability of performing ELISA testing for IgG and IgM antibody interpretation. (IgG indicates past infection or prior immunization and an immune status. IgM indicates active infection.) The ELISA for IgG can be utilized in testing the immune status of an individual.

Specimens for serologic testing and virus isolation should be obtained at the same time, as soon as measles is suspected. Collect one red-topped tube of blood within seven (7) to ten (10) days after the onset of illness. A second specimen (two weeks later) is required for a comparative approach, as in the CF test and/or conversion test. It is imperative that the lab slip indicates the onset date of the suspected case's signs and symptoms of illness and the time interval between the onset of symptoms and the date of blood collection. Without this information, the lab cannot accurately interpret the laboratory results. The blood is to either be spun down and the sera sent or, the whole blood sent refrigerated.

The CDC can perform measles culture and can differentiate between a vaccine strain and a wild type measles strain. The specimens of choice are throat swabs or urine collected as soon possible after the appearance of the rash. For future reference, the Measles Laboratory contact numbers are:

Measles Lab at the CDC
Lab Coordinator, Jennifer Rota (404) 639-1156
Lab Chief, Dr. William Bellini (404) 639-4183

Surveillance

Measles is a condition reportable within 24 hours of diagnosis.

The highly contagious measles virus is frequently imported into the United States by persons from other countries. Each imported measles case could start an outbreak, especially if under-vaccinated groups are exposed. Surveillance and prompt investigation of cases and contacts help to halt the spread of disease. Information obtained through surveillance is also used to assess progress towards disease elimination goals. Surveillance data are used to characterize persons, groups, or areas in which additional efforts are required to reduce disease incidence.

Epidemiologic Classification of Internationally-Imported and U.S.-Acquired

Internationally imported case: An internationally imported case is defined as a case in which measles results from exposure to measles virus outside the United States as evidenced by at least some of the exposure period (seven to 21 days before rash onset) occurring outside the United States and rash onset occurring within 21 days of entering the United States and there is no known exposure to measles in the U.S. during that time. All other cases are considered U.S.-acquired.
U.S.-acquired case: An U.S.-acquired case is defined as a case in which the patient had not been outside the United States during the 21 days before rash onset or, was known to have been exposed to measles within the United States.

U.S.-acquired cases are sub-classified into four mutually exclusive groups:

> **Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.
>
> **Imported-virus case:** a case for which an epidemiologic link to an internationally imported case was not identified, but for which viral genetic evidence indicates an imported measles genotype, i.e., a genotype that is not occurring within the United States in a pattern indicative of endemic transmission. An endemic genotype is the genotype of any measles virus that occurs in an endemic chain of transmission (i.e., lasting more than or equal to 12 months). Any genotype that is found repeatedly in U.S.-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.

Endemic case: a case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of measles virus transmission that is continuous for more than or equal to 12 months within the United States.

Unknown source case: a case for which an epidemiological or virological link to importation or to endemic transmission within the U.S. cannot be established after a thorough investigation. These cases must be carefully assessed epidemiologically to assure that they do not represent a sustained U.S.-acquired chain of transmission or an endemic chain of transmission within the U.S.

Note: Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases.

States may also choose to classify cases as "out-of-state-imported" when imported from another state in the United States. For national reporting, however, cases will be classified as either internationally imported or U.S.-acquired.

Report and Confirm Cases

Prompt recognition, reporting and investigation of measles are important because the spread of the disease can be limited with early case identification and vaccination of susceptible contacts. One laboratory-confirmed case of measles constitutes an outbreak and will require rapid mobilization for investigation and containment.

Investigation

The purpose of investigation is to prevent transmission to the susceptible population. Essential components of case investigation include establishing a diagnosis of measles, differentiating between other rash illnesses, obtaining immunization histories for confirmed cases, identifying sources of infection, assessing potential for transmission, identifying suspected cases as soon as possible and obtaining specimens for viral isolation.

1. Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information also may be collected at the direction of the state health department:

- Demographic information -name -address -date of birth -age -sex -ethnicity -race
- Reporting source -county -earliest date reported
- Clinical -date of rash onset -duration of rash -rash presentation -symptoms -date of onset of symptoms -hospitalizations -complications
- Outcome (case survived or died) -date of death
- Laboratory -serological test results -date of collection of specimen for virus isolation
- Vaccination status -number of doses of measles vaccine received -dates of measles vaccinations -manufacturer name -vaccine lot number -if not vaccinated, reason
- Epidemiological -transmission setting -source of transmission (e.g., age, vaccination status, relationship to decedent) -source of exposure (contact with probable or confirmed case, or contact with immigrants or travelers) -import status (indigenous, international import, or out -of-state import)
- Travel history

2. Verify whether diagnosis has been confirmed by blood test. If not, it is important to try and obtain a serum specimen within seven to ten days of onset of illness. Obtain the physician's permission and explain the importance to the parent/patient. The physician may agree to draw the blood himself and make arrangements for the public health nurse to pick up the specimen from his office. If a physician appears uncooperative, notify the regional Disease Surveillance Specialist (DSS) or the Immunization Section. A nurse may need to make a home visit to obtain the specimen. If the patient is to be brought into the health

unit for the blood test, be sure to set up a time and place that will minimize exposure to other health unit patients, (i.e., use a separate entrance without access to the waiting room, parking lot, etc.).

Even in outbreaks, laboratory confirmation should be obtained for as many cases as possible. Once community awareness is increased, many cases of febrile rash illness may be reported as suspected measles and the magnitude of the outbreak may be exaggerated if these cases are included in the absence of laboratory confirmation. This is particularly important as the outbreak is ending; at that point, laboratory confirmation should be sought for all suspected cases.

The occurrence of measles-like illness in recently vaccinated persons can pose particular difficulties in the outbreak setting. Ten percent of recipients of measles-containing vaccine may develop fever and rash approximately one week after vaccination and the vaccination of susceptible people results in the production of IgM antibody that cannot be distinguished from the antibody resulting from natural infection. A positive measles IgM test cannot be used to confirm the diagnosis of measles in persons with measles-like illness who received measles vaccine six to 45 days before onset of rash. A negative test would exclude the diagnosis. Persons with measles-like illness who received measles vaccine six to 45 days before onset of rash should be classified as confirmed cases of measles only if (1) they meet the clinical case definition and (2) they are epidemiologically linked to a laboratory-confirmed case. For persons receiving vaccine six to 14 days prior to rash onset, specimens for viral isolation should be obtained in addition to serologic testing (see "Laboratory Tests"); isolation of wild-type measles virus would allow confirmation of the case.

Obtain specimens (urine or nasopharyngeal mucus) for virus isolation from all cases (or from at least some cases in each outbreak) at the time of the initial investigation; do not wait to receive serologic test results.

3. Obtaining accurate and complete immunization histories on all confirmed cases. Measles case investigations should include complete immunization histories that document all doses of measles-containing vaccine. All confirmed case-patients should then be classified as recipients of one dose of measles-containing vaccine (as MMR, measles-rubella, or measles vaccine), two doses, three doses, or no doses of vaccine. The age of vaccination for each dose and the interval between doses should be noted. Written records with dates of vaccine administration are the only acceptable evidence of vaccination.

Some case-patients or their caregivers may have personal copies of immunization records available that include dates of administration; these are acceptable for reporting purposes. Usually immunization records must be sought from review of childcare or school records (generally available for children attending licensed childcare centers or kindergarten through high school), or from providers. Immunization registries, if available, can readily provide vaccination histories. In the absence of a registry, immunization records should be searched at providers' clinics or offices. As part of the initial case investigation, case-patients or their parents should be asked where all vaccines were received, including the names of private physicians and out-of-town or out-of-state providers. Records at public health departments and health centers should be reviewed and private physicians should be contacted and asked to review patient records for this information. With careful planning in an outbreak setting, it is possible to contact providers with a list of all case-patients reported to date for whom data are needed and to call back at a prearranged time, rather than repeatedly contacting providers for records on individual children.

4. Efforts should be made to identify the source of infection for every confirmed case of measles. Case-patients or their caregivers should be asked about contact with other known cases. In outbreak settings, such histories can often be obtained. When no history of contact with a known case can be found, opportunities for exposure to unknown cases should be sought. Such exposures may occur in schools (especially high schools with foreign exchange students), during air travel, through other contact with foreign visitors, while visiting tourist locations (casinos, resorts, theme parks), or in healthcare settings. Unless a history of exposure to a known case within seven to 21 days prior to onset of rash in the case is confirmed, case-patients or their caregivers should be closely queried about all these possibilities.

5. Identify contacts, trace sources of infection and identify those susceptible individuals.
Assessing potential for transmission and identify contacts. Transmission is particularly likely in households, schools and other institutions (colleges, prisons, etc.), and in healthcare settings. As part of the case investigation, the potential for further transmission should be assessed and contacts of the case-patient during the infectious period (four days before to four days after onset of rash) should be identified. In general, contacts who have not received two doses of measles-containing vaccine on or after the first birthday separated by at least one month, are considered susceptible. These susceptible contacts are at risk for infection and further transmission to others and should be vaccinated as quickly as possible.

Case investigation and vaccination of susceptible household contacts should not be delayed pending the return of laboratory results. Initial preparation for major control activities also may need to be started before the laboratory results are known. However, it is reasonable to delay major control activities, such as vaccinating an entire school, pending the return of laboratory results, which should be obtained as quickly as possible (within 24 hours).

6. Carry out active surveillance
Active surveillance for measles disease should be conducted during outbreaks. Local or state health departments should contact healthcare providers in outbreak areas to inform them of the outbreak and request reporting of any suspected cases. These activities are especially important in large cities and in cities with large numbers of international visitors.

7. Exclusion:
The case(s) should be excluded from school for at least four (4) days after the appearance of the rash.

8. Immunoprophylaxis of contacts
Available data suggest that live-virus measles vaccine, if given within 72 hours of measles exposure, will provide protection in some cases. Vaccine is the intervention of choice for control of measles outbreaks in schools and child care centers. For susceptible household contacts who are at least six months of age and are not immunocompromised or pregnant, vaccine is acceptable only if it can be given within 72 hours of exposure.

9. While immune globulin (IG) can be used within six (6) days for susceptible household or other contacts for whom risk of complications is very high, this is not usually a feasible alternative due to the difficulty in identifying cases and/or contacts within the specified time. IG should not be used in an attempt to control measles outbreaks.

Special follow-up is needed for schools, hospitals, child care centers, colleges, etc. If an outbreak occurs in these areas, assist the Immunization Section as needed.

10. School or child care center:

- Contact the School or child care center
  - to determine if any additional cases are occurring
  - to evaluate or have the school nurse evaluate immunization records of those enrolled
  - to arrange with the school or child care center to notify parents of students whose records do not indicate immunization against measles or other disease under containment procedures.

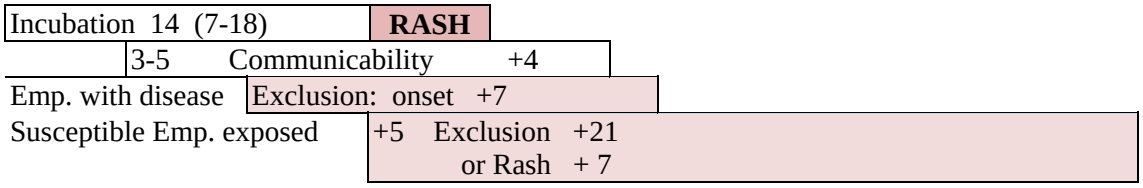
Recommend that children with inadequate immunization or no records, or who are immunocompromised be excluded until acceptable proof of immunization is provided or until the outbreak is contained (usually one full incubation period following the last reported case).

- Follow-up on all suspected cases

There is no evidence of enhanced risk from receiving live measles vaccine in persons who have previously received live measles vaccine or had measles. Therefore, when a child who has had the disease presents himself/herself to the health unit for future immunizations, the use of MMR to protect against mumps and rubella is indicated.

11. Health care facilities:
Incubation - 14 days from exposure to rash (range 7 to 18 days). Communicability starts three to five days before the rash (one to two days before onset of initial symptoms), and lasts four days after onset of rash. (Communicability is minimal the second day after the rash.) Transmission is by nasal or throat secretions with direct contact or airborne droplets.

Employees with active measles should be removed from direct patient contact until seven days after the rash appears. Susceptible employees exposed to a confirmed case should be removed from direct patient contacts from the fifth through the 21st day after exposure or seven days after the rash appears.



Serologic testing or immunization does not alter recommendation for exclusion because the results of testing or effect of vaccine would occur too late.

Prevention of transmission in outpatient setting:

- Identify at registration, patients who come in for a rash with fever and patients who cough
- Instruct these patients to wear a disposable surgical mask until they leave the facility or until examination by a physician has ruled out suspected measles
- If the facility allows it, have the patients wait in a remote area, far away from other patients
- Minimize the waiting time by sending these patients for examination rapidly
- Discharge the patient as rapidly as possible
- Personnel that cares for these patients should have received a measles vaccine (MMR) or have proof of antibody against measles. A 15-minute trip to the staff clinic can get anyone up-to-date on measles immunization.
- In case of exposure, live vaccine (MMR) should be offered to susceptible contacts within 72 hours of exposure.

12. Outbreak control
The primary strategy for control of measles outbreaks is achieving a high level of immunity in the population in which the outbreak is occurring. In practice, the population affected is usually rather narrowly defined (such as one or more schools); high immunity in the population is obtained by achieving high coverage with two doses of measles vaccine in the affected population. Persons who cannot readily document measles immunity should be vaccinated or excluded from the setting (school, hospital, etc.). Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Verbal reports of vaccination without written documentation should not be accepted. Persons who have been exempted from measles vaccination for medical, religious, or other reasons should be excluded from affected institutions in the outbreak area until 21 days after the onset of rash in the last case of measles. The recent experience in measles outbreaks shows that almost all persons who are excluded from an outbreak area because they lack documentation of immunity quickly comply with vaccination requirements.

If many cases are occurring among infants younger than 12 months of age, measles vaccination of infants as young as six months of age may be undertaken as an outbreak control measure. Monovalent measles vaccine is preferred, but MMR may be administered to children before the first birthday if monovalent measles vaccine is not readily available. In practice, this recommendation may take several months to implement and several months to halt once the outbreak has ended. Note that children vaccinated before their first birthday should be revaccinated when they are 12 to 15 months old and again when they are four to six years of age.

Control of outbreaks in schools and other institutions

During outbreaks in elementary, junior and senior high schools, colleges and other institutions of higher education, as well as other institutions where young adults may have close contact (such as prisons), a program of re-vaccination with MMR vaccine is recommended in the affected schools or institutions. Recent experience has indicated that measles outbreaks do not occur in schools in which all students are subject to a school requirement for two doses of measles vaccine. In general, voluntary efforts have been much less successful than mandatory two-dose requirements for control of outbreaks. Therefore, public health officials should strongly consider implementing mandatory two-dose requirements for children in affected schools and other institutions. The scope of vaccination effort needed will depend on 1) age-appropriate first- and second-dose coverage with MMR in the community 2) population density 3) resources available and 4) patterns of social contacts within the community. During an outbreak, strong consideration should be given to expanding two-dose requirements to all schools in the community.

In a school with a measles outbreak, all students and their siblings and all school personnel born in or after 1957 who cannot provide documentation that they have received two doses of measles-containing vaccine on or after their first birthday or cannot provide other evidence of measles immunity (such as serologic testing) should be vaccinated. Persons who cannot readily provide documentation of measles immunity should be vaccinated or excluded from the school or other institution. Persons revaccinated, as well as previously unvaccinated persons receiving their first dose as part of the outbreak control program may be immediately readmitted to school. Persons who continue to be exempted from or who refuse measles vaccination should be excluded from the school, childcare, or other institution until 21 days after the onset of rash in the last case of measles.

Control of outbreaks in medical settings

Persons who work in health-care facilities (including volunteers, trainees, nurses, physicians, technicians, receptionists and other clerical and support staff) are at increased risk of exposure to measles; all persons who work in such facilities in any capacity should be immune to measles to prevent any potential outbreak. If an outbreak occurs within or in the areas served by a hospital, clinic, or other medical or nursing facility, all personnel born in or after 1957 (including volunteers, trainees, nurses, physicians, technicians, receptionists and other clerical and support staff) should receive a dose of MMR vaccine, unless they have documentation of measles immunity. Serologic screening of health-care workers during an outbreak to determine measles immunity is not generally recommended, because stopping measles transmission requires the rapid vaccination of susceptible health-care workers, which can be impeded by the need to screen, wait for results, then contact and vaccinate the susceptible persons.

Susceptible personnel who have been exposed to measles should be relieved from patient contact and excluded from the facility from the fifth to the 21st day after exposure, regardless of whether they received vaccine or immune globulin after the exposure. Personnel who become ill should be relieved from all patient contact and excluded from the facility for seven days after they develop rash.

Role of community-wide vaccination efforts in outbreak control

Mass revaccination of entire communities is not of demonstrated benefit in control of measles outbreaks. Such activities may sometimes have to be undertaken because of political or other community demands for “action” and concerns about the acceptability of targeted interventions directed toward selected high-risk populations, but there is no epidemiological evidence that they are feasible or useful in controlling measles outbreaks.

Limited usefulness of quarantine in control of measles outbreaks

Imposing quarantine measures for outbreak control is usually both difficult and disruptive to schools and other institutions. Under special circumstances, such as during outbreaks in schools attended by large numbers of persons who refuse vaccination, restriction of an event or other quarantine measures might be

warranted. However, such actions are not recommended as a routine measure for control of most outbreaks.

Post-exposure vaccination and use of immunoglobulin to prevent measles in exposed persons

If given within 72 hours of exposure to measles, measles vaccine may provide some protection. In most settings, post-exposure vaccination is preferred over the use of immune globulin. However, immune globulin should be given to pregnant women and immunosuppressed person who are exposed to measles. Immune globulin may be preferred for infants younger than one year old who are household contacts of measles patients because it is likely that they will have been exposed more than 72 hours prior to measles diagnosis in the household member and they are at highest risk of complications from the disease.

Immunization

Measles vaccine is incorporated with mumps and rubella vaccine as a combined vaccine (MMR). The current Advisory Committee on Immunization Practices (ACIP) recommendations for routine vaccination indicates a first dose at 12 to 15 months of age with a second dose at school entry (4 to 6 years).

Measles Vaccine. The only measles vaccine currently licensed in the United States is a live further-attenuated strain prepared in chick embryo cell culture. Measles vaccine is available in monovalent (measles only) formulation and in combination formulations, ie, measles-rubella (MR) and measles-mumps-rubella (MMR) vaccines.

The MMR vaccine is the recommended product of choice in most circumstances, especially when administered at 12 months of age or older and including the routinely recommended second dose of measles vaccine, to also provide optimal protection against mumps and rubella. Vaccine (as a combination or monovalent product) in a dose of 0.5 mL is given subcutaneously. Measles and measles-containing vaccines can be given simultaneously with other vaccines.

Efficacy: Serum measles antibodies develop in approximately 95% of children immunized at 12 months of age and 98% of those immunized at 15 months of age. Protection conferred by a single dose is durable in most persons. However, a very small percentage of immunized persons may lose protection after several years. More than 99% of persons who receive two doses separated by at least one month (4 weeks) with both doses on or after their first birthday develop serologic evidence of measles immunity. Immunization is not deleterious for persons who already are immune.

Storage: Improperly stored vaccine may fail to protect against measles. Since 1979, an improved stabilizer has been added to the vaccine that makes it more resistant to heat inactivation. However, during storage before reconstitution, measles vaccine should be kept at 2°C to 8°C (36°F to 46°F) or colder. Freezing is not harmful to the lyophilized vaccine. The vaccine diluent (sterile water) vials may break if frozen and therefore, should not be frozen. Measles vaccine also must be protected from ultraviolet light (especially after reconstitution), which can inactivate the virus. Vaccine should be shipped at 10°C (50°F) or colder and may be shipped on dry ice. Reconstituted vaccine should be stored in a refrigerator and discarded if not used within eight hours.

Age of Routine Immunization.

The first dose should be given at 12 to 15 months of age. Delays in administering the first dose contributed to large outbreaks from 1989 to 1991. Initial immunization at 12 months of age is recommended for preschool-age children in high-risk areas, especially large urban areas.

The second dose is recommended routinely at school entry (ie., 4 to 6 years of age) but can be given at any earlier age (eg., during an outbreak or before international travel), provided the interval between the first and second doses is at least one month (four weeks). Children who were not re-immunized at school entry should receive the second dose by 11 to 12 years of age. If the child receives a dose of measles vaccine before 12 months of age, two additional doses are required beginning at 12 to 15 months of age and

separated by at least one month. By 2001, all school-age children should have received two doses of measles-containing vaccine.

High School Students and Older Persons. Because of the continuing occurrence of cases in older children and young adults, emphasis must be placed on identifying and appropriately immunizing potentially susceptible adolescents and young adults in high school, college and health care settings.

Persons should be considered susceptible unless they have documentation of appropriate immunization, physician-diagnosed measles, laboratory evidence of immunity to measles, or were born before 1957. For children, adolescents and adults born after 1956, two doses of measles vaccine are required for evidence of immunity. A parental report of immunization is not considered adequate documentation. Physicians should provide an immunization record for patients only if they have administered the vaccine or have seen a record documenting immunization.

Colleges and Other Institutions for Education Beyond High School. Colleges and other institutions should require that all entering students have documentation of physician-diagnosed measles, serologic evidence of immunity, birth before 1957, or receipt of two doses of measles-containing vaccines. Students without documentation of any measles immunization or immunity should receive a dose on entry, followed by a repeated dose one or more months (four weeks) later.

Immunization During an Outbreak. During an outbreak, monovalent measles vaccine may be given to infants as young as six months of age. If monovalent vaccine is not available, MMR may be given. However, seroconversion rates after MMR immunization are significantly lower in children immunized before the first birthday than are seroconversion rates in children immunized after the first birthday. Children, therefore, immunized before their first birthday should be immunized with MMR vaccine at 12 to 15 months and again at school entry (four to six years).

International Travel. Persons traveling to foreign countries should be immune to measles. For young children traveling to areas where measles is endemic or epidemic, the age for initial measles immunization may need to be lowered. Infants six to 11 months of age should receive a dose of monovalent measles (or MMR) vaccine before departure; then they should receive MMR vaccine at 12 to 15 months of age (at least one month [four weeks] after the initial measles immunization) and again at four to six years of age. Children 12 to 15 months of age should be given their first dose of MMR vaccine before departure. Children who have received one dose and are traveling to areas where measles is endemic or epidemic should receive their second dose before departure, provided the interval between doses is one month (four weeks) or more.

Health Care Facilities. Evidence of having had measles, measles immunity, or receipt of two measles immunizations is recommended before beginning employment for all health care professionals born after 1956.

Adverse Events. A temperature of 39.4°C (103°F) or higher develops in approximately 5% to 15% of susceptible vaccine recipients, usually between six and 12 days after MMR immunization; the fever generally lasts one to two days but may last for as many as five days. Most persons with fever are otherwise asymptomatic. Transient rashes have been reported in approximately 5% of vaccine recipients. Transient thrombocytopenia has occurred after administration of measles-containing vaccines, specifically MMR. The reported frequency of central nervous system conditions, including encephalitis and encephalopathy, is less than one per million doses administered in the United States. Because the incidence of encephalitis or encephalopathy after measles immunization in the United States is lower than the observed incidence of encephalitis of unknown cause, some or most of the rare reported severe neurologic disorders may be related coincidentally, rather than causally, to measles immunization. After re-immunization, reactions are expected to be clinically similar but much less frequent in occurrence because most of these vaccine recipients are already immune.

High-titer vaccines administered during the mid-1980s in several developing countries were associated with increased mortality in females several months to years after immunization. These high-titer vaccines were never licensed in the United States and are no longer in use in foreign countries.

Seizures. As with any condition that induces fever during the second year of life, children predisposed to febrile seizures can experience seizures after measles immunization. Most are simple febrile seizures and do not increase the risk of subsequent epilepsy or other neurologic disorders. Children with personal histories of seizures or children whose first-degree relatives have histories of seizures may be at a slightly increased risk of a seizure but should be immunized because the benefits greatly outweigh the risks.

Subacute Sclerosing Panencephalitis. Measles vaccine, by protecting against measles, significantly reduces the possibility of developing SSPE.

Measles vaccine is not associated with an increased risk of autism or inflammatory bowel disease.

Precautions and Contraindications

Febrile Illnesses. Children with minor illnesses, with or without fever, such as upper respiratory tract infections, may be immunized. Fever per se is not a contraindication to immunization. However, if other manifestations suggest a more serious illness, the child should not be immunized until recovery.

Allergic Reactions. Hypersensitivity reactions occur rarely and usually are minor, consisting of wheal and flare reactions or urticaria at the injection site. Reactions have been attributed to trace amounts of neomycin or gelatin, or some other component in the vaccine formulation. Anaphylaxis is rare. Measles vaccine is produced in chick embryo cell culture and does not contain significant amounts of egg white (ovalbumin) cross-reacting proteins. Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including MMR), and skin testing of children allergic to eggs is not predictive of reactions to MMR vaccine. Persons with allergies to chickens or feathers are not at increased risk of reaction to the vaccine.

Children who have had a significant hypersensitivity reaction following the first dose of measles vaccine should be (1) tested for measles immunity and, if immune, not receive a second dose or (2) receive evaluation and possible skin testing before receiving a second dose. Children who have had an immediate anaphylactic reaction to prior measles immunization should not be re-immunized but require testing to determine whether they are immune.

Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should receive measles vaccine only in settings where such reactions could be managed and after consultation with an allergist or immunologist. Most often, however, neomycin allergy manifests as a contact dermatitis, which is not a contraindication to receiving measles vaccine.

Thrombocytopenia. Rarely, MMR vaccine can cause clinically apparent transient and benign thrombocytopenia within two months of immunization. In prospective studies, the reported incidence was one case per 25,000 to 40,000 immunized children, with a temporal clustering two to three weeks after immunization. By passive surveillance, the reported rate was approximately one per 100,000 doses distributed in Canada and one per two million doses distributed in the United States. Based on case reports, the risk of vaccine-associated thrombocytopenia may be higher for persons who previously experienced thrombocytopenia, especially when it occurred in temporal association with earlier MMR immunization. The decision to immunize these children should be based on the benefits of protection against measles, mumps, and rubella in comparison with the risks of a recurrence of thrombocytopenia after immunization. No reports of thrombocytopenia associated with receipt of MMR vaccine have resulted in death.

Recent Administration of IG. Immune Globulin preparations interfere with the serologic response to measles vaccine for variable periods depending on the dose administered. If vaccine is given at less than the indicated intervals, as may be warranted if the risk of exposure to measles is imminent, the child should be re-immunized at or after the appropriate interval for immunization unless serologic testing indicates that measles-specific antibodies were produced.

If IG is to be administered in preparation for international travel, administration of vaccine should precede receipt of IG by at least two weeks to preclude interference with replication of the vaccine virus.

Tuberculosis. Tuberculin skin testing is not a prerequisite for measles immunization and measles vaccine does not exacerbate tuberculosis. If tuberculin skin testing is otherwise indicated, it can be done on the day of immunization. Otherwise, testing should be postponed for four to six weeks because measles immunization temporarily may suppress tuberculin skin test reactivity.

Altered Immunity. Immunocompromised patients with disorders associated with increased severity of viral infections should not be given live measles virus vaccine while immunodeficient. Their risk of exposure to measles can be reduced by immunizing their close susceptible contacts. Management of immunodeficient and immuno suppressed patients exposed to measles can be facilitated by prior knowledge of their immune status. Susceptible patients with immunodeficiencies should receive IG after measles exposure.

Corticosteroids. For patients who have received high doses of corticosteroids for 14 days or more and who are not otherwise immunocompromised, the recommended interval before immunization is at least one month.

HIV Infection. Measles immunization (given as MMR vaccine) is recommended at the usual ages for persons with asymptomatic HIV infection and for those with symptomatic infection who are not severely immunocompromised because measles can be severe and often fatal in patients with HIV infection. Severely immunocompromised HIV-infected infants, children, adolescents and young adults, as defined by low CD4+ T-lymphocyte counts or percentage of total lymphocytes, should not receive measles virus–containing vaccine because vaccine-related pneumonitis has been reported. All members of the household of an HIV-infected person should receive measles vaccine unless they are HIV-infected and severely immunosuppressed, were born before 1957, have had physician-diagnosed measles, have laboratory evidence of measles immunity, have had age-appropriate immunizations, or have a contraindication to measles vaccine.

Regardless of immunization status, symptomatic HIV-infected patients who are exposed to measles should receive IG prophylaxis because immunization may not provide protection.

Personal or Family History of Seizures. Children with this history should be immunized after advising the parents or guardians that the risk of seizures after measles immunization is increased slightly. Because fever induced by measles vaccine usually occurs between six and 12 days after immunization, prevention of vaccine-related febrile seizures is difficult. Parents should be alert to the occurrence of fever after immunization and should treat their children appropriately. Children receiving anticonvulsants should continue such therapy after measles immunization. Prophylactic use of anticonvulsants may not be feasible, because therapeutic concentrations (eg, phenobarbital) are not achieved for some time after initiation of therapy.

Pregnancy. Live-virus measles vaccine, when given as a component of MR or MMR, should not be given to women known to be pregnant or who are considering becoming pregnant within three months of immunization. Women who are given monovalent measles vaccine should not become pregnant for at least 30 days. This precaution is based on the theoretical risk of fetal infection, which applies to the administration of any live-virus vaccine to women who might be pregnant or who might become pregnant shortly after immunization. No evidence, however, substantiates this theoretical risk. In the immunization of adolescents and young adults against measles, asking women if they are pregnant, excluding those who are and explaining the theoretical risks to the others are recommended precautions.

Hospital precaution and isolation: In addition to standard prescautions, airborne precautions are indicated for four days after the onset of the rash in otherwise healthy children and for the duration of illness in immunocompromised patients.