Chapter 7: Measles

Paul A. Gastanaduy, MD, MPH; Susan B. Redd; Nakia S. Clemmons, MPH; Adria D. Lee, MSPH; Carole J. Hickman, PhD; Paul A. Rota, PhD; Manisha Patel, MD, MS

I. Disease Description

Measles is an acute viral illness caused by a virus in the family paramyxovirus, genus *Morbillivirus*. Measles is characterized by a prodrome of fever (as high as 105°F) and malaise, cough, coryza, and conjunctivitis, followed by a maculopapular rash.[1] The rash spreads from head to trunk to lower extremities. Measles is usually a mild or moderately severe illness. However, measles can result in complications such as pneumonia, encephalitis, and death. Approximately one case of encephalitis[2] and two to three deaths may occur for every 1,000 reported measles cases.[3]

One rare long-term sequelae of measles virus infection is subacute sclerosing panencephalitis (SSPE), a fatal disease of the central nervous system that generally develops 7–10 years after infection. Among persons who contracted measles during the resurgence in the United States (U.S.) in 1989–1991, the risk of SSPE was estimated to be 7–11 cases/100,000 cases of measles.[4] The risk of developing SSPE may be higher when measles occurs prior to the second year of life.[4]

The average incubation period for measles is 11–12 days,[5] and the average interval between exposure and rash onset is 14 days, with a range of 7–21 days.[1,6] Persons with measles are usually considered infectious from four days before until four days after onset of rash with the rash onset being considered as day zero.

II. Background

Epidemiology of measles in the United States

Pre-elimination era

In the decade prior to the licensure of live measles vaccine in 1963, an average of 549,000 measles cases and 495 measles deaths were reported annually.[7] However, almost every American was affected by measles during their lifetime, and it is estimated that 3–4 million measles cases occurred each year.[8,9] Following implementation of a one dose measles vaccine program, there was a rapid and significant reduction in the reported incidence of measles in the United States through the 1980s,[10] resulting in declines in measles-related hospitalizations and deaths.[11] By the late 1980s, however, measles outbreaks were still occurring among school-aged children who had received a single dose of measles vaccine. In 1989, a second-dose vaccination schedule was recommended by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).[11]

During 1989–1991, a resurgence of measles occurred when over 55,000 cases and 123 deaths were reported. The epidemiology during the resurgence was characterized mainly by cases in preschool-aged children living in poor urban areas who had not been vaccinated on time with one dose of measles vaccine.[12] Following the resurgence, a commitment of resources for improved implementation of the timely administration of the first dose of the vaccine, and increased implementation of two doses among school-aged children, led to further declines in measles cases.

In 2000, endemic measles was declared "eliminated[1]" from the United States.[13]

[1] *Elimination is defined as the absence of endemic measles cases for a period of 12 months or more, in the presence of adequate surveillance (World Health Organization)*

Post-elimination era

During 2001–2008, 557 measles cases were reported in the United States.[14, 15] The median number of measles cases reported per year was 56 (range: 37–140 cases/year). The majority of US-resident case-patients were unvaccinated (66%) or had unknown vaccination status (16%). Of the 557 reported measles cases, 232 (42%) were importations (median of 26 importations/year). In comparison, during 2009–2014, 1,264 measles cases were reported in the United States. The median number of measles cases reported per year was 130 (range: 55–667 cases/year). The majority of US-resident case-patients were unvaccinated (74%) or had unknown vaccination status (16%). Of the 1,264 reported measles cases, 275 (22%) were importations (median of 45 importations/year). Among the 989 US-acquired cases reported during 2009–2014, 673 (68%) were epidemiologically linked to these importations, 256 (26%) either had virologic evidence of importation or had been linked to those cases with virologic evidence of importation, and 60 (6%) had unknown source. Unknown source cases represent cases where epidemiologic or virologic link to an imported case was not detected.

Measles incidence has remained below one case per million since 1997, except in 2014, when 667 measles cases were reported, representing a reported incidence of 2.08 cases per million.[14] The epidemiology of measles in 2014 was characterized by (1) a high proportion (92%) of cases among U.S. residents who were unvaccinated or who had unknown vaccination status and (2) more spread from imported cases than in other years. In 2015, 191 measles cases were reported; 28 (15%) were importations, and 142 (80%) of 178 cases among U.S. residents were unvaccinated or had an unknown vaccination status. In recent years, most of the importations were the result of unvaccinated U.S. travelers who had traveled to measles endemic countries, including countries in the World Health Organization (WHO) European and Western Pacific Regions.[14]

Although measles elimination has been achieved in the United States, importation of measles will continue to occur as measles remains endemic in many other parts of the world. Thus, current measles epidemiology in the United States is determined by characteristics of the imported cases and their susceptible contacts.

Measles outbreaks in the United States in the post-elimination era

From 2001 through 2008, 38 outbreaks[2] of measles were reported (annual median no. of outbreaks, 4 [range, 2–10 outbreaks]); outbreaks had a median size of four cases (range: 3–34).[14] From 2009 through 2014, 66 outbreaks of measles were reported (annual median no. of outbreaks, 10 [range, 4–23 outbreaks]); outbreaks had a median size of 5 cases (range: 3–383).[14] Outbreaks of measles in the United States mostly involve individuals who are directly exposed to imported measles cases or who are infected during a resulting chain of transmission, and who are either unvaccinated or had unknown vaccine status. The settings of measles transmission have included households, educational institutions (e.g., schools, day care), churches, health care facilities, homeless shelters, and other congregate settings. Lack of adherence to existing recommendations for measles prevention among groups at high risk (for example, individuals who travel internationally), can spread measles to susceptible populations, including infants too young to be vaccinated and unvaccinated persons by choice.[16, 17] Because of high population immunity, high measles vaccine effectiveness, and the immediate implementation of control measures, generally the sizes of measles outbreaks in the United States are limited. However, recent large outbreaks emphasize the importance of maintaining high levels of measles immunity across the population through routine measles vaccine coverage. The largest measles outbreak documented in the United States in more than two decades (383 cases) occurred in an under-immunized Amish community in Ohio over 4 months (March–July) in 2014.[18] From December 2014 through March 2015, a measles outbreak consisting of 147 cases that originated in Disney theme parks in California spread to seven other U.S. states and two neighboring countries.[19, 20]

Responding to measles cases and outbreaks is time consuming and costly for local and state health departments.[21, 22] The overall costs to health departments to contain 16 outbreaks during 2011 amounted to an estimated $2.7 million to $5.3 million U.S. dollars. The economic burden of controlling measles spread in health care settings amounts to an estimated $19,000 to $114,286 U.S. dollars per case.

[2] *National reporting: An outbreak is defined as a chain of transmission including 3 or more cases linked in time and space.*

Global measles

Despite tremendous achievements towards global measles mortality reduction and elimination goals, globally, in 2015, there were 254,928 measles cases reported and an estimated 134,200 measles deaths (i.e., approximately 367 deaths/day).[23] During 2015, measles outbreaks were reported in several countries in the African, European, and Eastern Mediterranean regions.[23]

In the Americas, under the leadership of the Pan American Health Organization (PAHO), Ministries of Health implemented an aggressive measles elimination program in 1994. By 2002, scientific evidence suggested that endemic transmission of measles virus in the Americas was interrupted for ≥12 months, [24] however, imported cases from endemic areas of the world continued to occur, resulting in sizable outbreaks in several countries, including Ecuador, Canada, and the United States. More recently, a large measles outbreak in Brazil, with sustained transmission lasting over a year, ended in July 2015.[25] In September 2016, after over two decades of commitments and efforts by Member States to control measles, the Region of the Americas was the first in the world to verify the elimination of measles.[25]

Important measures are also underway to achieve measles elimination in other regions. Countries in all six WHO regions have adopted measles elimination goals, and four WHO regions endorsed the Global Vaccine Action Plan to eliminate measles by 2015; although these elimination goals were not accomplished. The Global Vaccine Action Plan has also set a target for measles elimination in five WHO regions by 2020.[23]

Achieving elimination in other regions of the world will have direct benefits in the United States.

III. Maintenance of Elimination

The declaration of endemic measles elimination in the United States was made in 2000.[9, 13] The key challenges to maintaining the elimination of measles from the United States are

- vaccinating children at age 12–15 months with a first dose of measles, mumps, rubella (MMR) vaccine;
- ensuring that school-age children receive a second dose of MMR vaccine;
- vaccinating high-risk groups, such as health care personnel and international travelers including infants 6 to 11 months of age;
- maintaining measles awareness among health care personnel and the public; and
- working with U.S. Government agencies and international agencies, including the WHO, on global measles mortality reduction and elimination goals.

In addition, pockets of unvaccinated populations can pose a risk to maintaining elimination.[15, 26] Thus, rapid detection of cases is necessary so that appropriate control measures can be quickly implemented. This is to prevent imported strains of measles virus from establishing endemic chains of transmission. Outbreak preparedness and response remains one of the five core strategies in the 2012–2020 WHO strategic plan for global measles and rubella.[27]

IV. Vaccination

Live attenuated measles virus vaccine is incorporated into combination MMR vaccine and combination measles, mumps, rubella, and varicella (MMRV) vaccines. Monovalent measles vaccine is not available in the United States.

For prevention of measles, two doses of MMR vaccine are recommended routinely for children, with the first dose at age 12 through 15 months and the second dose at ages four through six years (school entry).[28]

For prevention of measles among adults, two doses of MMR vaccine are also recommended for adults at high risk, including international travelers, college and other post-high school students, and health care personnel born during or after 1957.[28] All other adults, born during or after 1957, without other presumptive evidence of measles immunity, should be vaccinated with one dose of MMR vaccine.

Vaccination recommendations for an outbreak setting are discussed in the "Control Measures" section in this chapter.

For more details on health care personnel please see the section "Health care settings" in this chapter.

Travel recommendations

Children 6–11 months of age who travel internationally should receive one dose of MMR vaccine optimally at least two weeks prior to travel. Because serologic response to the measles component of the vaccine varies among infants 6–11 months of age, children vaccinated before age 12 months should receive two additional doses of MMR or MMRV vaccine on or after the first birthday according to the routine recommended schedule.[28]

Children ≥12 months of age and adults who plan to travel outside the United States should receive two doses of MMR vaccine, separated by at least 28 days.

V. Presumptive Evidence of Immunity

Acceptable presumptive evidence of measles immunity includes at least one of the following:[28]

- written documentation of adequate vaccination— receipt of one or more doses of a measles-containing vaccine administered on or after the first birthday for preschool-age children and adults not at high risk, and two doses of measles-containing vaccine for school-age children and adults at high risk for exposure transmission (i.e., health care personnel, international travelers, and students at post-high school educational institutions); or
- laboratory evidence of immunity; or
- birth before 1957; or
- laboratory confirmation of disease.

Persons who do not meet the above criteria are considered susceptible and should be vaccinated unless contraindicated.

For health care settings please see the section "Health care settings" below as the criteria are slightly different.

VI. Case Definition

The following case definition for case classification of measles cases, including case classifications for importation status, has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2012.[29]

Case definition for case classification

Clinical description:

- An acute illness characterized by:
  - generalized, maculopapular rash lasting ≥3 days; and
  - temperature ≥101°F or 38.3°C; and
  - cough, coryza, or conjunctivitis

Probable:

- In the absence of a more likely diagnosis, an illness that meets the clinical description with:
  - no epidemiologic linkage to a laboratory-confirmed measles case; and
  - noncontributory or no measles laboratory testing.

Confirmed:

- An acute febrile rash illness† with:
  - isolation of measles virus‡ from a clinical specimen; or
  - detection of measles virus-specific nucleic acid‡ from a clinical specimen using polymerase chain reaction; or
  - IgG seroconversion‡ or a significant rise in measles immunoglobulin G antibody‡ using any evaluated and validated method; or

- a positive serologic test for measles immunoglobulin M antibody[‡§]; or
- direct epidemiologic linkage to a case confirmed by one of the methods above.

[†] *Temperature does not need to reach ≥101°F/38.3°C and rash does not need to last ≥3 days.*
[‡] *Not explained by MMR vaccination during the previous 6–45 days.*
[§] *Not otherwise ruled out by other confirmatory testing or more specific measles testing in a public health laboratory.*

Note: Genotype identification by a WHO reference laboratory (CDC or a public health laboratory that has validated their measles virus sequence analysis) is required to distinguish wild type from vaccine strain if vaccinated within 21 days of rash onset.

Epidemiologic classification of internationally-imported and US-acquired

International importation: 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 (7–21 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 United States during that time.

All other cases are considered US-acquired.

US-acquired case: An US-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.

US-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 ≥12 months). Any genotype that is found repeatedly in US-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 ≥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 United States cannot be established after a thorough investigation. These cases must be carefully assessed epidemiologically to assure that they do not represent a sustained US-acquired chain of transmission or an endemic chain of transmission within the United States.

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 within the United States. For national reporting, however, cases will be classified as either internationally imported or US-acquired. The possibility that a patient was exposed within his or her state of residence should be excluded; therefore, the patient either must have been out of state continuously for the entire period of possible exposure (at least 7–21 days before onset of rash) or have had one of the following types of exposure while out of state: a) face-to-face contact with a person who had probable or confirmed measles, or b) attendance in the same institution as a person with measles (e.g., in a school, classroom, or childcare center).

VII. Laboratory Testing

Collection of virologic and serologic specimens is recommended for every case.

Laboratory confirmation is essential for all outbreaks and all sporadic measles cases. Detection of measles-specific IgM antibody and measles RNA by real-time RT-PCR are the most common methods for confirmation of measles infection. Efforts should be made to obtain a serum sample and throat swab (or nasopharyngeal swab) from suspected cases at first contact. Urine samples may also contain virus and when feasible to do so, collection of both respiratory and urine samples can increase the likelihood of detecting virus. Staff at the CDC Measles Laboratory are available for consultation and can assist with confirmatory testing as needed for measles. For details on all types of specimens (serum, respiratory, urine) collection and transport, see the CDC Measles Laboratory website at http://www.cdc.gov/measles/lab-tools/index.html.

Because measles is a rare disease in the United States, even with the excellent laboratory tests available, false positive results for measles IgM will occur. 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 (i.e., those who meet the clinical case definition, especially if they have risk factors for measles, such as being unvaccinated, recent history of travel abroad, without an alternate explanation for symptoms, for example epi-linked to known parvovirus case) or those with fever and generalized maculopapular rash with strong suspicion of measles.

During a measles investigation when community awareness is increased, many cases of febrile rash illness may be reported as suspected measles, and the magnitude of the situation may be exaggerated if these cases are included in the absence of laboratory confirmation. This is particularly important as the investigation is ending; at that point, laboratory confirmation should be sought for all suspected cases. Occasionally, suspected cases may include vaccinated individuals. For these cases, laboratory confirmation may be challenging. An overview of diagnostic tools is described below.

Virus isolation in cell culture and measles RNA detection (RT-PCR)

Clinical specimens for real-time polymerase chain reaction (RT-PCR) and virus isolation should be collected at the same time as samples taken for serologic testing. The preferred specimens for virus isolation or RT-PCR are throat or nasopharyngeal swabs, but urine may also contain virus. Virus isolation and RNA detection are more likely to be successful when the specimens are collected early (ideally within three days of rash onset, but up to ten days post rash may be successful). Isolation of measles virus in cell culture or detection of measles RNA by RT-PCR in clinical specimens confirms the diagnosis of measles.

However, a negative virus isolation or negative RT-PCR results do not rule out measles because both methods are affected by the timing of specimen collection and the quality and handling of the clinical specimens.

Successful isolation of measles virus in culture or direct detection of measles RNA by RT-PCR in the clinical sample is particularly helpful for case confirmation when serology results are inconclusive. The Vero/hSLAM cell line, a recombinant cell line with a receptor for measles virus, has greatly improved the ability to isolate measles virus in cell culture.

Molecular analysis to determine genotype of measles

Determination of the measles genotype provides the only means to distinguish between wild type virus infection and a rash caused from a recent measles vaccination. In addition, the collection of appropriate specimens from which virus or viral RNA can be obtained or amplified is extremely important for molecular epidemiologic surveillance to identify the genotypes associated with imported cases of measles. This information is used to track transmission pathways, link cases to countries overseas, and to document the absence of endemic circulation of measles in the United States.[30] Sequence analysis and genotyping for measles virus is conducted at the CDC Measles Laboratory. Refer to the CDC Measles Laboratory website for additional information on sample collection, processing and the genetic analysis of measles.

Serologic testing

The state health department can provide guidance regarding available laboratory services. At the direction of the state health department, health care providers and state and local health departments may send serum specimens from suspected measles cases to the CDC Measles Laboratory. For detailed information on blood collection and shipping, refer to the CDC Measles Laboratory website at http://www.cdc.gov/measles/lab-tools/index.html.

There is no single serologic laboratory test capable of confirming with 100% confidence every true case of measles. Public health laboratories that use commercial measles assay kits are encouraged to fully characterize and validate the kits in their laboratories using known test panels of positive and negative specimens. Information regarding the performance characteristics of many of the commercially available enzyme immunoassays (EIA) kits is available by contacting the CDC Measles Laboratory. The reference laboratory at CDC uses an IgM assay developed at CDC for measles serologic testing of IgM. The assay is a capture IgM format EIA that utilizes a recombinant measles nucleoprotein (NP) antigen and tends to have high sensitivity and specificity compared to some commercial EIAs.

Use of IgM for confirmation of measles

Unvaccinated persons

Following measles virus infection in an unvaccinated individual, measles IgM antibodies appear within the first few days (1–4 days) of rash onset, peak within the first week post rash onset and are rarely detected after 6–8 weeks. Measles IgG antibodies are generally produced and detectable a few days after the IgM response. The timing of the IgM and the IgG response varies among individuals but IgG should be detectable by 7–10 days post rash onset. IgG levels peak approximately two weeks post rash onset and persist for life.

Upon exposure to wild type measles virus, an unvaccinated person may have detectable IgM as soon as the first day of rash onset. However, depending on the sensitivity of the assay used, a proportion of serum samples (23% in a study using CDC capture IgM assay[31]) collected within 72 hours after rash onset may give false negative results. If a negative result is obtained from serum collected within 72 hours after rash onset, a second serum should be collected ≥72 hours after rash onset. Measles IgM is detectable for at least 30 days after rash onset and frequently longer.

Following vaccination, measles IgM may not be detectable until 8–14 days after vaccination and measles IgG may not be detectable for up to three weeks post vaccination.[32]

Note: When a patient with suspected measles has been recently vaccinated (6–45 days prior to blood collection) neither IgM nor IgG antibody responses can distinguish measles disease from the response to vaccination. Determination of the measles genotype is necessary when measles symptoms occur following an exposure to wild type virus and MMR vaccine had been provided as postexposure prophylaxis.

Vaccinated persons

Individuals who have been previously exposed to measles antigen may have a modified disease presentation. These cases are usually detected during an outbreak or after a known exposure to a confirmed measles case. In rare instances, such cases can occur without a known exposure or other risk factor.

Vaccinated persons may not have an IgM response or it may be transient and not detected depending on timing of specimen collection, therefore a negative IgM test in vaccinated persons suspected of having measles should not be used to rule out the case; RT-PCR testing may be the best method to confirm such cases. If viral testing results are noncontributory, additional serological testing can be performed for highly suspicious cases. See the sections below.

Additional tests for measles infection

Testing for measles-specific IgM from persons with rash and fever can produce false positive IgM results. As discussed above, false negative results can also occur in a previously vaccinated person.

Ruling out a false positive IgM by testing a second serum

- If the acute sample was IgG negative, a second serum can be collected at ≥10 days after the acute sample. If this serum is IgG negative, measles can be ruled out.
- If the acute serum was IgG positive, a second serum, collected ≥2 weeks after the acute specimen, can be tested for a significant rise in IgG between paired serum samples.

Tests for IgG rise or seroconversion such as plaque reduction neutralization (PRN) and avidity testing may be helpful in certain situations. A brief description for the utility of these assays is given below. More information is available on the CDC Measles webpage. Requests for testing should be directed to the Measles Laboratory at CDC. (See Chapter 22, *Laboratory Support for the Surveillance of Vaccine-Preventable Diseases* [https://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html])

IgG antibody seroconversion or demonstration of a rise in titer using IgG EIA

Unvaccinated persons

If classification of a case cannot be made after testing a serum sample collected ≥72 hours after rash or detection of measles virus from a viral specimen was not successful, a convalescent serum sample can be collected. A convalescent serum sample should be collected 10–30 days after the acute serum. In immunologically naïve persons, the measles IgG response starts slowly and, depending on the assay, can be detected by day 3–7 after rash onset (range: 1–10 days), but typically persists for a lifetime.

Note: IgG testing of paired serum samples requires the demonstration of a significant (usually four-fold) rise in the titer of antibody against measles using an assay that has been validated for this use. The test for IgG antibody should be conducted with acute and convalescent serum samples at the same time using the same test. IgG avidity assessments would also be informative on such specimens, since low avidity results would rule in a case of measles in this instance (See Avidity of IgG below).

Note: A recent systematic review of published literature found no reported confirmed instances of human-to-human transmission of the measles vaccine virus.[33]

Vaccinated persons

When measles is suspected in previously vaccinated persons, the acute serum may be IgM negative and IgG positive. Measles infection in such cases is characterized by a rapid and robust IgG response.[34,35] If a second serum sample collected 5–10 days later remains IgM negative, then the paired serum samples can be tested in a PRN assay or a quantitative or semi-quantitative IgG EIA validated for such use. Refer to the CDC Measles Laboratory website for more information at http://www.cdc.gov/measles/lab-tools/index.html.

The occurrence of measles-like illness in recently vaccinated persons can pose particular difficulties. Fever and rash are known to occur 6–12 days post-vaccination in a small percent of vaccinated persons.[1] A positive measles IgM test cannot be used to confirm the diagnosis of measles in persons with measles-like illness who received measles vaccine 6–45 days before onset of rash due to the measles IgM antibody response to the vaccine. Specimens for viral isolation should be obtained in addition to serologic testing (see "Laboratory Testing" section above); isolation of wild type measles virus would allow confirmation of the case. In the absence of strain typing to confirm wild type infection, cases in persons with measles-like illness who received measles vaccine 6–45 days before onset of rash should be classified as confirmed cases only if a) they meet the clinical case definition and b) they are epidemiologically linked to a laboratory-confirmed case.

Plaque reduction neutralization assay (PRN)

The gold standard test for serologic evidence of recent measles infection is a four-fold rise in titer as measured in a measles virus plaque reduction neutralization test (PRN or PRNT) between acute and convalescent serum samples. Unlike the IgG EIA, this test measures measles functional (neutralizing) antibodies, requires specialized reagents, and is labor and time intensive. Only in rare situations would such testing be deemed necessary. Prior approval should be obtained from the CDC Measles Laboratory.

Avidity of IgG

A single acute-phase serum sample can be tested for IgG avidity; however samples must have detectable IgG. Low avidity IgG confirms a recent measles infection (or recent vaccination). Avidity testing can distinguish between primary and secondary vaccine failures. Avidity testing requires specialized reagents and their use is limited to unusual cases (prior approval required) usually in an outbreak setting when cases with modified or nonclassic presentation of measles are detected.

Specimen collection

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or disease confirmation. Guidelines have been published for specimen collection and handling for viral and microbiologic agents (https://stacks.cdc.gov/view/cdc/7590. Information is also available on using CDC laboratories as support for reference and disease surveillance (https://www.cdc.gov/ncezid/dsr/specimen-management-branch.html); this includes:

- a central website for requesting lab testing (https://www.cdc.gov/laboratory/specimen-submission/index.html);
- the form required for submitting specimens to CDC (See Appendix 23, Form # CDC 0.5034);
- information on general requirements for shipment of etiologic agents (see Appendix 24)—although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories; and
- the CDC Infectious Diseases Laboratories Test Directory, which not only contains a list of orderable tests for that institution, but also detailed information such as appropriate specimen types, collection methods, specimen volume, and points of contact.

The APHL/CDC Vaccine Preventable Disease Reference Centers (https://www.aphl.org/programs/infectious_disease/Documents/ID_VPDQuickReferenceGuide_updated62016.pdf) can perform RT-PCR to detect measles RNA and measles genotyping.

Specific instructions for specimen collection and shipping may be obtained from the CDC measles website (https://www.cdc.gov/measles/lab-tools/rt-pcr.html#specimen-shipping) or by contacting the CDC Viral Vaccine Preventable Diseases Branch at 404-639-4181. Specimens for virus isolation and genotyping should be sent to CDC as directed by the State Health Department.

For additional information on use of laboratory testing for surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

VIII. Reporting and Case Notification

Case reporting within a jurisdiction

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[36] These regulations and laws list the diseases to be reported and describe those persons or groups responsible for reporting, such as health care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. You may contact your local or state health department for reporting requirements in your state.

Case notification to CDC

Since continuous endemic measles transmission has been eliminated, measles is an immediately notifiable disease. Measles cases should be reported promptly (within 24 hours[3]) by the state health department to the CDC or directly to Susan Redd at NCIRD, CDC by telephone: 404-639-8763 or by e-mail (SBR1@cdc.gov). Notifications of confirmed cases using the event code 10140 should then be electronically reported by the state health department to the National Notifiable Diseases Surveillance System (NNDSS) with the next regularly scheduled electronic transmission.

[3] *CSTE List of Nationally Notifiable Diseases:* http://www.cste.org/resource/resmgr/PDFs/CSTENotifiableConditionListA.pdf

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.

Please also refer to the measles surveillance worksheet for a complete list of the key variables that should be collected during case investigations (Appendix 8).

- **Demographic information**
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Residency (e.g., Did the case reside in the United States or is a foreign visitor?)
- **Reporting source**
  - State
  - County
  - Date first reported to a health department
- **Clinical Symptoms**
  - Date of onset of symptoms
  - Date of rash onset
  - Prodromal symptoms (i.e., cough, coryza, conjunctivitis, fever [note highest temperature])
  - Rash duration
  - Complications
- **Outcome (case survived or died)**
  - Date of death
  - Results of postmortem examination
  - Death certificate diagnoses
  - Hospitalization
- **Laboratory**
  - Serological tests:
    - type of specimen (IgM, IgG, avidity, PRN)
    - date of collection of specimen
    - results
  - Virus isolation tests:
    - type of specimen (PCR, culture)
    - date of collection of specimen
    - results

- **Vaccination status** (including postexposure prophylaxis)
  - Number of doses of measles vaccine received
  - Dates of measles vaccinations
  - If not vaccinated, reason
  - Postexposure prophylaxis type (vaccine, IGIV, IGIM)
  - Date of administration of postexposure prophylaxis
- **Epidemiological**
  - Transmission setting (e.g., household, school, health care setting, event)
  - Source of infection (e.g., age, vaccination status, relationship to case, contact with probable or confirmed case, or contact with immigrants or travelers, or international travel)
  - Import status (indigenous/endemic, international import, or out-of-state import, linked or traceable to an international importation)
  - Travel history in the three weeks prior to symptom onset, including flight or maritime information
  - Date of return to United States
  - Number of contacts

IX. Importance of Rapid Identification and Surveillance

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.

Confirmed and suspect case identification

Active surveillance for measles disease should be conducted for every confirmed measles case to assure timely reporting of suspected cases in the population known to be affected as well as other segments of the community that may be at high risk of exposure or in whom vaccination coverage is known to be low. Efforts should be made to obtain clinical specimens for viral detection (see "Laboratory Testing" section above). Active surveillance should be maintained until at least two incubation periods after the last confirmed case is reported (e.g., two maximum incubation periods [21 days from exposure to rash] or 42 days after rash onset in last case).

If the case-patient was traveling by plane or ship during the infectious period, the CDC Quarantine Station (operated by the Division of Global Migration and Quarantine) with jurisdiction for the reporting state should be contacted for assistance in the investigation and contact tracing of potentially exposed passengers and crew at http://www.cdc.gov/quarantine/QuarantineStationContactListFull.html. If unable to contact the QS, call the DGMQ 24-hour number at 866-694-4867 for assistance. Information that should be collected and shared with DGMQ includes date(s) of travel, departure and arrival locations, and flight or ship carrier and number.

Enhancing surveillance

Because measles importations occur every year in the United States, additional surveillance effort may be required to ensure that appropriate and timely diagnosis of rash illnesses and reporting of suspected cases continues. In addition, the rapid investigation and reporting of all suspected cases and recording of vaccination history and import status for all cases has become increasingly important.

Additional guidelines for enhancing surveillance are given in Chapter 19, "Enhancing Surveillance."
https://www.cdc.gov/vaccines/pubs/surv-manual/chpt19-enhancing-surv.html

Monitoring surveillance indicators

Regular monitoring of surveillance indicators, including time intervals between diagnosis and reporting and completeness of reporting, may identify specific areas of the surveillance and reporting system that need improvement. An important indicator of the adequacy of the measles surveillance system is the detection of importations. In the absence of measles endemic transmission, imported cases or cases linked to importations should be detected. A program which reports no imported cases in settings where endemic measles has been eliminated cannot be assumed to have adequate measles surveillance. For more information on surveillance indicators, see Chapter 18, "Surveillance Indicators." https://www.cdc.gov/vaccines/pubs/surv-manual/chpt18-surv-indicators.html

The following indicators should be monitored:

- The proportion of confirmed cases reported to the NNDSS with complete information
- The median interval between rash onset and notification of a public health authority, for confirmed cases
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source
- The proportion of cases for which at least one clinical specimen for virus isolation was collected

X. Case and Contact Investigation

All reports of suspected measles cases should be investigated immediately.

In the measles post-elimination era, a single case of measles is considered a public health priority that requires rapid evaluation for likelihood of measles and appropriate public health response; additional effort is required to ensure that appropriate and timely diagnosis of rash illnesses and reporting of suspected cases continues in order to prevent outbreaks and re-establishment of endemic disease transmission.

The measles surveillance worksheet (see Appendix 8 https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix08-2-mea-wrsht.pdf) should be used as a guideline for collecting demographic and epidemiologic data during case investigation. Essential components of case investigation include establishing a diagnosis of measles, obtaining immunization histories for confirmed cases, identifying sources of infection, assessing potential for transmission and identifying contacts without presumptive evidence of immunity, classifying importation status, and obtaining specimens for genotyping.

As measles continues to be endemic in many regions of the world, importations of measles occur every year in the United States. Each imported measles case could result in transmission of measles to susceptible individuals if exposed. Surveillance and prompt investigation of cases and their susceptible contacts is important because the spread of the disease can be limited with early case identification and public health response including vaccination and quarantine of susceptible contacts without presumptive evidence of immunity. However, because some imported measles cases are not detected in our surveillance system, maintaining a high alertness for measles is needed since not every "sporadic" case occurring in the community can be linked to an importation.

Information obtained through surveillance is also used to describe current measles epidemiology and to evaluate prevention policies and achievement of goals including maintenance of disease elimination. Surveillance data are used to characterize persons, groups, or areas in which additional efforts are required to reduce risk of measles disease and outbreaks.

Identify cases and establish a diagnosis

An essential first step in a measles case investigation is to obtain necessary clinical information to determine whether or not a reported case is clinically compatible with measles and to obtain key epidemiological information. If the case was reported within three days of onset of rash, the case may not meet the clinical case definition (see section "Case definition") and there should be appropriate follow-up to establish a rash duration of at least three days. However public health action, if needed, should not be delayed. Suspected cases of measles should have laboratory confirmation. Efforts should be made to obtain clinical specimens for viral testing (see the section "Laboratory Testing").

In the measles post-elimination era, most cases of febrile rash illness seen in physician's offices that meet the clinical case definition will not be measles. However, health care providers should maintain a high index of suspicion for measles in clinically compatible cases especially among unvaccinated persons and among persons who recently traveled abroad or who have had contact with persons such as travelers or international visitors. In addition, not every sporadic measles case is linked to a known importation, so cases that raise high suspicion of measles, irrespective of associated risk factors, should be investigated for measles unless an alternative diagnosis is likely (e.g., known epidemiological link to a parvovirus case).

It is important to consider measles in the differential diagnoses of parvovirus, dengue, Kawasaki disease, and scarlet fever. In addition, when evaluating patients with suspected measles who have negative tests for acute measles infection, additional testing for rubella can be considered.

Obtain accurate and complete immunization histories

Measles case investigations should include complete immunization histories that document all doses of measles-containing vaccine. Acceptable proof of vaccination is documented administration of live measles virus-containing vaccine. Written or electronic records with dates of vaccine administration are the only acceptable evidence of vaccination. 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/college records or from providers; if the case is a health care personnel, immunization records may be available at the health care facility. Immunization registries are now very useful sources of vaccination histories for children and adolescents.

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.

All confirmed case-patients should then be classified as recipients of one dose of measles-containing vaccine (as MMR, MMRV, MR or M), two doses, three or more doses, or no doses of vaccine. The date of vaccination for each dose and the interval between doses should be noted.

Written documentation of the date of administration are the only doses that are considered to be valid; self-reported doses and history of vaccination is not valid. The vaccination status of persons for whom vaccination status cannot be verified should be classified as unknown. Persons are categorized as unvaccinated if they report that they had no history of being vaccinated; if available, immunization records should be checked to verify lack of vaccine receipt.

Identify the source of infection

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. 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, during air travel, through other contact with recent travelers or foreign visitors, while visiting tourist locations (casinos, resorts, theme parks), in health care settings, or in churches. Unless a history of exposure to a known case within 7–21 days prior to onset of rash in the case is confirmed, case-patients or their caregivers should be closely queried about all these possibilities.

Assess potential for transmission and identify contacts without presumptive evidence of immunity

In the event of a confirmed measles case, local or state health departments should contact health care providers in their areas through the media or Epi-X to inform them of the confirmed case and request immediate reporting of any suspected cases. Previously unreported cases may be identified by reviewing emergency room logs, electronic medical records, or laboratory records. Hospital emergency rooms and physicians serving affected communities are usually recruited to participate in active surveillance.

General guidelines

Tracking what information is collected and what still needs to be collected. Tracking is easily accomplished by constructing a line listing of cases, allowing ready identification of known and unknown data and ensuring complete case investigation. The line listing is an essential component of every outbreak investigation (Table 1).

Identifying risk of transmission in the population affected by the outbreak. As part of the case investigation, the potential for further transmission should be evaluated, and an assessment should be made of exposed contacts of the case-patient (and their presumptive evidence of immunity during the infectious period [four days before to four days after onset of rash, day of rash onset being day zero]). In a closed setting the measles virus has been reported to have been transmitted by airborne or droplet exposure up to two hours after the measles case occupied the area.[37]

Based on the findings of individual case investigations, the population affected by the outbreak should be characterized in terms of

- person (who is getting measles and how many case-patients have had zero, one, and two doses of measles vaccine?),
- place (where are the cases?), and
- time (when did it start and is it still going on?). (For more information on data analysis, see Chapter 20, "Analysis of Surveillance Data.")

These essential data elements allow public health officials to

- identify the population at risk of infection (unvaccinated preschool-age children, high school students who have only received one dose of measles vaccine, persons who visited the emergency room of Hospital A on a certain day);
- determine where transmission is occurring or likely to occur (transmission is particularly likely in households, daycare, schools, health care settings, and in congregate settings such as churches and other institutions [colleges, prisons, etc.]); and
- identify persons who are at highest risk of infection or transmission (other unvaccinated children, students attending other schools, immunocompromised persons, pregnant women, health care personnel, infants aged <12 months etc.).

Table 1. Example of line listing for recording data in a measles outbreak investigation

Case ID	Name (Last, First)	Age	Date of Birth	Rash onset date	Source of exposure	Blood draw date	IgM result	Viral specimen (type, date and result)	MMR-1 date	MMR-2 date	Reason for Not Vaccinating	Case status
1	Doe, Jane	15 yr	12/1/1999	12/31/2014	id #2	1/3/2014			2/16/2000	—		—
2	Smith, Stacey	13 mo	11/5/2013	12/16/2014		12/21/2014	+		Unvax	—		lab confirmed
3	Doe, Henry	11 yr	12/26/2003	12/26/2014	id #2	1/3/2014			Unvax	—		—
4	Smith, Joe	26 yr	12/15/1988	12/30/2014	id #2	1/3/2014			?	—		—

XI. Control Measures

In general, the most effective control efforts are those that are targeted based upon epidemiologic data, rather than those that are directed at the entire community. Neither susceptibility nor risk of exposure is uniformly distributed throughout the community, and resources available for control may be limited. Therefore, it is essential that data be used to determine the scope of the investigation and the potential for spread and that intervention be based on those determinations using public health judgment to guide investigation and control efforts. The primary strategy is achieving a high level of immunity in the population affected.[28]

Initiation of investigation and prioritization of contacts

State and local health departments should use their judgment to prioritize such investigations according to epidemiology and identified transmission settings. Settings at highest risk of transmission based on the epidemiology of the outbreak may be prioritized for public health response.

If suspected and probable cases are investigated, postexposure prophylaxis of household contacts without presumptive evidence of immunity should not be delayed pending the return of laboratory results. Other high priority groups for contact investigation are 1) close contacts other than household (e.g., persons who shared the same room or airspace in various settings), 2) health care settings because of the risk of transmission to persons at high risk of serious complications, and 3) schools/child care centers, colleges or other close settings where a defined number of persons have congregated (e.g., churches) because of high contact rates and transmission potential. In all these settings, exposures usually result in an identified number of susceptible contacts to follow up on individually. However, efforts to identify the likelihood of exposure in larger settings such as hospitals (e.g., patients and health care personnel in ER) may be helpful. In particular, one should identify individuals at high risk for severe disease including infants who are not vaccinated, immunocompromised individuals, and pregnant women.

Initial preparation for major control activities may need to be started before the laboratory results are known. However, it is reasonable to delay major control activities, such as checking presumptive evidence of immunity and enforcing student exclusion, pending the return of laboratory results, which should be obtained as quickly as possible (within 24 hours).

If resources are constrained, other exposure settings will more commonly be lower priority to investigate, though public health decisions should be guided by the epidemiologic investigation. For exposures at such venues as restaurants, stadiums, and malls, communicating with the general public through radio, TV, Epi-X, or other media, may be used to reach potentially exposed persons rather than individual contact tracing. Persons can be guided to their physicians or the health department for assessment of immunity status and the need for vaccination.

Additional guidelines for enhancing surveillance are given in Chapter 19, "Enhancing Surveillance."

Isolation of cases and exclusion of contacts without presumptive evidence of immunity

Case-patients should be isolated for four days post rash onset.

Exposed persons who cannot readily document presumptive evidence of measles immunity should be offered postexposure prophylaxis (PEP) or excluded from the setting (school, hospital, day care). For assessment of presumptive evidence of immunity of contacts, 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 and who do not receive appropriate postexposure prophylaxis within the appropriate time should be excluded from affected institutions in the outbreak area until 21 days after the onset of rash in the last case of measles.

Quarantine and its use

Quarantine (most commonly voluntary quarantine) of exposed persons has been implemented especially where unvaccinated or populations at high risk were affected. In such situations, quarantine has helped to contain the spread of the disease to the surrounding community.[18,38,39,42] Compliance with quarantine can be ensured at the discretion of the health department. When deciding about quarantine, factors to consider include

- immune status of the individual,
- presumptive evidence of immunity,
- whether the person is at high risk or not, and
- transmission settings.

Imposing quarantine measures for outbreak control is 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.

Postexposure vaccination and use of immunoglobulin to prevent measles in exposed susceptible persons

Presumptive evidence of measles immunity should be assessed for all identified contacts.

The MMR vaccine, if administered within 72 hours of initial measles exposure, and immunoglobulin (IG), if administered within six days of exposure, may provide some protection or modify the clinical course of disease among susceptible persons. However, vaccination should be offered at any interval following exposure in order to offer protection from future exposures.

There is limited data regarding the effectiveness of MMR vaccine and IG PEP against disease prevention. Thus, individuals who receive MMR vaccine or IG as PEP should be monitored for signs and symptoms consistent with measles for at least one incubation period.[28] IG may prolong the incubation period so extending the monitoring period for individuals who received IG as PEP may be considered (see Prevention and control strategies in medical settings).

Infectious or potentially infectious persons requiring medical attention (e.g., a susceptible contact in quarantine who develops measles-like symptoms), should be advised to call ahead before visiting a clinic or emergency department to ensure appropriate precautions are in place prior to the medical encounter.

Except in health care settings, unvaccinated persons who receive their first dose of MMR vaccine within 72 hours postexposure may return to childcare, school, or work.

Individuals who are at risk for severe disease and complications from measles (e.g., infants <12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons regardless of vaccination status because they might not be protected by the vaccine) should receive IG.

IG administered intramuscularly (IGIM) is recommended for infants <12 months of age, and IG administered intravenously (IGIV) for severely immunocompromised persons and pregnant women who are exposed to measles. For infants 6 through 11 months of age, MMR vaccine can be given in place of IG, if administered within 72 hours of exposure.[28] IGIM can be given to other persons who do not have evidence of measles immunity, but priority should be given to persons exposed in settings with intense, prolonged, close contact (e.g., household, daycare, classroom). However, postexposure use of IGIM might be limited because of volume limitations; persons who weigh >30 kg will receive less than the recommended dose and will have lower titers than recommended. For exposed persons without evidence of measles immunity, a rapid IgG antibody test can be used to inform immune status, provided that administration of IG is not delayed.

After receipt of IG, individuals cannot return to health care settings. In other settings such as childcare, school, or work, factors such as immune status, intense or prolonged contact, and presence of populations at risk, should be taken into consideration before allowing these individuals to return. These factors may decrease the effectiveness of IG or increase the risk of disease and complications depending on the setting to which they are returning.

The recommended dose of IG given intramuscularly is 0.5 mL/kg of body weight (maximum dose = 15 mL) and the recommended dose of IG given intravenously is 400 mg/kg.

Note that children vaccinated before their first birthday should be revaccinated when they are 12–15 months old and again when they are 4–6 years of age. Also, any nonimmune person exposed to measles who received IG should subsequently receive MMR vaccine, which should be administered no earlier than 6 months after IGIM administration or 8 months after IGIV administration, provided the person is then ≥12 months of age and the vaccine is not otherwise contraindicated.

IG should not be used to control measles outbreaks, but rather to reduce the risk for infection and complications in the person receiving it.

Role of community-wide vaccination efforts in outbreak control

Physicians in affected communities should use the opportunity of a confirmed measles case for reminder/recall to ensure that all their patients are up to date with MMR vaccine requirements.

Community-wide vaccination clinics are rarely indicated but targeted clinics may be held to reach affected populations (e.g., vaccination for health care workers; a work setting clinic with affected adults; or offering clinics at health departments in under-immunized communities).

For outbreaks with sustained, community-wide transmission affecting preschool-aged children or adults and with ongoing risk of exposure, health departments may consider a second dose for children aged 1 through 4 years or adults in these affected areas (including visitors) who have received 1 dose; the second dose given at least 28 days after the first dose.

For outbreaks with sustained, community-wide transmission affecting infants <12 months of age and with ongoing risk of exposures to infants, health departments may consider vaccination of infants aged 6–11 months in these affected areas (including visitors) with 1 dose of MMR vaccine. This recommendation should be made following careful assessment of the benefit of early protection against measles during a period of increased transmission and exposure, and risk of decreased immune response following subsequent MMR doses in infants vaccinated at <12 months of age compared with infants vaccinated at ≥12 months of age.[41,42] Decisions to vaccinate infant visitors <12 months of age should follow local health department guidance of the affected area (e.g., if no recommendation was made to vaccinate infant residents, vaccination of infant visitors is not recommended). This dose does not count as one of the two recommended doses; infants who receive one dose of MMR vaccine before their first birthday should receive two more doses according to the routinely recommended schedule (one dose at 12 through 15 months of age and another dose at 4 through 6 years of age or at least 28 days later).[28]

Day care centers, schools and other educational institutions

Measles cases in schools, colleges, and other institutions, such as day care centers where close contact may exist, require rapid public health investigation for response and for evaluation of risk of further transmission. In educational institutions where there are high rates of vaccine exemptors, the potential risk of spread of the disease is high. Control measures include the following actions:

- Exclusion and isolation of cases (they can return on the fifth day after rash onset if not immunocompromised)
- Offering vaccine for those who are not up-to-date with age-appropriate vaccination (first dose to unvaccinated, second dose to those with one documented dose can be given at least 28 days after the first dose)
- IG if immunocompromised (please refer the following section: Postexposure vaccination and use of immunoglobulin to prevent measles in exposed susceptible persons)
- Persons who continue to be exempted from or who refuse measles vaccination should be excluded from the school, childcare, or other institutions until 21 days after rash onset in the last case of measles[38,43]

All students and all school personnel born in or after 1957 who cannot provide adequate presumptive evidence of immunity should be vaccinated. Persons receiving their second dose and previously unvaccinated persons receiving their first dose appropriately (i.e., before, or within 72 hours of, exposure) as part of the outbreak control program may be immediately readmitted to school. However these individuals should be monitored for signs and symptoms of measles.

Health care settings

Persons who work in health care settings (including volunteers, trainees, nurses, physicians, technicians, receptionists, and other clerical and support staff) are at increased risk of exposure to measles and at increased risk of transmission to persons at high risk of severe measles. All persons who work in such settings and have the potential for exposure to potentially infectious patients or materials (e.g., contaminated air) should have presumptive evidence of immunity to measles to prevent any potential outbreak.[21, 44]

Presumptive evidence of immunity and routine vaccine recommendations for health care personnel

Health care personnel (HCP) have slightly different criteria for acceptable presumptive evidence of immunity. All HCP should have presumptive evidence of immunity to measles.[21, 44] This information should be documented and readily available (ideally through electronic medical records) at the work location.

Presumptive evidence of immunity to measles for health care personnel includes any of the following.

- Written documentation of vaccination with 2 doses of live measles or MMR vaccine administered at least 28 days apart,*
- Laboratory evidence of immunity,†
- Laboratory confirmation of disease, or
- Birth before 1957.‡

Although birth before 1957 is considered as presumptive evidence of immunity, for unvaccinated HCP born before 1957 that lack laboratory evidence of measles immunity or laboratory confirmation of disease, health care facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval.

---

* *The first dose of measles-containing vaccine should be administered on or after the first birthday; the second dose should be administered no earlier than 28 days after the first dose.*

† *Measles immunoglobulin (IgG) in the serum; equivocal results should be considered negative.*

‡ *The majority of persons born before 1957 are likely to have been infected naturally and may be presumed immune, depending on current state or local requirements. For unvaccinated personnel born before 1957 who lack laboratory evidence of measles immunity or laboratory confirmation of disease, health care facilities should consider vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval. For unvaccinated personnel born before 1957 who lack laboratory evidence of measles immunity or laboratory confirmation of disease, health care facilities should recommend 2 doses of MMR vaccine during an outbreak of measles.*

Prevention and control strategies in medical settings

In a medical setting, both the occupational health and infection prevention and control practitioners have a role. When a measles case occurs in a health care setting, including outpatient and long-term care facilities, the following measures should be undertaken:

- Implementation of airborne and standard precautions for patients in whom measles is suspected or confirmed.[45]
- Airborne precautions include isolation in a negative air pressure isolation room, also known as airborne infection isolation (AII) or airborne infection isolation room (AIIR). In clinic settings where a negative air pressure isolation room may not be available, a single room with the door closed and away from susceptible contacts may be used when evaluating persons in whom measles is suspected.
- In addition, suspect or confirmed measles patients should be asked to wear a medical mask.[44]
- Immediate review of evidence of measles immunity in all exposed staff (see "Presumptive evidence of immunity for health care personnel").
- Vaccination of personnel without presumptive evidence of immunity.
- Exclusion of HCP with active measles illness for four days after the rash appears.
- HCP without presumptive evidence of immunity should be offered the first dose of MMR vaccine and excluded from work from day 5 after the first exposure to day 21 following after their last exposure.

An effective vaccination program is the best approach to prevent health care associated measles transmission. Health Care Infection Control Practices Advisory Committee (HICPAC) and CDC have recommended that secure, preferably computerized, systems should be used to manage vaccination records for HCP so records can be retrieved easily as needed.[44] Failure to have such records can be costly and can increase resources needed to respond to the outbreak.[46]

If a measles case or an outbreak occurs within or in the areas served by a hospital, clinic, or other medical or nursing facility, all personnel regardless of birth year, should receive two doses of MMR vaccine, unless they have other documentation of measles immunity.[44] Birth year before 1957 is not acceptable presumptive evidence of immunity during an outbreak. Health care facilities should provide MMR vaccine to all personnel without presumptive evidence of measles immunity at no charge. Recently vaccinated HCP (i.e., prior to exposure or the outbreak) do not require any restriction in their work activities. Those with documentations of one vaccine dose may remain at work and should receive the second dose. Because of the possibility, albeit low, of measles vaccine failure in HCP, all staff entering the room of a person with suspect or confirmed measles should use respiratory protection consistent with airborne infection control precautions (i.e., use of an N95 respirator), regardless of presumptive immunity status.[44]

Serologic screening of HCP during an outbreak to determine measles immunity prior to vaccination is not recommended, because preventing measles transmission requires the rapid vaccination of HCP without presumptive evidence of immunity, which can be impeded by the need to screen, wait for results, and then contact and vaccinate susceptible persons. Results from serological testing, if performed, can inform on need for the second MMR vaccine dose.

HCP without presumptive evidence of immunity who have been exposed to measles should be relieved from patient contact and excluded from work from the 5th day after the first exposure through the 21st day after the last exposure, regardless of whether they received vaccine or intramuscular immune globulin after the exposure. Personnel who develop measles should be relieved from all patient contact and excluded from work for four days after they develop rash.[44]

Hospital patient contacts of a case, who do not have presumptive evidence of measles immunity, should be vaccinated or offered immune globulin or placed on airborne precautions until 21 days after their last exposure to the case-patient or four days after the onset of rash should they develop measles.[45] If immune globulin is administered to an exposed person, observations should continue for signs and symptoms of measles for 28 days after exposure since immune globulin may prolong the incubation period.[44]

Additional information

Because investigating an outbreak requires many person-days of work, personnel are frequently transferred to the activity from other areas in the health department or from other health departments and may only be involved in outbreak investigation for a few days before they are replaced by others. This turnover in personnel can cause problems unless activities are organized so that the status of the investigation is documented at all times. Some practical suggestions for organizing this activity are listed here.

- Identify a team leader for case investigators so that at least one person knows about all the new cases called in that day and what still needs to be done. Daily briefings are a good way of keeping the whole staff informed of the status of the investigation.
- Use a logbook (electronic spreadsheet preferred) to record all suspected cases as they are received. The person who receives the initial telephone call should attempt to obtain the information needed to fill in the line listing (see Table 1).
- Create a column in the logbook for actions needed for each suspected case (“draw blood,” “call pediatrician for vaccination history,” “notify contacts”).
- Keep the logbook in one well defined location, preferably with folders containing the case investigations of all the cases that have been reported. It is useful to have one stack of all confirmed cases, one stack of suspected or probable cases awaiting further investigation or lab results, and a separate stack of discarded cases.

- Establish protocols for control measures necessary for all likely situations (exposure in a childcare center, school, doctor's office, workplace) and clearly define who (local health officer, immunization program manager) will make the decision to proceed when a case investigator identifies a situation that might require major investments of health department resources (such as vaccinating an entire school).

Acknowledgements

Prior versions of this chapter were authored by Preeta Kutty, Jennifer Rota, William Bellini, Albert Barskey, and Gregory Wallace.

References

1. Strebel P, Papania MJ, Gastanaduy PA, Goodson JL. Measles vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 7th ed. Philadelphia, PA: WB Saunders; 2017. p. 579–618.
2. Miller DL. Frequency of complications of measles, 1963. *Br Med J* 1964;2(5401):75–8.
3. Gindler J, Tinker S, Markowitz L, Atkinson W, Dales L, Papania MJ. Acute measles mortality in the United States, 1987–2002. *J Infect Dis* 2004;189 (Suppl 1):S69–77. doi: 10.1086/378565
4. Bellini WJ, Rota JS, Lowe LE, et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* 2005;192(10):1686–93. doi: 10.1086/497169
5. Klinkenberg D, Nishiura H. The correlation between infectivity and incubation period of measles, estimated from households with two cases. *J Theor Biol* 2011;284(1):52–60. doi: 10.1016/j.jtbi.2011.06.015
6. American Academy of Pediatrics. Measles. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors. 2009 Red Book: report of the committee on infectious diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009. p. 444–6.
7. Hinman AR, Orenstein WA, Bloch AB, et al. Impact of measles in the United States. *Rev Infect Dis* 1983;5(3):439–44.
8. Langmuir AD. Medical importance of measles. *Am J Dis Child* 1962;103:224–6.
9. Orenstein WA, Papania MJ, Wharton ME. Measles elimination in the United States. *J Infect Dis* 2004;189 (Suppl 1):S1–3. doi: 10.1086/377693
10. van Panhuis WG, Grefenstette J, Jung SY, et al. Contagious diseases in the United States from 1888 to the present. *N Engl J Med* 2013;369(22):2152–8. doi: 10.1056/NEJMms1215400
11. Hinman AR, Orenstein WA, Papania MJ. Evolution of measles elimination strategies in the United States. *J Infect Dis* 2004;189 (Suppl 1):S17–22. doi: 10.1086/377694
12. Atkinson WL, Orenstein WA, Krugman S. The resurgence of measles in the United States, 1989–1990. *Annu Rev Med* 1992;43:451–63. doi: 10.1146/annurev.me.43.020192.002315
13. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. *J Infect Dis* 2004;189 (Suppl 1):S43–7. doi: 10.1086/377696
14. Fiebelkorn AP, Redd SB, Gastanaduy PA, et al. A comparison of postelimination measles epidemiology in the United States, 2009–2014 versus 2001–2008. *J Pediatric Infect Dis Soc* 2017 Mar 01;6(1):40–8. doi: 10.1093/jpids/piv080
15. Fiebelkorn AP, Redd SB, Gallagher K, et al. Measles in the United States during the postelimination era. *J Infect Dis* 2010;202(10):1520–8. doi: 10.1086/656914
16. CDC. Measles—United States, January 4–April 2, 2015. *MMWR Morb Mortal Wkly Rep* 2015;64(14):373–6. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6414a1.htm
17. CDC. Measles—United States, January 1–May 23, 2014. *MMWR Morb Mortal Wkly Rep* 2014;63(22):496–9. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6322a4.htm
18. Gastanaduy PA, Budd J, Fisher N, et al. A measles outbreak in an underimmunized Amish community in Ohio. *N Engl J Med* 2016;375(14):1343–54. doi: 10.1056/NEJMoa1602295
19. CDC. Measles outbreak—California, December 2014–February 2015. *MMWR Morb Mortal Wkly Rep* 2015;64(6):153–4. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6406a5.htm?s_cid=mm6406a5_w

20. Schuchat A, Fiebelkorn AP, Bellini W. Measles in the United States since the millennium: perils and progress in the postelimination era. *Microbiol Spectr* 2016;4(2):EI10-0006-2015. doi: 10.1128/microbiolspec.EI10-0006-2015
21. Fiebelkorn AP, Redd SB, Kuhar DT. Measles in healthcare facilities in the United States during the postelimination era, 2001–2014. *Clin Infect Dis* 2015;61(4):615–8. doi: 10.1093/cid/civ387
22. Ortega-Sanchez IR, Vijayaraghavan M, Barskey AE, Wallace GS. The economic burden of sixteen measles outbreaks on United States public health departments in 2011. *Vaccine* 2014;32(11):1311–7. doi: 10.1016/j.vaccine.2013.10.012
23. CDC. Progress toward regional measles elimination—worldwide, 2000–2015. *MMWR Morb Mortal Wkly Rep* 2016;65(44):1228–33. doi: 10.15585/mmwr.mm6544a6
24. de Quadros CA, Izurieta H, Venczel L, et al . Measles eradication in the Americas: progress to date. *J Infect Dis* 2004; 189 Suppl 1:S227–35.
25. Pan American Health Organization. Region of the Americas is declared free of measles. Washington, DC: PAHO; 2016 [published 27 Septembet 2016; cited 13 December 2017]; http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles
26. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med* 2009;360(19):1981–8. doi: 10.1056/NEJMsa0806477
27. WHO. Global measles and rubella strategic plan : 2012–2020. Geneva: WHO; 2012 [cited 2016 April 23] http://apps.who.int/iris/bitstream/10665/44855/1/9789241503396_eng.pdf
28. CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2013;62(RR-04):1–34. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm
29. CSTE. Public health reporting and national notification for measles. CSTE position statement 12-ID-07. Atlanta, GA: CSTE; 2012. http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/ps/12-id-07final.pdf
30. Rota PA, Brown K, Mankertz A, et al. Global distribution of measles genotypes and measles molecular epidemiology. *J Infect Dis* 2011;204 (Suppl 1):S514–23. doi: 10.1093/infdis/jir118
31. Helfand RF, Heath JL, Anderson LJ, Maes EF, Guris D, Bellini WJ. Diagnosis of measles with an IgM capture EIA: the optimal timing of specimen collection after rash onset. *J Infect Dis* 1997;175(1):195–9. doi: 10.1093/infdis/175.1.195
32. Helfand RF, Kebede S, Gary HE Jr, Beyene H, Bellini WJ. Timing of development of measles-specific immunoglobulin M and G after primary measles vaccination. *Clin Diag Lab Immunol* 1999;6(2):178–80.
33. Greenwood KP, Hafiz R, Ware RS, Lambert SB. A systematic review of human-to-human transmission of measles vaccine virus. *Vaccine* 2016;34(23):2531–6. doi: 10.1016/j.vaccine.2016.03.092
34. Rota JS, Hickman CJ, Sowers SB, Rota PA, Mercader S, Bellini WJ. Two case studies of modified measles in vaccinated physicians exposed to primary measles cases: high risk of infection but low risk of transmission. *J Infect Dis* 2011;204 (Suppl 1):S559–63. doi: 10.1093/infdis/jir098
35. Hickman CJ, Hyde TB, Sowers SB, et al. Laboratory characterization of measles virus infection in previously vaccinated and unvaccinated individuals. *J Infect Dis* 2011;204 (Suppl 1):S549–58. doi: 10.1093/infdis/jir106
36. Roush S, Birkhead G, Koo D, Cobb A, Fleming D. Mandatory reporting of diseases and conditions by health care professionals and laboratories. *JAMA* 1999;282(2):164–70. doi: 10.1001/jama.282.2.164
37. De Jong JG, Winkler KC. Survival of measles virus in air. *Nature* 1964;201:1054–5.
38. Sugerman DE, Barskey AE, Delea MG, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. *Pediatrics* 2010;125(4):747–55. doi: 10.1542/peds.2009-1653
39. Dayan GH, Ortega-Sanchez IR, LeBaron CW, Quinlisk MP; Iowa Measles Response Team. The cost of containing one case of measles: the economic impact on the public health infrastructure—Iowa, 2004. *Pediatrics* 2005;116(1):e1–4. doi: 10.1542/peds.2004-2512

40. Parker AA, Staggs W, Dayan GH, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. *N Engl J Med* 2006;355(5):447–55. doi: 10.1056/NEJMoa060775
41. Brinkman ID, de Wit J, Smits GP, et al. Early measles vaccination during an outbreak in The Netherlands: reduced short and long-term antibody responses in children vaccinated before 12 months of age. *J Infect Dis* 2019.
42. Gans HA, Yasukawa LL, Sung P, et al. Measles humoral and cell-mediated immunity in children aged 5-10 years after primary measles immunization administered at 6 or 9 months of age. *J Infect Dis* 2013;207:574-82.
43. CDC. Measles, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1998;47(RR-8):1–57. https://www.cdc.gov/mmwr/preview/mmwrhtml/00053391.htm
44. CDC. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60(RR-7):1–45. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6007a1.htm?s_cid=rr6007a1_w
45. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory C. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control* 2007;35(10 Suppl 2):S65–164. doi: 10.1016/j.ajic.2007.10.007.
46. Chen SY, Anderson S, Kutty PK, et al. Health care-associated measles outbreak in the United States after an importation: challenges and economic impact. *J Infect Dis* 2011;203(11):1517–25. doi: 10.1093/infdis/jir115