

Measles

MEASLES IS AN ACUTE VIRAL INFECTIOUS DISEASE. There are references to measles as far back as the 7th century A.D. The disease was described by Rhazes in the 10th Century A.D. as “more dreaded than smallpox.”

In 1846, Peter Panum described the incubation period of measles and lifelong immunity. Enders and Peebles isolated the virus in human and monkey kidney tissue culture in 1954. The first live attenuated vaccine was licensed for use in the U.S. in 1963 (Edmonston B strain).

Measles Virus

The measles virus is a paramyxovirus, genus Morbillivirus. It is 100 to 200nm in diameter, with a core of single-stranded RNA, and is closely related to the rinderpest and canine distemper viruses. Measles virus has six structural proteins, of which three are complexed to the RNA and three are associated with the viral membrane envelope. Two of the membrane envelope proteins are most important in pathogenesis. They are (1) F (fusion): glycosylated; responsible for fusion of virus and host cell membranes, viral penetration, and hemolysis and (2) H (hemagglutinin): glycosylated; responsible for adsorption of virus to cells and provides antigen for hemagglutination.

There is only one antigenic type of measles virus. Although recent studies have documented changes in the H glycoprotein, these changes do not appear to be epidemiologically important (*i.e.*, no change in vaccine efficacy has been observed).

Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin, is destroyed in the stomach, and has a short survival time (<2 hours) in the air, or on objects and surfaces.

Measles

- Highly contagious acute viral illness
- Prevaccine era: virtually universal infection in childhood with frequent epidemics
- Postvaccine era: >98% reduction in cases
- Recent resurgence due to low vaccination coverage levels

Measles Virus

- Paramyxovirus
- One antigenic type
- Recent variation in hemagglutinin glycoprotein identified
- Rapidly inactivated by heat and light

Measles Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 2-3 days after exposure
- Secondary viremia 5-7 days after exposure with spread to tissues

Measles Clinical Course

Prodrome

- Incubation period 10-12 days
- Stepwise increase in fever to >103 F
- Cough, coryza, conjunctivitis
- Koplik spots

Measles Clinical Course

Rash

- 2-4 days after prodrome, 14 days after exposure
- Maculopapular, becomes confluent
- Begins on face and head
- Spreads to trunk, arms, legs
- Persists 5-6 days
- Fades in order of appearance

Pathogenesis

Measles is a systemic infection. The primary site of infection is the respiratory epithelium of the nasopharynx. Two to three days after invasion and replication in the respiratory epithelium and regional lymph nodes, a primary viremia occurs with subsequent infection of the reticuloendothelial system. Following further viral replication in regional and distal reticuloendothelial sites, there is a second viremia, which occurs 5 to 7 days after initial infection. During this viremia, there may be infection of the respiratory tract and other organs. Measles virus is shed from the nasopharynx beginning with the prodrome until 3-4 days after rash onset.

Clinical Features

Incubation period

From exposure to prodrome averages 10-12 days. From exposure to rash onset averages 14 days (range, 7-18 days).

Prodrome

The prodrome lasts 2-4 days (range 1-7 days). It is characterized by fever, which increases in stepwise fashion, often peaking as high as 103 -105 F. This is followed by the onset of cough, coryza (runny nose), and/or conjunctivitis.

Koplik's spots, an exanthem present on mucous membranes, is considered to be pathognomonic for measles. It occurs 1-2 days before rash to 1-2 days after rash, and appears as punctate blue-white spots on bright red background on buccal mucosa.

Rash

The measles rash is a maculopapular eruption which usually lasts 5-6 days. It begins at the hairline, then involves the face and upper neck. Over the next 3 days, the rash gradually proceeds downward and outward, reaching the hands and feet.

The maculopapular lesions are generally discrete, but may become confluent, particularly on the upper body. Initially, lesions blanch with fingertip pressure. By 3-4 days, most do not blanch with pressure. Fine desquamation occurs over more severely involved areas. The rash fades in the same order that it appears, from head to extremities.

Other symptoms and signs

Other symptoms of measles include anorexia, diarrhea, especially in infants, and generalized lymphadenopathy.

Complications

Approximately 30% of reported measles cases have one or more complications. Complications of measles are more common among children <5 and adults >20 years of age.

From 1985 through 1992, **diarrhea** was reported in 8% of reported cases, making this the most commonly reported complication of measles. **Otitis media** is reported in 7% of reported cases, and occurs almost exclusively in children. **Pneumonia** (6% of reported cases) may be viral or superimposed bacterial, and is the most common cause of death. Acute **encephalitis** is reported in approximately 0.1% of reported cases. Onset generally occurs 6 days after rash onset (range 1-15 days), and is characterized by fever, headache, vomiting, stiff neck, meningeal irritation, drowsiness, convulsions, and coma. Cerebrospinal fluid shows pleocytosis and elevated protein. Case fatality rate is approximately 15%. Some form of residual neurologic damage occurs in as many as 25%. **Seizures** (with or without fever) are reported in 0.6% to 0.7% of reported cases.

Death from measles has been reported in approximately 1-2 per 1,000 reported cases in the United States in recent years. As with other complications of measles, the risk of death is higher among young children and adults. Pneumonia accounts for about 60% of deaths. The most common causes of death are pneumonia in children and acute encephalitis in adults.

Subacute sclerosing panencephalitis (SSPE)

Subacute sclerosing panencephalitis (SSPE) is a rare degenerative central nervous system disease believed to be due to persistent measles virus infection of the brain. Average onset occurs 7 years after measles (range 1 month-27 years), and occurs in five to ten cases per million reported measles cases. The onset is insidious, with progressive deterioration of behavior and intellect, followed by ataxia (awkwardness), myoclonic seizures, and eventually death. SSPE has been extremely rare since the early 1980s.

Measles during pregnancy

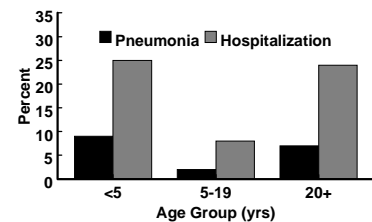
Measles illness during pregnancy results in a higher risk of premature labor, spontaneous abortion, and low-birth-weight infants. Birth defects (with no definable pattern of malformation) have been reported rarely, without confirmation that measles was the cause.

Measles Complications

Condition	Percent reported
Any complication*	29
Diarrhea	8
Otitis media	7
Pneumonia	6
Encephalitis	0.1
Death	0.2
Hospitalization	18

*includes hospitalization
Based on 1985-1992 surveillance data

Measles Complications by Age



Other Measles Syndromes

Atypical measles

This syndrome occurs only in persons who received inactivated (“killed”) measles vaccine (KMV) and are subsequently exposed to wild-type measles virus. Between 600,000 and 900,000 persons received KMV in the U.S. from 1963 to 1967. KMV sensitized the recipient to measles virus antigens without providing protection. Subsequent infection with measles virus leads to signs of hypersensitivity polyserositis. The illness is characterized by fever, pneumonia, pleural effusions, and edema.

The rash is usually maculopapular or petechial but may have urticarial, purpuric, or vesicular components and appears first on the wrists or ankles. Atypical measles may be prevented by revaccinating with live measles vaccine. Moderate to severe local reactions with or without fever may follow vaccination; these reactions are less severe than with infection with wild measles virus.

Modified measles

This syndrome occurs primarily in patients who received immune globulin (IG) as post-exposure prophylaxis and in young infants who have some residual maternal antibody. It is usually characterized by a prolonged incubation period, mild prodrome, and sparse, discrete rash of short duration. Similar mild illness has been reported among previously vaccinated persons.

Hemorrhagic measles

Rarely reported in the United States, hemorrhagic measles is characterized by high fever (105 -106 F), seizures, delirium, respiratory distress, and hemorrhage into the skin and mucous membranes.

Measles in the immunocompromised host

Measles in an immunocompromised person may be severe, with a prolonged course. It is reported almost exclusively in persons with T-cell deficiencies (certain leukemias, lymphomas, and Acquired Immunodeficiency Syndrome [AIDS]). It may occur without typical rash, and a patient may shed virus for several weeks after the acute illness.

Measles in developing countries

In developing countries, measles may result in high attack rates among children <12 months of age. Measles is more severe in malnourished children, particularly those with vitamin A deficiency. Complications include diarrhea, dehydration, stomatitis, inability to feed, and bacterial infections (skin and elsewhere). The case fatality rate may be as high as 25%. Measles is also a leading cause of blindness in African children.

Laboratory Diagnosis

Viral isolation

Isolation of measles virus is not recommended as a routine method to diagnose measles. However, virus isolates are extremely important for molecular epidemiologic surveillance to help determine the geographic origin of the virus and the viral strains circulating in the United States.

Measles virus can be isolated from urine, nasopharyngeal aspirates, heparinized blood, or throat swabs. Specimens for virus culture should be obtained from every clinically suspected case of measles and should be shipped to the state public health laboratory or CDC, at the direction of the state health department. Clinical specimens for viral isolation should be collected at the same time as, and in addition to, samples taken for serologic testing. Because virus is more likely to be isolated when the specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until laboratory confirmation is obtained. Clinical specimens should ideally be obtained within 7 days of rash onset, and should not be collected if the opportunity to collect a specimen is more than 10 days after rash onset. A detailed protocol for collection of specimens for viral isolation is included in Appendix H.

Serology

Serologic testing, most commonly by enzyme-linked immunoassay (ELISA or EIA), is widely available and may be diagnostic if done at the appropriate time. Generally, a previously susceptible person exposed to either vaccine or wild type measles virus will first mount an IgM response and then a IgG response. The IgM response will be transient (1–2 months) and the IgG response should persist for many years. Uninfected persons should be IgM negative and will either be IgG negative or IgG positive depending upon their previous infection history.

Measles Laboratory Diagnosis

- Isolation of measles virus from clinical specimen (e.g., nasopharynx, urine)
- Significant rise in measles IgG by any standard serologic assay (e.g., enzyme immunoassay, hemagglutination inhibition)
- Positive serologic test for measles IgM antibody

ELISA tests for IgM antibody require only a single serum specimen and are diagnostic if positive. The preferred reference test is a capture IgM test developed by CDC. This test should be used to confirm every case of measles that is reported to have some other type of laboratory confirmation. IgM capture tests for measles are often positive on the day of rash onset. However, in the first 72 hours after rash onset, up to 20% of tests for IgM may give false-negative results. Tests which are negative in the first 72 hours after rash onset should be repeated. IgM is detectable for at least 28 days after rash onset and frequently longer.

A variety of tests for IgG antibodies to measles are available and include ELISA tests, hemagglutination inhibition, indirect fluorescent antibody tests, microneutralization, and plaque reduction neutralization. Complement fixation, while widely used in the past, is no longer recommended.

IgG testing for measles requires the demonstration of a rise in the titer of antibody against measles virus, so two serum specimens are always required. The first specimen should be drawn as soon after rash onset as possible. The second specimen should be drawn 10–30 days later. The tests for IgG antibody should be conducted on both 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 depends on the test. ELISA values are not titers and increases in ELISA values do not directly correspond to four-fold or greater titer rises.

Tests for IgG antibody require two serum specimens and a confirmed diagnosis cannot be made until the second specimen is obtained. As a result, IgM tests are generally preferred.

Classification of Measles Cases

Clinical classification of measles cases

A suspect case is any rash illness with fever.

A probable case meets the **measles case definition** of generalized maculopapular rash lasting 3 days, with fever $\geq 38.3^{\circ}\text{C}$ (101°F); and cough, or coryza, or conjunctivitis and has no or noncontributory serologic or virologic testing.

A confirmed case meets the case definition, and is epidemiologically linked to another confirmed or probable case; or is laboratory confirmed.

Measles

Clinical Case Definition

- Generalized rash lasting ≥ 3 days
AND
- Temperature $\geq 38.3^{\circ}\text{C}$ (101°F)
AND
- Cough, or coryza, or conjunctivitis

Only confirmed cases should be reported to *Morbidity and Mortality Weekly Report (MMWR)*, but confirmed and probable cases should be reported as soon as possible to local or state health department.

Epidemiologic classification

An **indigenous case** is any case which cannot be proved to be imported (or epidemiologically linked within two generations to an imported case).

An **imported case** is a case which has its source outside the state. To classify a case as imported requires documentation that the person either had face-to-face contact with a case of measles outside the state, or was out of state for the entire period when he or she might have become infected. An **international case** is classified as imported from another country if onset of rash is within 18 days of entering the United States.

Epidemiology

Occurrence

Measles occurs throughout the world.

Reservoir

Measles is a human disease. There is no known animal reservoir, and an asymptomatic carrier state has not been documented.

Transmission

Measles transmission is primarily person to person via large respiratory droplets. Airborne transmission via aerosolized droplet nuclei has been documented in closed areas (*e.g.*, office examination room) for up to 2 hours after a person with measles occupied the area.

Temporal pattern

In temperate areas, measles disease occurs primarily in the late winter and spring.

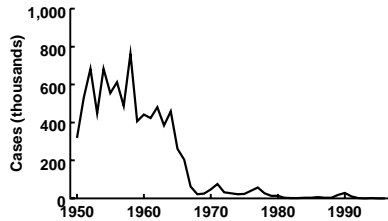
Communicability

Measles is highly communicable, with >90% secondary attack rates among susceptible persons. Measles may be transmitted from 4 days prior to 4 days after rash onset. Maximum communicability occurs from onset of prodrome through the first 3-4 days of rash.

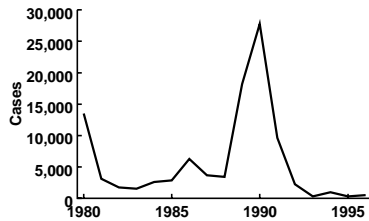
Measles Epidemiology

- Reservoir Human
- Transmission Respiratory - person to person
Airborne
- Temporal pattern Peak late winter and spring
- Communicability Maximum 4 days before to
4 days after rash onset

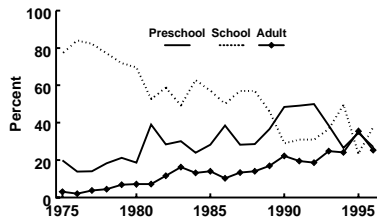
Measles - United States, 1950-1996



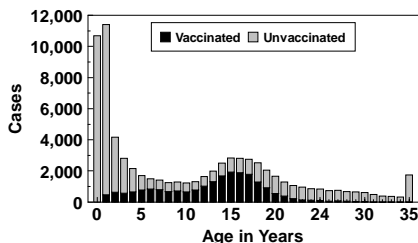
Measles - United States, 1980-1996



Measles - United States, 1975-1996
Age Distribution of Reported Cases



Measles Vaccination Status by Age



Source: 1985-1992 measles surveillance data, NIP, CDC

Secular Trends in the United States

Before 1963, approximately 500,000 cases and 500 deaths were reported annually with epidemic cycles every 2-3 years. However, the actual number of cases was estimated at 3-4 million annually. More than 50% of persons had measles by age 6 and more than 90% had measles by age 15. Highest incidence was in 5-9 year-olds, who generally accounted for more than 50% of reported cases.

Following licensure of vaccine in 1963, the incidence of measles decreased by more than 98%, and 2-3 year epidemic cycles no longer occurred. Because of this success, a 1978 Measles Elimination Program set a goal to eliminate indigenous measles by October 1, 1982 (26,871 cases were reported in 1978). The 1982 elimination goal was not met, but in 1983, only 1,497 cases were reported (0.6 cases per 100,000 population), the lowest annual total ever reported up to that time.

The incidence of measles increased annually after 1983, to 6,282 cases (2.6/100,000 population) in 1986, and decreased slightly to approximately 3,500 cases (1.5 per 100,000 population) in 1987-1988.

During 1980-1988, a median of 57% of reported cases were among school-aged persons (5-19 years of age), and a median of 29% were among children <5 years of age. A median of 8% of cases were among infants <1 year of age.

From 1985 through 1988, 42% of cases occurred in persons who were vaccinated on or after their first birthdays. During these years, 68% of cases in school-aged children (5-19 years) had been appropriately vaccinated. In contrast, only 16% of cases in children 16 months to 4 years of age were appropriately vaccinated. The occurrence of measles among previously vaccinated children led to the recommendation for a second dose in this age group.

From 1980 through 1988, a median of two measles-associated deaths per year were reported, for a median death-to-case ratio (DCR) of 0.64 deaths per 1,000 reported cases.

Measles resurgence in 1989-1991

In 1989 through 1991, a dramatic increase in cases occurred. During these 3 years a total of 55,622 cases were reported (18,193 in 1989; 27,786 in 1990; 9,643 in 1991). In addition to the increased number of cases, a change in age distribution of cases also occurred. Prior to the resurgence, school-aged children had accounted for the largest proportion of reported cases. During the resurgence, 45% of all reported cases were in children <5 years of age. In 1990, 48% of patients were in this age group, the first time that the proportion of cases in children <5 years of age exceeded the proportion of cases in 5-19-year-olds. Thirty-five percent of cases were among school-aged persons (5-19 years old).

Overall incidence rates were highest for Hispanics and blacks and lowest for non-Hispanic whites. Among children <5 years of age the incidence of measles among blacks and Hispanics was four to seven times higher than among non-Hispanic whites.

A total of 123 measles-associated deaths were reported (death-to-case ratio = 2.2 per 1,000 cases). Forty-nine percent of deaths were among children <5 years of age. Ninety percent of fatal cases had no history of vaccination. Sixty-four deaths were reported in 1990, the largest annual number of deaths from measles since 1971.

The most important cause of the measles resurgence of 1989-1991 was low vaccination coverage. Measles vaccine coverage was low in many cities, including some which experienced large outbreaks among preschool-aged children throughout the early to mid-1980s. Surveys in areas experiencing preschool-type measles outbreaks indicated that as few as 50% of children had been vaccinated against measles by their second birthdays, and that black and Hispanic children were less likely to be age-appropriately vaccinated than white children.

Measles susceptibility of infants less than one year of age may have increased. During the 1989-1991 measles resurgence, incidence rates for infants were more than twice as high as those in any other age group. The mothers of many infants who developed measles were young, and their measles immunity was most often due to vaccination rather than infection with wild virus. As a result, a smaller amount of antibody was transferred across the placenta to the fetus, compared with antibody transfer from mothers who had higher antibody titers that resulted from wild virus infection. The lower quantity of antibody resulted in immunity that waned more rapidly, making infants susceptible at a younger age today than infants were in the past.

Measles Resurgence 1989-1991 United States

• Cases	55,622
• Age group affected	Children <5 yrs
• Hospitalizations	>11,000
• Deaths	125
• Direct medical costs	>\$150 million

The increase in measles in 1989-1991 was not limited to the United States. Large outbreaks of measles were reported by many other countries of North and Central America, including Canada, El Salvador, Guatemala, Honduras, Jamaica, Mexico, and Nicaragua.

Measles in 1992-1996

Reported cases of measles declined rapidly after the 1989-1991 resurgence. This decline was due primarily to intensive efforts to vaccinate preschool-aged children. Measles vaccination levels among 2 year-old children have increased from 70% in 1990 to 91% in 1996.

A total of 2,237 measles cases were reported in 1992, of which 50% were among children <5 years of age. Since 1993, fewer than 1000 cases have been reported annually. Available data strongly suggest that measles transmission was completely interrupted in the fall of 1993. For a six week period, no indigenous measles cases were reported. All cases were imported or importation-related. Measles incidence increased to 963 cases in 1994, due primarily to several large outbreaks among persons with religious and philosophic exemption to vaccination. In 1995, a record low 281 cases were reported. The 1996 provisional total was 488 cases.

Since 1994, cases among preschool-aged children have become less common, and those among school children have increased. An increased proportion of cases have occurred among adults. In 1973, persons over 20 years of age accounted for only about 3 percent of cases. In 1994, adults accounted for 24 percent of cases, and in 1995, this age group accounted for 35 percent of all reported cases.

Measles outbreaks

Measles outbreaks are classified into two major types based on the predominant age group affected. "Preschool" and "school-aged" outbreaks are those in which children <5 and persons 5-19 years of age, respectively, account for the greatest number of cases.

Preschool-type outbreaks involve predominantly unvaccinated children <5 years of age. In contrast, outbreaks among school-aged children involve highly vaccinated populations. In some large school-aged outbreaks, over 95 percent of cases have occurred in persons with histories of vaccination on or after their first birthday (*i.e.*, because of vaccine failure).

Measles - United States, 1993-1996

Year	Cases
1993	312
1994	963
1995	281
1996	488

Measles Outbreaks

Outbreaks categorized by predominant age group affected

Preschool-aged	<ul style="list-style-type: none"> • Predominant age group <5 years • Most cases unvaccinated • Relatively large number of cases • Inner-city minority populations affected
School-aged	<ul style="list-style-type: none"> • Predominant age group 5-18 years • Most cases vaccinated • Relatively small number of cases • Junior and senior high schools

From 1985 through 1988, the majority of outbreaks occurred in highly vaccinated school-aged populations. An annual median of 47 school-aged outbreaks occurred, six of which involved >100 persons. These outbreaks accounted for a median of 51% of all reported measles cases. Outbreaks among preschool-aged children accounted for an annual median of 20% of reported cases during this time.

In 1989-1991, both the number and size of outbreaks increased, and preschool-type outbreaks became more prominent. Over 200 outbreaks were reported each year, several of which included greater than 1000 cases each. These large outbreaks all involved predominately preschool-aged children. Large preschool outbreaks occurred in several inner city areas, including Los Angeles, Houston, Milwaukee, Chicago, Dallas, New York City, and Philadelphia. In these outbreaks, the majority of cases occurred among unvaccinated black and Hispanic children. In 1989-1991, outbreaks among school-aged children continued to occur, but accounted for a relatively small proportion of cases.

Since 1993, the largest outbreaks of measles have occurred in populations that refuse vaccination, including communities in Utah and Nevada, and Christian Scientist schools in Missouri and Illinois. Small outbreaks were reported in unvaccinated preschool populations, vaccinated school populations, college students, and adult communities, but these outbreaks were much smaller than those reported during 1989-1991. No large preschool-type outbreak has been reported since 1992.

Measles Vaccine

Historical background

Measles virus was first isolated by John Enders in 1954. The first measles vaccines were licensed in 1963. In that year, both an inactivated (“killed”) and a live attenuated vaccine (Edmonston B strain) were licensed for use in the United States. The inactivated vaccine was withdrawn in 1967 because it did not protect against measles virus infection. Furthermore, recipients of inactivated measles vaccine frequently developed a unique syndrome, atypical measles, if infected with wild-type measles virus (see Atypical Measles, above). The original Edmonston B vaccine was withdrawn in 1975, because of a relatively high frequency of fever and rash in recipients. A live, further attenuated vaccine (Schwarz strain) was first introduced in 1965 but also is no longer used in the United States. Another live, further attenuated strain vaccine (Moraten strain) was licensed in 1968. These further attenuated vaccines caused fewer reactions than the original Edmonston B vaccine.

Measles Outbreaks, United States, 1985-1993

Location	Year(s)	No. Cases	Type
Los Angeles, CA	1987-92	12,226	Preschool
Chicago, IL	1989-90	3,100	Preschool
New York, NY	1990-92	3,065	Preschool
Dallas, TX	1989-90	2,300	Preschool
Houston, TX	1988-89	1,700	Preschool
Philadelphia, PA	1990-91	1,500	Preschool
New York, NY	1986-87	1,400	Preschool
Milwaukee, WI	1989-90	1,300	Preschool
San Diego, CA	1988-90	1,300	Preschool
Fresno, CA	1989-90	1,300	Preschool

Measles Vaccine

- **Composition** Live virus (Moraten strain)
- **Efficacy** 95% (Range, 90%-98%)
- **Duration of Immunity** Lifelong
- **Schedule** 2 Doses

Should be administered with mumps and rubella as MMR

Recommended Age for MMR

- MMR recommended at 12-15 months of age
- Most children susceptible to measles by 12 months of age due to waning maternal antibody
- Seroconversion to measles vaccine virus slightly lower at 12 months (93%) than at 15 months (98%)
- Routine recommendation for second dose of measles antibody makes difference in seroconversion less important

MMR Vaccine Failure

- 2%-5% do not respond to one or more components of first dose
- May not be apparent until person develops disease (usually measles)
- Caused by antibody, damaged vaccine, incorrect records, other?
- Second dose

Two-dose Recommendation

- Intended to produce measles immunity in persons who failed to respond to the first dose
- Eliminate school outbreaks
- Most persons with vaccine failure respond to a second dose
- Use MMR

The only measles virus vaccine now available in the United States is a live, more attenuated Enders-Edmonston strain (formerly called “Moraten”) which is prepared in chick embryo fibroblast cell culture.

Age of administration

The recommended age of administration of measles vaccine has changed several times. In 1963, a single dose of vaccine was recommended at 9 months of age. The recommended age of vaccination was increased to 12 months in 1965, and to 15 months in 1976. This increase in the minimum age of vaccination was recommended because of improved seroconversion in older children. Older children responded more predictably because of less interference from passive maternal antibody (i.e., maternal antibody was more likely to have waned at 15 months than at 12 months). In 1989, a second dose of measles-containing vaccine was recommended at entry to kindergarten or first grade (4-5 years), to reduce measles susceptibility among school children resulting from vaccine failure. In 1994, the age of the first dose was lowered to 12 months from 15 months.

Response to vaccination

Measles vaccine produces an inapparent or mild, noncommunicable infection. Measles antibodies develop in approximately 95% of children vaccinated at 12 months of age and 98% of children vaccinated at 15 months of age. Approximately 2%-5% of children who receive only one dose of MMR vaccine fail to respond to it (i.e. primary vaccine failure). MMR vaccine failure may occur because of passive antibody in the vaccine recipient, damaged vaccine, incorrect records, and possibly other reasons. Most children who fail to respond to the first dose will respond to the second dose. Studies indicate that more than 99% of persons who receive two doses of measles vaccine (with the first dose administered no earlier than the first birthday) develop serologic evidence of measles immunity.

Although the titer of vaccine-induced antibodies is lower than that following natural disease, both serologic and epidemiologic evidence indicate that vaccine-induced immunity appears to be long-term and probably life-long in most individuals. Most vaccinated persons who appear to lose antibody show an anamnestic immune response upon revaccination indicating that they are probably still immune. Although revaccination can increase antibody titer in some persons, available data indicate that the increased titer may not be sustained. Some studies indicate that secondary vaccine failure (waning immunity) may occur after successful vaccination, but this appears to occur very rarely and to only play a minor role in measles transmission and outbreaks.

Measles immunity

Persons generally can be considered immune to measles if they 1) were born before 1957, 2) have documentation of physician-diagnosed measles, 3) have laboratory evidence of immunity to measles, or 4) have documentation of adequate vaccination. Since most areas have implemented the two-dose schedule in only one or two school-age groups at a time, criteria for adequate vaccination currently vary depending on state and local vaccination policy. In general, adequate vaccination for preschool-aged children (12 months of age and older) is one dose of MMR. For school- and college-age children, adequate vaccination is either one or two doses of MMR, depending on the vaccination requirements of the state and/or facility.

Persons working in medical settings are at higher risk of measles than the general population. As a result, adequate vaccination for persons born during or after 1957 who work in medical facilities consists of 2 doses of MMR or other live measles-containing vaccine separated by at least one month (i.e. minimum of 28 days) with the first dose administered no earlier than the first birthday. Although birth before 1957 is generally considered acceptable evidence of measles immunity, measles has occurred in some unvaccinated persons born before 1957. Medical facilities should consider recommending a dose of MMR for unvaccinated workers born before 1957 who lack a history of measles disease or laboratory evidence of measles immunity.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental history of vaccination, by itself, is not considered adequate documentation. A health care worker should not provide an immunization record for a patient unless that health care worker has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record.

Routine Vaccination

Preschool-aged children

Measles vaccine should be administered as combined measles-mumps-rubella (MMR) vaccine. The first dose of MMR vaccine should be administered to all children who do not have a medical contraindications at 12-15 months of age (i.e. on or after a child's first birthday).

Measles Immunity

- Born before 1957
- Documentation of physician-diagnosed measles
- Laboratory evidence of immunity to measles
- Documentation of adequate vaccination

School-aged children and adolescents

A second dose of MMR is recommended to produce immunity in those who failed to respond to the first dose. The second dose of MMR vaccine should routinely be given at age 4-6 years, before a child enters kindergarten or first grade. The preadolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR (with the first dose administered no earlier than the first birthday). The 2-dose MMR vaccination strategy is a key element in the measles elimination effort.

The second dose of MMR may be administered as soon as one month (i.e. minimum of 28 days) after the first dose. Children who have already received two doses of MMR vaccine at least 1 month apart, with the first dose administered no earlier than the first birthday, do not need an additional dose when they enter school. Children without documentation of adequate vaccination against measles, rubella, and mumps or other acceptable evidence of immunity to these diseases when they enter school should be admitted after receipt of the first dose of MMR. A second dose should be administered as soon as possible, but no less than 1 month after the first dose.

Adults (age \geq 18 years)

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. With the exception of women who might become pregnant (see rubella, chapter 9) and persons who work in medical facilities, birth before 1957 generally can be considered acceptable evidence of immunity to measles, rubella, and mumps. Adults born before 1957 may receive MMR vaccine, unless otherwise contraindicated. Although not specifically recommended for most persons born before 1957, such adults, including those who may be at increased risk of acquiring severe measles, can receive two doses of MMR provided they are administered no less than 1 month (i.e. minimum of 28 days) apart.

Vaccination of Other Groups

Certain groups of adults may be at increased risk for exposure to and transmission of these diseases and should receive special consideration for vaccination. These persons include persons attending colleges and other post-high school educational institutions, persons working in medical facilities, and international travelers.

Colleges and other institutions

Post-high school educational institutions are potential high-risk areas for measles, rubella, and mumps transmission because of large concentrations of susceptible persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where they are implemented and enforced. As a result, colleges, universities, technical and vocational schools, and other institutions for post-high school education should require documentation of two doses of MMR vaccine or other acceptable evidence of measles, rubella, and mumps immunity before entry for all students.

Students who have no documentation of live measles, rubella, or mumps vaccination or other acceptable evidence of measles, rubella, and mumps immunity at the time of enrollment should be admitted to classes only after receiving the first dose of MMR. A second dose of MMR should be administered no less than 1 month (i.e. minimum of 28 days) later. Students with evidence of prior receipt of only one dose of MMR or other measles-containing vaccine on or after their first birthday should receive a second dose of MMR, provided at least one month has elapsed since their previous dose.

Medical facilities

Persons who work in medical facilities are at higher risk for acquiring measles than the general population. Between 1985 and 1991, at least 795 measles cases occurred in adult health care workers, including nurses, physicians, laboratory and radiology technicians, clerks, assistants and students. An overall decline in measles incidence occurred after the 1989-91 measles resurgence with a total of 36 cases during 1993-96 occurring among persons working in medical facilities. However, transmission in a medical facility occurred in 15 of the 75 measles outbreaks reported during 1993-1996.

All persons who work within medical facilities should have evidence of immunity to measles and rubella. Because any health care worker (i.e. medical or non-medical, paid or volunteer, full time or part time, student or non-student, with or without patient-care responsibilities) who is measles or rubella susceptible can contract and transmit these diseases, all medical facilities (i.e. inpatient and outpatient, private and public) should ensure measles and rubella immunity among those who work within their facilities (a possible exception might be a facility which treats only elderly patients considered at low risk for measles and rubella and their complications).

High-Risk Adults

- **College students**
- **Health-care personnel**
- **International travelers**

Adequate vaccination for health care workers born during or after 1957 consists of two doses of a live measles-containing vaccine and at least one dose of a live rubella-containing vaccine. Health care workers needing a second dose of measles-containing vaccine should be revaccinated at least one month (i.e. minimum of 28 days) after their first dose.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who do not have a history of prior measles disease or laboratory evidence of measles immunity, and those without laboratory evidence of rubella immunity.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity. If the return and timely vaccination of those screened cannot be assured, serologic testing before vaccination should not be done.

International travelers

Measles is endemic or epidemic in many countries throughout the world. Although proof of immunization is not required for entry into the United States, persons traveling or living abroad should have evidence of measles immunity. Adequate vaccination in persons who travel outside the United States is two doses of MMR.

Revaccination

The following groups of persons should be considered unvaccinated and should receive at least one dose of measles vaccine. Those (1) vaccinated before the first birthday, (2) vaccinated with killed measles vaccine (KMV), (3) vaccinated with KMV followed by live vaccine less than 4 months after the last dose of KMV, (4) vaccinated prior to 1968 with an unknown type of vaccine (the vaccine may have been KMV), (5) or vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type (revaccination not necessary if IG was given with Edmonston B vaccine).

Measles Vaccine Indications for Revaccination

- Vaccinated before the first birthday
- Vaccinated with killed measles vaccine (KMV)
- Vaccinated with KMV followed by live vaccine within 3 months
- Vaccinated prior to 1968 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

Post-exposure prophylaxis

Live measles vaccine provides permanent protection and may prevent disease if given within 72 hours of exposure.

Immune globulin (IG) may prevent or modify disease and provide temporary protection if given within 6 days of exposure. The dose is 0.25 ml/kg body weight, maximum 15 ml intramuscularly. The recommended dose of IG for immunocompromised persons is only 0.5ml/kg of body weight (maximum 15ml) intramuscularly. IG may be especially indicated for susceptible household contacts of measles patients, particularly contacts <1 year of age (for whom the risk of complications is highest). Live measles vaccine should be given about 5 months later when the passive measles antibodies should have disappeared, if the child is then 12 months of age or older. IG should not be used to control measles outbreaks.

Adverse Events Following Vaccination

Adverse events following measles vaccine (except allergic reactions) represent replication of measles vaccine virus with subsequent mild illness. These events occur 5-12 days postvaccination. Adverse events only occur in persons who are susceptible to infection. There is no evidence of increased risk of adverse events following MMR vaccination in persons who are already immune to the diseases.

Fever is the most common adverse event following MMR vaccination. Although measles, rubella, and mumps vaccines may cause fever after vaccination, the measles component of MMR vaccine is most often associated with this adverse event. After MMR vaccination, 5%-15% of vaccinated children may develop a temperature of $\geq 103^{\circ}\text{F}$ ($\geq 39.4^{\circ}\text{C}$) usually occurring 7-12 days after vaccination and generally lasting 1-2 days. Most persons with fever are otherwise asymptomatic.

Measles- and rubella-containing vaccines, including MMR, may cause a transient **rash**. Rashes, usually appearing 7-10 days after MMR or measles vaccination, have been reported in approximately 5% of vaccinees.

MMR vaccine may rarely cause **thrombocytopenia** within the 2 months after vaccination. Estimates of the frequency of clinically apparent thrombocytopenia from Europe are 1 case per 30,000 to 40,000 vaccinated children, with a temporal clustering of cases occurring 2 to 3 weeks after vaccination. The clinical course of these cases was usually transient and benign, although hemorrhage occurred rarely. The risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination. Based

MMR Adverse Events

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25% (susc. women)
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

on case reports, the risk for MMR-associated thrombocytopenia may be higher for persons who have previously had immune thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine.

Transient **lymphadenopathy** sometimes occurs following receipt of MMR or other rubella-containing vaccine and **parotitis** has been reported rarely following receipt of MMR or other mumps-containing vaccine.

Arthralgias and other **joint symptoms** are reported in up to 25% of susceptible adult women given MMR vaccine. This adverse event is associated with the rubella component (see rubella chapter for more details).

Allergic reactions following the administration of MMR or any of its component vaccines are rare. Most of these reactions are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR or its component vaccines are extremely rare. Allergic reactions including rash, pruritus, and purpura have been temporally associated with mumps vaccination but are uncommon and usually mild and of brief duration.

Contraindications to Vaccination

Persons with **severe allergy** (i.e. hives, swelling of the mouth or throat, difficulty breathing, hypotension, and shock) to gelatin or neomycin, or who have had a severe allergic reaction to a prior dose of MMR, should generally not be vaccinated with MMR except with extreme caution.

In the past, persons with a history of anaphylactic reactions following egg ingestion were considered to be at increased risk of serious reactions after receipt of measles- or mumps-containing vaccines, which are produced in chick embryo fibroblasts. However, recent data suggest that most anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens, but to other components of the vaccines (such as gelatin). The risk for serious allergic reactions such as anaphylaxis following receipt of these vaccines by egg-allergic persons is extremely low and skin-testing with vaccine is not predictive of allergic reaction to vaccination. Therefore, MMR may be administered to egg-allergic children without prior routine skin testing or the use of special protocols.

MMR vaccine does not contain penicillin. A history of penicillin allergy is not a contraindication to MMR vaccination.

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to prior dose or vaccine component
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

Measles and Mumps Vaccines and Egg Allergy

- Measles and mumps viruses grown in chick embryo fibroblast culture
- Studies have demonstrated safety of MMR in egg allergic children
- Vaccinate without testing

Because of the possible, although extremely low, risk of serious anaphylaxis following receipt of MMR vaccine, it is prudent that all persons be kept under observation for at least 15 minutes after vaccination.

Women known to be pregnant should not receive measles vaccine. Pregnancy should be avoided for 1 month following receipt of measles vaccine and 3 months if given as combined MMR vaccine. Close contact with pregnant women is **NOT** a contraindication to MMR vaccination of the contact. Breastfeeding is **NOT** a contraindication to vaccination of either the woman or the breastfeeding child.

Persons with **moderate to severe illness** should not be vaccinated until the illness has resolved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse event, such as fever. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illness are not contraindications to measles vaccination. One recent study suggested that seroconversion to measles vaccine was reduced in children with upper respiratory infections. However, multiple previous and subsequent studies have not confirmed this finding.

Replication of vaccine viruses can be enhanced in immunodeficient persons. Severe immunosuppression can be due to a variety of conditions, including congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids. Evidence based on case reports has linked measles vaccine virus infection to subsequent death in six severely immunocompromised persons. For this reason, patients who are severely immunocompromised for any reason should not be given MMR vaccine. Healthy susceptible close contacts of severely immunocompromised persons should be vaccinated.

In general, persons receiving large daily doses of corticosteroids (≥ 2 mg/kg per day or ≥ 20 mg per day of prednisone) for 14 days or more should not receive MMR vaccine because of concern about vaccine safety. MMR and its component vaccines should be avoided for at least one month after cessation of high dose therapy.

Persons receiving low dose or short course (<14 days) therapy, long-term alternate-day treatment, maintenance physiologic doses, or topical, aerosol, intra-articular, bursal, or tendon injections may be vaccinated. Although persons receiving high doses of systemic corticosteroids daily or on alternate days during an interval of less than 14 days generally can receive MMR or its component vaccines immediately after cessation of treatment, some experts prefer waiting until two weeks after completion of therapy.

Patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive MMR or its component vaccines.

HIV-infected persons

Measles disease may be severe in HIV-infected persons. Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse events in HIV-infected persons without evidence of severe immunosuppression, although antibody responses have been variable. MMR vaccine is recommended for all asymptomatic HIV-infected persons, and should be considered for symptomatic persons who are not severely immunosuppressed. Asymptomatic children do not need to be evaluated and tested for HIV infection before MMR and other measles-containing vaccines are administered. A theoretical risk of an increase (probably transient) in HIV viral load following MMR vaccination exists because such an effect has been observed with other vaccines. The clinical significance of such an increase is not known.

MMR and other measles-containing vaccines are **not recommended for HIV-infected persons with evidence of severe immunosuppression** (see table), primarily because of the report of a case of measles pneumonitis in a measles vaccinee who had an advanced case of AIDS.

Age-specific CD4+ T-lymphocyte count and percent of total lymphocytes as criteria for severe immunosuppression in HIV-infected persons.

Criteria	age <12 months	age 1-5 years	age 6-12 years	age ≥13 years
Total CD4+ T-lymphocytes	<750 per μ L	<500 per μ L	<200 per μ L	<200 per μ L
<i>OR</i>	<i>OR</i>	<i>OR</i>	<i>OR</i>	<i>OR</i>
CD4+ T-lymphocytes (as % of total lymphocytes)	<15 %	<15 %	<15 %	<14 %

Receipt of antibody-containing blood products (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to measles vaccine. The length of time that such passively acquired antibody persists depends on the concentration and quantity of blood product received. For instance, vaccination is recommended to be delayed for 3 months following receipt of immune globulin for prophylaxis of hepatitis A, but a 7-11 month delay is recommended following administration of intravenous immune globulin, depending on the dose – see Table 8 in the ACIP's 1994 *General Recommendations on Immunization* (included in Appendix A).

MMR Vaccine and HIV Infection

- MMR recommended for persons with asymptomatic HIV infection
- NOT recommended for those with evidence of severe immunosuppression
- Prevacination HIV testing not recommended

Children who have a history of thrombocytopenic purpura or **thrombocytopenia** may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination. No deaths have been reported as a direct consequence of vaccine induced thrombocytopenia. The decision to vaccinate with MMR depends on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella. The benefits of immunization are usually greater than the potential risks, and administration of MMR vaccine is justified, because of the even greater risk for thrombocytopenia after measles or rubella disease. However, deferring a subsequent dose of MMR vaccine may be prudent if the previous episode of thrombocytopenia occurred in close temporal proximity to (i.e. within 6 weeks after) the previous dose of the vaccine. Serologic evidence of measles immunity in such persons may be sought in lieu of MMR vaccination.

Tuberculin testing (PPD)

Tuberculin testing (PPD) is not a prerequisite for vaccination with MMR or other measles-containing vaccine. PPD testing has no effect on the response to MMR vaccination. However, measles vaccine (and possibly mumps, rubella, and varicella vaccines) may suppress the response to PPD in a person infected with *Mycobacterium tuberculosis*. To minimize the risk of a false-negative interpretation, PPD testing should be delayed for 4-6 weeks after MMR vaccination. If PPD testing is needed, it should be done prior to MMR vaccination. It is also acceptable to apply the PPD and administer MMR simultaneously, since the mild immunosuppressive effect of the vaccine will not occur for several days after vaccination.

PPD and Measles Vaccine

- Apply PPD first - give MMR when skin test read
- Apply PPD at same time as MMR
- Delay PPD 4-6 weeks if MMR given first

Summary - Measles

- <1,000 cases per year
- Outbreaks due to low vaccination levels
- Outbreaks due to vaccine failure
- 2 dose recommendation

