

Measles Virus: Disease & Prevention

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Measles Virus

- **Paramyxovirus**, genus *Morbillivirus*.
- 120–250 nm in diameter, **single-stranded RNA core**
- Closely related to the rinderpest and canine distemper viruses
- Two important membrane envelope proteins:
 - **F (fusion) protein**: fusion of virus and host cell membranes, viral penetration, and hemolysis
 - **H (hemagglutinin) protein**: adsorption of virus to cells
- **Only one antigenic type** of measles virus

Pathogenesis & Transmission

- **Invasion and replication in the respiratory epithelium** and regional lymph nodes
- **2-3 days later**, a primary viremia → infection & replication in the reticuloendothelial system.
- **5–7 days after initial infection**: secondary viremia
 - May cause infection of the respiratory tract and other organs.
- **Virus shedding** from the nasopharynx beginning with the **prodrome until 3–4 days after rash onset**
- **No** known animal reservoir, or asymptomatic carrier state

Pathogenesis & Transmission:

- **Transmission primarily person to person** via large respiratory droplets.
 - **Airborne transmission via aerosolized droplet nuclei** documented in closed areas up to 2 hours after a person with measles occupied the area
 - **Contagious from 4 days pre- → 4 days post-rash onset**
 - **Highly communicable, $\geq 90\%$ secondary attack rate** among susceptibles
- **Seasonality:**
 - late winter and spring in temperate climates
 - After the rainy season in tropical climates

Clinical Features

- **Incubation period** from exposure to prodrome, averages **10–12 days**
 - From exposure to rash onset averages 14 days (range, 7–21 days).
- **Prodrome lasts 2–4 days** (range 1–7 days)
 - Increasing **fever, as high as 103°F –105°F, followed by cough, coryza, conjunctivitis.**
 - **Koplik spots/ buccal mucosa** (1–2 days pre-rash to 1–2 days post-rash onset)
- **Maculopapular rash lasting 5–6 days:**
 - **Hairline → face and upper neck → downward and outward** to the hands and feet
 - **lesions are generally discrete, can become confluent**, particularly on the upper body
 - Initially, lesions blanch with fingertip pressure for 3–4 days
 - **Fine desquamation** occurs over more severely involved areas
 - **Rash fades in the same order that it appears**, from head to extremities
- Anorexia, diarrhea, generalized lymphadenopathy

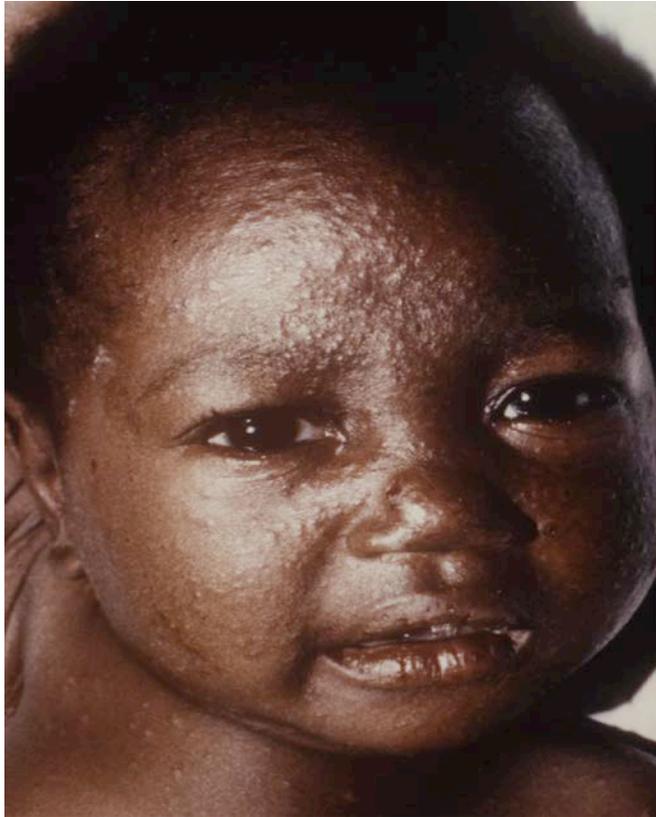
Rash & Conjunctivitis



Confluence of Rash



Rash in a dark-skinned child
3-month-old boy, day 2 of rash



Desquamation,
Recovery Stage



CDC Public Health Image Library #4358, 1969 and # 6887, late '60s

Koplick's Spots



Complications:

- 30% of cases have ≥ 1 complications
- Most common in children < 5 years & adults ≥ 20 years of age
 - Diarrhea (8%), Otitis media (7%, almost exclusively in children)
 - Pneumonia (6%): viral or superimposed bacterial
 - Acute encephalitis (0.1%)
 - Onset about 6 days after rash onset (1–15 days) : fever, headache, vomiting, stiff neck, meningeal irritation, drowsiness, convulsions, and coma.
 - Cerebrospinal pleocytosis and elevated protein
 - Case-fatality rate approximately 15%
 - Residual neurologic damage in up to 25%
- Death (0.2%, United States, 1985-1992):
 - Highest risk in young children and adults
 - Pneumonia accounts for about 60% of overall deaths
 - Most common cause of death in children is pneumonia and in adults, acute encephalitis

Other Significant Complications:

- **Subacute sclerosing panencephalitis (SSPE):**
 - **Rare degenerative central nervous system disease:** 5-10/ million measles cases, extremely rare since the early '80s.
 - Persistent measles virus infection of the brain?
 - **Onset** occurs an average of **7 years after measles** (range 1 month–27 years),
 - **Insidious onset** with progressive deterioration of behavior and intellect, followed by ataxia, myoclonic seizures, and **eventually death**
- **Measles during pregnancy:**
 - Higher risk of **premature labor, spontaneous abortion, low-birthweight infants**
 - Birth defects have been rare

Other Significant Complications:

- **“Atypical measles”:**
 - 600,000 to 900,000 persons received inactivated vaccine in the US (1963-67)
 - Subsequent infection with measles virus leads to **hypersensitivity polyserositis**
 - **Fever, pneumonia, pleural effusions, and edema**
 - Rash is usually maculopapular or petechial, but may have urticarial, purpuric, or vesicular components
 - **Appears first on the wrists or ankles**
 - May be prevented by revaccinating with live measles vaccine
- **Modified measles** primarily in immune globulin (IG) recipients as post-exposure prophylaxis and in young infants who have some residual maternal antibody.
 - Prolonged incubation period, mild prodrome, and sparse, discrete rash of short duration.

Other Significant Complications:

- Hemorrhagic measles:
 - rarely reported in the United States
 - high fever (105°F–106°F), seizures, delirium, respiratory distress, and hemorrhage into the skin and mucous membranes.
- **Measles in immunocompromised persons:**
 - severe with a prolonged course.
 - almost exclusively in persons with **T-cell deficiencies** (certain leukemias, lymphomas, AIDS)
 - may occur without typical rash
 - viral shedding for several weeks after the acute illness.
- **Measles in developing countries:**
 - high attack rates among children younger than 12 months of age.
 - more severe in **malnourished children**, particularly those with **vitamin A deficiency**
 - complications: diarrhea, dehydration, stomatitis, inability to feed, and bacterial infections (skin and elsewhere)
 - case-fatality rate up to 25%
 - a leading cause of blindness in African children

Pre-vaccine era United States

- Measles became a nationally notifiable disease in 1912
 - In the first decade of reporting, an average of 6,000 measles-related deaths were reported each year.
- In the decade before 1963 when vaccine became available
 - nearly all children got measles by 15 years of age
 - 3 to 4 million people infected each year
 - annual estimates of 400- 500 deaths, 48,000 hospitalizations, and 1,000 encephalitis cases

Measles Vaccine Timeline

- **1954** - John Enders isolates Measles virus
- **1963** – Live attenuated and inactivated vaccines; recommended at 9 months of age
- **1965** – Live further attenuated vaccine recommended at 12 months of age
- **1967** – Killed vaccine withdrawn; age of vaccination changed to 15 months
- **1968** – Live further attenuated vaccine (Edmonston-Enders strain)
- **1971** – Combined measles-mumps-rubella vaccine
- **1989** – Two-dose schedule recommended:
 - ACIP & AAFP: 15 months & 4-6 years
 - AAP: 15 months & just before middle school entry
- **1994** – **Harmonized schedule:** 12-15 months & 4-6 years
- **2000** – Measles declared absent from the United States
- **2005** – Combined measles-mumps-rubella-varicella vaccine

Measles Vaccine

- **Efficacy**
 - 95% when given at 12 months of age
 - 98% when given at 15 months of age
- **Duration of Immunity**
 - lifelong
- **2%-5% first dose** recipients do not respond
 - Pre-existing antibody, damaged vaccine, incorrect records
 - Most with primary vaccine failure respond to 2nd dose
- **Second dose** failure is rare

Vaccination schedules

- **MMR Vaccine:**
 - First dose at 12-15 months
 - Doses given at <12 months should not be counted as valid, revaccinate at ≥ 12 months
 - Second dose at 4-6 years, or any time ≥ 4 weeks after the first dose
- **MMR and MMRV Vaccine:**
 - **First dose:** either MMR + varicella vaccines or MMRV vaccine
 - Unless the parent/caregiver expresses preference for MMRV, CDC recommends MMR and varicella vaccines for the first dose
 - **Second dose:** MMRV preferred over separate MMR and varicella vaccines

Vaccination of adults:

- 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 ≥ 1 dose of MMR-containing vaccine or other acceptable evidence of immunity to these three diseases
- With the exception of women who might become pregnant, and health care workers:
 - birth before 1957 considered acceptable evidence of immunity to measles, mumps, and rubella.
- Adults at increased risk of being exposed to measles
 - College students, Persons working in medical facilities, International travelers

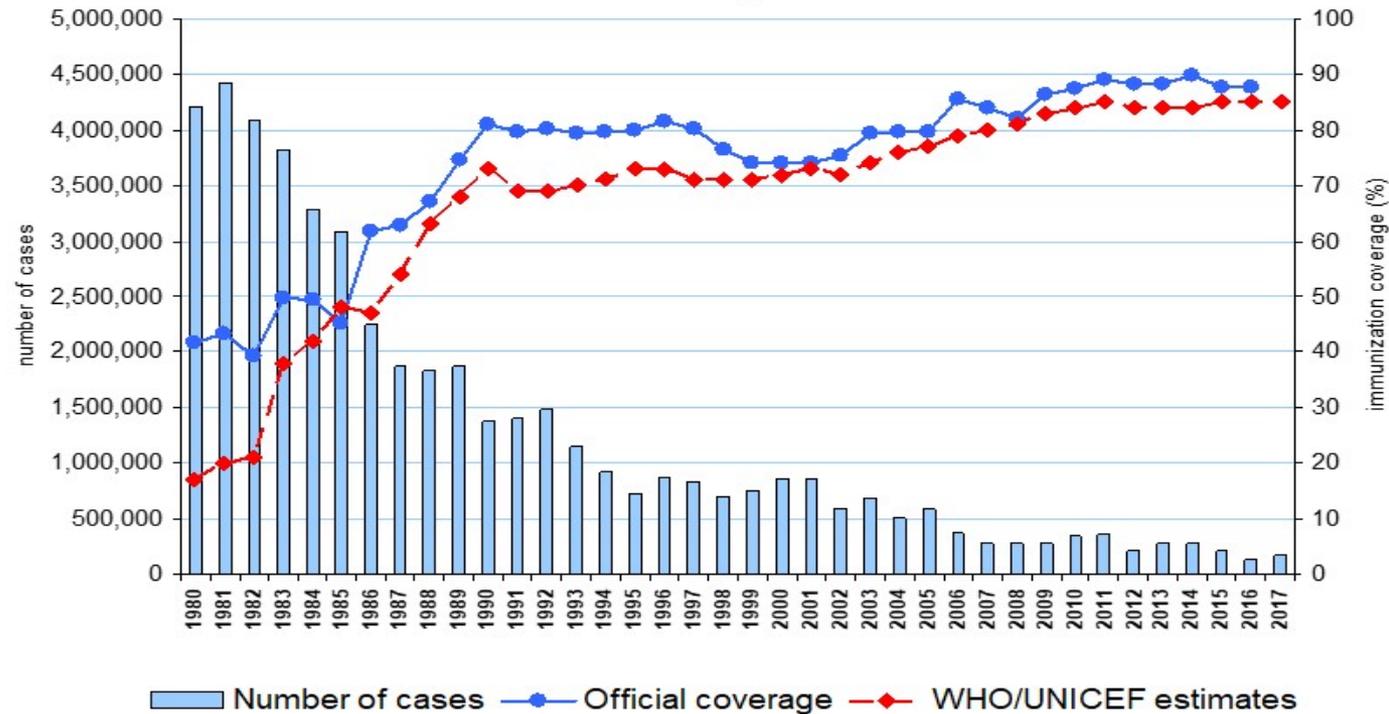
Post-exposure prophylaxis with vaccine

- Vaccine provides permanent protection and may prevent disease if given within 72 hours of exposure
- IG may prevent or modify disease and provide temporary protection if given within 6 days of exposure.
 - especially for susceptible household contacts of measles patients, particularly contacts ≤ 1 year of age
 - If the child is 12 months of age or older, live measles vaccine should be given about 5 months later
 - IG should not be used to control measles outbreaks
 - 0.5 mL/kg, maximum 15 mL IM or IGIV, 400mg/kg.

Indications for Revaccination

- Vaccination before the first birthday
- Vaccinated with killed measles vaccine
- Vaccinated from 1963 through 1967 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

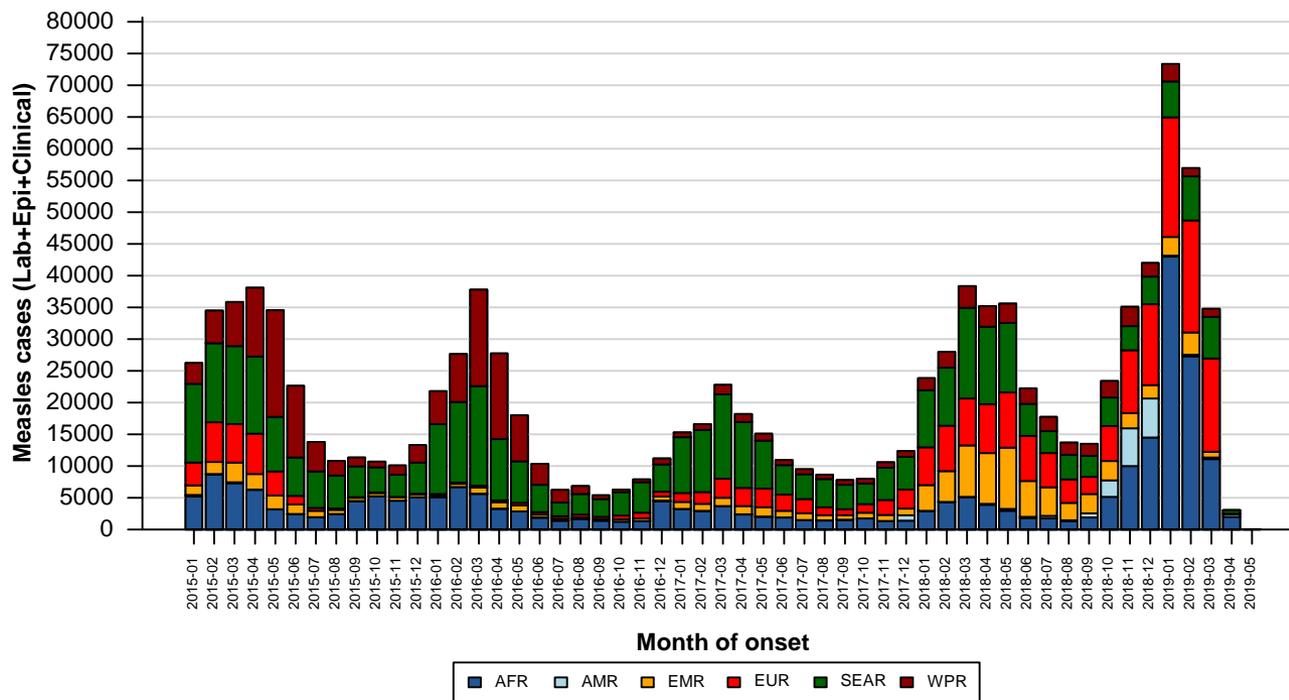
Measles global annual reported cases and MCV1 coverage, 1980-2017



Source: WHO/IVB database, 2018
 194 WHO Member States.
 Data as of September 2018



Measles cases by month and WHO Region (2015-19)

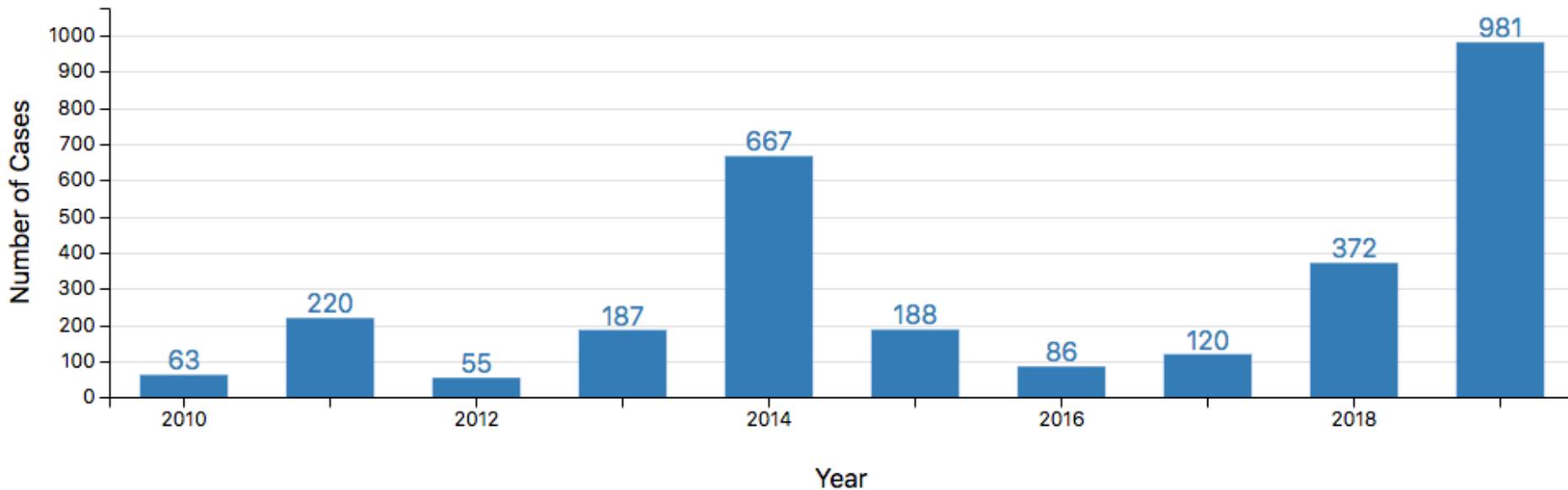


Notes: Based on data received 2019-05 - Data Source: IVB Database - This is surveillance data, hence for the last month(s), the data may be incomplete.

United States (2010-2019)

Number of Measles Cases Reported by Year

2010-2019**(as of May 31, 2019)



2018 - 2019 Measles Outbreak in Rockland County:

As of June 6, 2019, there are **259** confirmed reported cases of measles in Rockland County.

Vaccination rates for confirmed measles cases in Rockland County as of June 6, 2019:

- 77.6% have had 0 MMRs
- 4.6% have had 1 MMR
- 3.5% have had 2 MMRs
- 14.3 unknown status

Age groups for the confirmed measles cases in Rockland County as of June 6, 2019:

- Less than 1 year old: 12.0%
- 1-3 years: 25.5%
- 4-6 years: 13.5%
- 7-18 years: 29.0%
- 19+ years: 20.1%

MMR Contraindication and Precautions

- History of anaphylactic reactions to neomycin
- History of severe allergic reaction to any component of the vaccine
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product
- Personal or family (sibling or parent) history of seizures of any etiology (MMRV only)

MMR Adverse Events

- Arthralgias (susceptible women)
 - 25%
- Rash, pruritis, purpura
 - not common
- MMR Vaccine and Autism
 - no convincing evidence that any vaccine causes autism or autism spectrum disorder
 - There is much evidence that vaccines do not cause either

MMR Adverse Reactions

- Fever: 5-15%
 - MMR: $\geq 103^{\circ}\text{F}$, 7 -12 days post-vaccination, lasting 1-2 days
 - MMRV: 21.5%, in children 12–23 months of age
 - one additional febrile seizure per 2,300–2,600 children who received the first dose of MMRV vaccine, vs. MMR and varicella vaccine as separate injections
- Rash, 7 to 10 days post-vaccination: 5%,
- Thrombocytopenia ≤ 2 months after vaccination: 1/30,000-40,000 doses
- Lymphadenopathy: rare
- Allergic reactions: rare

Vaccine Injury Compensation Program, Table Injuries

<https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf>

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
III. Vaccines containing measles, mumps, and rubella virus or any of its components (e.g., MMR, MM, MMRV)	A. Anaphylaxis B. Encephalopathy or encephalitis	≤4 hours. 5-15 days (not less than 5 days and not more than 15 days).
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
IV. Vaccines containing rubella virus (e.g., MMR, MMRV)	A. Chronic arthritis	7-42 days (not less than 7 days and not more than 42 days).
V. Vaccines containing measles virus (e.g., MMR, MM, MMRV)	A. Thrombocytopenic purpura	7-30 days (not less than 7 days and not more than 30 days).
	B. Vaccine-Strain Measles Viral Disease in an immunodeficient recipient	
	—Vaccine-strain virus identified	Not applicable.
	—If strain determination is not done or if laboratory testing is inconclusive	≤12 months.

Questions?

Lab diagnosis

- 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 person with a 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 samples taken for serologic testing. Because the virus is more likely to be isolated when specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until serologic confirmation is obtained. Clinical specimens should be obtained within 7 days, and not more than 10 days, after rash onset. A detailed protocol for collection of specimens for viral isolation is available on the [CDC website](#).
- Serologic testing, most commonly by enzyme-linked immunoassay (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 an 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 be either IgG negative or IgG positive, depending upon their previous infection or vaccination history.
- EIA for IgM antibody requires only a single serum specimen and is 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 that are negative in the first 72 hours after rash onset should be repeated. IgM is detectable for at least 30 days after rash onset and frequently longer.
- A variety of tests for IgG antibodies to measles are available and include EIA, hemagglutination inhibition (HI), indirect fluorescent antibody tests, microneutralization, and plaque reduction neutralization. Complement fixation, while widely used in the past, is no longer recommended.
- IgG testing for acute measles requires demonstration of a four-fold rise in 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 depend on the test.