

**AMY PORTER, MD, PhD**

Fellow, Rainbow Center for Comprehensive Care, Rainbow Babies and Children's Hospital, University Hospitals Cleveland Medical Center, Cleveland, OH

**JOHANNA GOLDFARB, MD**

Professor Emerita, Education Institute, Cleveland Clinic; Course Director, Microbiology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Measles: A dangerous vaccine-preventable disease returns

**ABSTRACT**

Although a safe and effective vaccine has been available for over 6 decades, vaccine hesitancy in the United States and social and political unrest globally have led to under-vaccination. As a result, in recent months, vaccine control of measles has been threatened with an alarming upswing in measles cases nationally and internationally. Here, we review the disease and its management in view of recent outbreaks.

**KEY POINTS**

Measles is highly contagious and can have serious complications, including death.

Measles vaccine is given in a 2-dose series. People who have received only 1 dose should receive either 1 or 2 more doses, depending on the situation, so that they are protected.

The diagnosis of measles is straightforward when classic signs and symptoms are present—fever, cough, conjunctivitis, runny nose, and rash—especially after a known exposure or in the setting of outbreak. On the other hand, in partially vaccinated or immunosuppressed people, the illness presents atypically, and confirmation of diagnosis requires laboratory testing.

Management is mostly supportive. Children—and probably also adults—should receive vitamin A.

Since disease can be severe in the unvaccinated, immune globulin and vaccine are given to the normal host with an exposure and no history of vaccine or immunity.

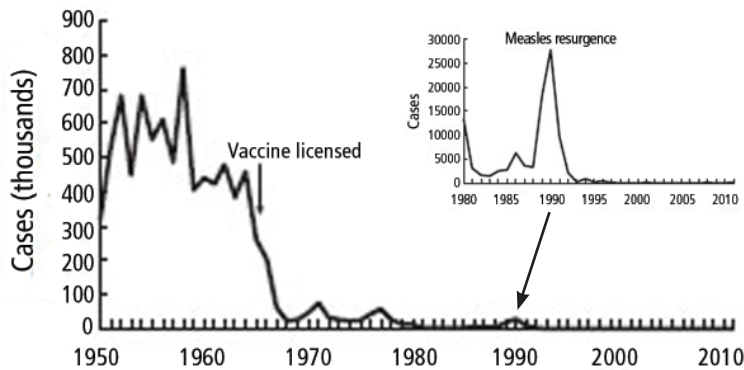
doi:10.3949/ccjm.86a.19065

**M**EASLES, AN ANCIENT, highly contagious disease with a history of successful control by vaccination, is now threatening to have an epidemic resurgence. Until recently, measles vaccination largely controlled outbreaks in the United States. The Global Vaccine Action Plan under the World Health Organization aimed to eliminate measles worldwide. Nonetheless, the vaccine refusal movement and slow rollout of vaccine programs globally have interfered with control of the virus. A record number of measles cases have emerged in recent months: more than 700 since January 2019.<sup>1</sup> Approximately 70% of recent cases were in unvaccinated patients, and almost all were in US residents.

This update reviews the history, presentation and diagnosis, complications, management, contagion control, and emerging threat of a measles epidemic. It concludes with recommendations for clinical practice in the context of the current measles outbreaks.

## ■ FROM UBIQUITOUS TO ERADICATED—AND BACK

Before the measles vaccine was developed and became available in the 1960s, outbreaks of measles occurred predictably every year in the United States and other temperate regions. During yearly outbreaks, measles was so contagious that household contacts had attack rates above 95%. Most cases occurred in very young children, and because infection with the virus causes lifelong immunity, it could be safely assumed that by adulthood, everyone was immune. In an outbreak in the Faroe Islands in 1846, no one who had been



**Figure 1.** Effect of measles vaccine on incidence of measles in the United States.

From the US Centers for Disease Control and Prevention.

alive in the last major outbreak 65 years earlier became ill, but everyone under age 65 was at high risk with “high attack rates,” estimated as 99% from other outbreaks (reviewed by Krugman et al<sup>2</sup>).

In isolated regions previously free of measles, adults did not have immunity, and when exposed, they often developed severe disease. When European settlers brought measles and smallpox to the Americas beginning in the late 15th century, these diseases decimated whole populations of native peoples who had never been exposed to them.

The wide accessibility and promotion of the measles vaccine over the last 6 decades has dramatically decreased the incidence of measles in the United States (Figure 1). The disease was declared eliminated in 2000.

That was premature. A number of outbreaks have occurred since then; the largest in the United States (before 2019) was in 2000. Over half of the 667 cases reported during that outbreak were in an underimmunized Amish community in Ohio.<sup>3</sup>

Now it emerges again.

## PRESENTATION CAN VARY

Measles is an acute viral illness. In endemic areas or during outbreaks, measles should be suspected in a patient who has the classic triad of the 3 “Cs”: **cough, conjunctivitis, and coryza** (runny nose).

**Koplik spots**, the prodromal rash on mucous membranes such as inside the mouth, are bluish-white against a red background (Figure 2). They confirm the diagnosis for the experi-

enced clinician before the onset of the characteristic **morbilliform rash** (Figure 3). The rash appears several days after the fever begins and corresponds with the immune response to the infection; it typically spreads from the head down. Extreme malaise is characteristic; in fact, children infected with measles are described as “feeling measly.”

The presentation varies somewhat among certain groups.

**Nonimmune pregnant women** have an especially severe course, likely related to the relative immune suppression of pregnancy.

**In immune-suppressed states**, measles is not only more severe, it is also difficult to diagnose because the rash can be absent.

**In partially vaccinated children and adults**, the disease may present atypically, without cough, conjunctivitis, and coryza, and it may be milder, lacking some of the extreme malaise typical of measles and with a shortened course. Measles infection in people who received the inactivated measles vaccine that was briefly available from 1963 to 1967 is also associated with atypical measles syndrome, a severe hypersensitivity reaction to the measles virus. Atypical measles can be prevented by revaccination with a live-virus vaccine.

## DIAGNOSIS MAY NEED TO BE CONFIRMED

The diagnosis of measles is straightforward when all of the signs and symptoms are present. In partially vaccinated populations, however, the diagnosis may need to be confirmed by serologic or polymerase chain reaction (PCR) testing.

## Differential diagnosis

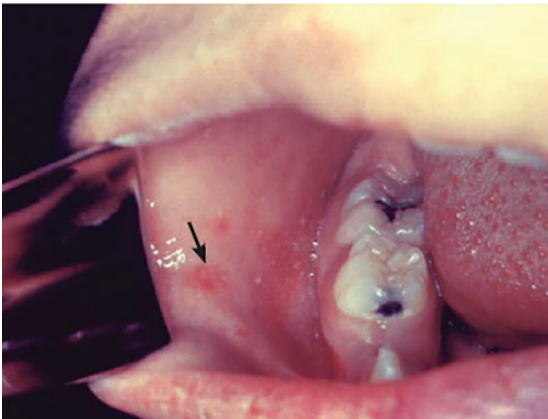
The differential diagnosis of the fever and a rash typical of measles in children, especially when accompanied by severe malaise, includes the following:

**Kawasaki disease.** However, the red eyes of Kawasaki are an injection of the bulbar conjunctivae with sparing of the limbus. No eye exudate is present, and respiratory illness is not part of the disease.

**Drug eruptions** can present with a morbilliform rash and sometimes fever, but not the other signs of measles in either adults or children.

**Scarlet fever** has a different rash, the sand-

**In outbreaks, suspect measles in a patient with the 3 Cs: cough, conjunctivitis, coryza**



**Figure 2.** Koplik spots arise during the viral prodrome and are critical for the clinical diagnosis of measles before the onset of rash.

From the US Centers for Disease Control and Prevention.

paper rash typical of toxin-mediated disease.

**Rubella** tends to cause mild respiratory symptoms and illness rather than the severe disease of measles and other rash-causing viral infections in children and infants.

### Confirmation in confusing cases

To confirm a diagnosis of measles, samples from throat, nasal, and posterior nasopharyngeal swabs should be collected with a blood specimen for serology and sent to the state public health laboratory.<sup>4</sup> The US Centers for Disease Control and Prevention gives instructions on who should be tested and with which tests.<sup>4</sup>

Most testing now uses PCR for viral RNA, as viral culture is more costly and takes longer. For accurate diagnosis, samples for PCR must be obtained during the acute illness.

The serologic gold standard for diagnosis is a 4-fold rise or fall in immunoglobulin G (IgG) titer of paired serum samples sent 10 days to 2 weeks apart around the illness. The IgM test may be negative initially, and a negative test cannot be used to rule out the diagnosis. Confirmed cases should be reported to public health authorities.

### ■ COMPLICATIONS: EARLY AND LATE

Frequent complications of measles infection include those related to the primary viral infection of respiratory tract mucosal surfaces, as well as bacterial superinfections. Complications are most likely in children under age 5, nonimmune adults, pregnant women, and



**Figure 3.** Morbilliform rash of measles.

From the US Centers for Disease Control and Prevention.

immunocompromised people. Typical complications include otitis media, laryngotracheobronchitis (presenting as a croupy cough), pneumonia, and diarrhea.

Late sequelae of measles infection are related in part to serious mucosal damage and generalized immune suppression caused by the virus. Even after recovery from acute infection, children can have persistent diarrhea and failure to thrive, with increased mortality risk in the months after infection. Tuberculosis can reactivate in patients already infected, and new tuberculosis infection can be especially severe. Further, tuberculosis skin tests become less reliable immediately after measles infection. Severe disease and fatalities are increased in populations that have baseline vitamin A deficiency and malnutrition.

Death from measles is most often caused by viral pneumonia, secondary bacterial pneumonia, and postviral encephalitis. Before the vaccine era, measles encephalitis occurred in the United States in about 1 in 1,000 measles cases.

Subacute sclerosing panencephalitis is a rare, late, and often fatal complication of measles that presents 7 to 10 years after acute measles infection, usually in adolescence. Beginning with myoclonic jerks, stiffening, and slow mental deterioration, it progresses over 1 to

**The CDC has instructions on who should be tested, and with what test**



TABLE 1

### Vitamin A for acute measles infection: World Health Organization recommendations

Vitamin A once daily for 2 days, at the following doses:

Children 12 months of age or older: 200,000 IU

Infants 6–11 months of age: 100,000 IU

Infants < 6 months: 50,000 IU

Another dose is recommended 4–6 weeks after the onset of the acute infection if vitamin A deficiency is likely to be present.

Information from reference 5.

3 years, with a relentless degenerative course leading to death. Since the introduction of the measles vaccine in 1957, this disease has essentially disappeared in the United States.

#### SUPPORTIVE CARE, INFECTION CONTROL

Management of measles and its complications is primarily supportive.

**Vitamin A** should be given to all children with acute disease to decrease the risk of complications, including blindness and death (Table 1). Most likely, adults with acute infection should also get vitamin A, though there are no data to support or refute the recommendation in this population.<sup>5</sup>

#### Preventing contagion

Measles infection has an incubation period of 8 to 12 days. Individuals are contagious 4 days before to 4 days after rash onset in the normal host but longer in those lacking immune function. Cases can occur up to 21 days after exposure during the contagious period.

The disease is highly contagious, so hospitalized patients should be cared for with airborne precautions. It is crucial that caretakers be vaccinated properly, so that they can care for patients safely. Recommendations for preventing secondary cases by prompt vaccination and giving immune globulin are detailed below, including specific recommendations for individuals with immune system suppression.

The current US public health policy regarding measles vaccine booster doses began in response to the widespread measles outbreak in the United States from 1989 to 1991. Cases occurred more commonly in unvac-

inated individuals and in young adults who had received only 1 dose of vaccine.

Today, the policy in areas where measles has been controlled is to vaccinate between 12 and 15 months of age and to boost with a second dose before starting kindergarten. In outbreak situations, the first dose should be given at 6 months of age, with a repeat dose at 12 to 15 months of age and the usual booster before starting kindergarten.

Most adults born in the United States between 1957 and 1989 received only 1 dose of measles vaccine, and a single dose confers immunity for most but not all. Accordingly, if such an individual is traveling or living in an endemic area (eg, India, Brazil, Brooklyn, NY), then a booster is recommended without checking a titer (Table 2).

Anyone born after 1989, if vaccinated appropriately, has received 2 doses of measles vaccine; thus, there is no need for booster doses or titers. In fact, titers are not recommended in most people because of the high rate of false-negative results and because there is no harm in receiving an extra dose of the measles-mumps-rubella (MMR) vaccine (it can actually boost immunity).<sup>6</sup> Healthcare institutions check titers in employees for patient safety.

Those born before 1957 can be presumed to have had natural measles, which confers lifelong immunity (Table 3).<sup>7</sup>

#### CURRENT THREAT

In 2000, measles was considered controlled in the United States, thanks to the national vaccination policy. But despite overall control, small numbers of cases continued to occur each year, related to exposure to cases imported from areas of the world endemic with measles.

Within the last year, however, major outbreaks have emerged. Incompletely vaccinated populations and unvaccinated individuals are the reason for the progression of current outbreaks.<sup>8</sup>

Until there is broader acceptance of the vaccine and better adherence to vaccine policies nationally and globally, measles cannot be completely eradicated. But with high vaccination rates, it is predicted that this infection can be controlled and ultimately eradicated.

Measles deaths are most often caused by viral pneumonia, secondary bacterial pneumonia, and postviral encephalitis

TABLE 2

**Measles, mumps, and rubella vaccination: CDC recommendations**

Patient category	Recommendations
<b>Routine vaccination</b>	
Patient with no evidence of immunity to measles, mumps, or rubella (see <b>Table 3</b> )	Give 1 dose of measles, mumps, and rubella (MMR) vaccine
<b>Special situations</b>	
Pregnancy with no evidence of immunity to rubella	MMR is contraindicated during pregnancy After pregnancy (before discharge from healthcare facility), give 1 dose of MMR
Nonpregnant women of childbearing age with no evidence of immunity to rubella	Give 1 dose of MMR
Human immunodeficiency virus (HIV) infection with CD4 count $\geq 200$ cells/ $\mu$ L for at least 6 months and no evidence of immunity to measles, mumps, or rubella	Give 2-dose series of MMR at least 4 weeks apart MMR is contraindicated in HIV infection with CD4 count $< 200$ cells/ $\mu$ L
Severe immunocompromising conditions	MMR is contraindicated
Students in postsecondary educational institutions, international travelers, and household or close personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella	1 dose MMR if previously received 1 dose MMR, or 2-dose series MMR at least 4 weeks apart if previously did not receive any MMR
Healthcare personnel born in 1957 or later with no evidence of immunity to measles, mumps, or rubella	2-dose series MMR at least 4 weeks apart for measles or mumps, or at least 1 dose MMR for rubella; if born before 1957, consider 2-dose series MMR at least 4 weeks apart for measles or mumps, or 1 dose MMR for rubella

From the US Centers for Disease Control and Prevention.

**RECOMMENDATIONS**

In the midst of an outbreak and with rising public awareness of the threat of measles, it is important to recognize that MMR vaccination is the most effective way to prevent spread of the virus and maintain measles elimination in the United States. With this in mind, there are several key facts and recommendations regarding vaccination:

**Recommendations on vaccination**

- In measles-controlled populations, all children should be vaccinated between 12 and 15 months of age and again before kindergarten.
- In outbreak settings, children should receive a first vaccine dose at 6 months of age, a second at 12 to 15 months of age, and a third before kindergarten.
- Children who have received 2 measles

vaccine doses can be assumed to be fully vaccinated and thus protected as long as the first dose was after 12 months of age. If the first dose was before 12 months of age, a child needs 3 doses.

- Adults born before 1957 can be assumed to have had measles infection and to be immune.
- Adults who were immunized with the inactivated measles vaccine available between 1963 and 1967 should receive 1 dose of live virus vaccine.
- Boosters are recommended for young adults who did not receive a second dose of vaccine and for adults with an uncertain history of immunization. There is no need to check titers before giving a booster, but if a positive titer is available in an adult, a booster is not needed.
- Healthcare providers should vaccinate unvaccinated or undervaccinated US residents

TABLE 3

## US Centers for Disease Control and Prevention criteria for evidence of immunity to measles

### At least one of the following:

Written documentation of adequate vaccinations including 1 or more doses of measles vaccine given after 12 months of age (preschool-age children) and adults "not at high risk"

Written documentation of 2 doses of vaccine for school-age children and adults at high risk: college students, healthcare personnel, and international travelers

Laboratory evidence of immunity

Laboratory confirmation of measles

Birth before 1957

Information from reference 4.

traveling internationally (as long as they do not have contraindications) or traveling within the country to areas with outbreaks of measles.

### Recommendations on vaccination after exposure to measles

- Vaccine is recommended for a nonimmune contact, including anyone with a history of only a single dose of vaccine.
- If a child got a first dose of vaccine before 12 months of age, give the second dose as soon as he or she turns 1 year old, or at least 28 days after the first dose.
- Vaccine must be given within 72 hours of

exposure to confer protection (or at least decrease disease severity).

- The second dose of vaccine should be given at least 28 days after the first dose.

### Recommendations on immune globulin after exposure to measles

- Immune globulin is recommended for anyone with exposure and no history of vaccination or immunity.
- Immune globulin can be given up to 6 days after exposure to prevent or decrease the severity of measles in immunocompromised hosts who have not been previously vaccinated. It is best to give it as early as possible.
- Immune globulin is given intramuscularly at 0.5 mL/kg, up to a maximum dose of 15 mL.
- Pregnant women and immunocompromised hosts without immunity should receive immunoglobulin intravenously. Children and adults who have had a recent bone marrow transplant and likely do not yet have a reconstituted immune system should be treated with immune globulin to prevent infection, as vaccine cannot be given immediately after transplant. This is also true for other immunocompromised individuals who have not been vaccinated and who are not candidates for vaccine because of the severity of their immune suppression.
- Children with human immunodeficiency virus infection are routinely vaccinated. As long as they have evidence of serologic immunity, they do not need additional treatment.

**Give vitamin A to all children with acute disease to decrease the risk of severe disease and complications**

### REFERENCES

1. Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Measles. In Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics 2018; 537–550.
2. Krugman S, Giles JP, Friedman H, Stone S. Studies on immunity to measles. J Pediatr 1965; 66:471–488. PMID:14264306.
3. Gastañaduy PA, Budd J, Fisher N, et al. A measles outbreak in an underimmunized Amish community in Ohio. N Engl J Med 2016; 375(14):1343–1354. doi:10.1056/NEJMoa1602295.
4. Centers for Disease Control and Prevention. Measles (rubeola). www.cdc.gov/measles/index.html. Accessed May 16, 2019.
5. World Health Organization. Measles vaccines: WHO position paper—April 2017. Wkly Epidemiol Rec 2017; 92(17):205–227. PMID:28459148

6. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome and mumps, 2013; summary: recommendations of the Advisory Committee on Immunization Practices ACIP. MMWR Recomm Rep 2013 Jun 14; 62(RR-4):1–34. PMID:23760231
7. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention. Immunization for health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011 Nov 25; 60(RR-7):1–45. PMID:22108587
8. Patel M, Lee AD, Redd SB, et al. Increase in measles cases—United States, January 1–April 26, 2019. MMWR Morb Mortal Wkly Rep 2019; May 3; 68(17):402–404. doi:10.15585/mmwr.mm6817e1

ADDRESS: Johanna Goldfarb, MD, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, EC40, 9500 Euclid Avenue, Cleveland, OH 44195; goldfaj@ccf.org