



Measles Update in an Era of Vaccine Hesitancy and Global Pandemic

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The measles virus is highly communicable. Discovered in 1757, it became a nationally notifiable disease in 1912, when an estimated 6000 related deaths were reported annually. In the 1960s, public health vaccination efforts began in earnest with the licensure of the first measles vaccine in 1963. In 2000, measles was officially declared eliminated in the Americas as endemic cycles were demonstrated to have been broken. However, more recently, measles outbreaks have risen dramatically, particularly in 2019 when there were 22 outbreaks (1274 reported cases) in the United States alone, largely in underimmunized and close-knit communities. The resurgence of measles infections has also been fueled by rising vaccine hesitancy and vaccine misinformation/disinformation not only against the measles vaccine but also against many other vaccines given in childhood. Today, measles continues to occur in high enough numbers to necessitate that health care professionals must recognize signs and symptoms, develop appropriate treatment strategies, and implement prevention measures, including efforts to increase vaccination in susceptible populations.

Measles, also known as rubeola, is caused by an enveloped RNA virus (genus *Morbillivirus*, family *Paramyxoviridae*). Seasonal peak incidence of infection tends to occur in late winter and spring. Attack rates in susceptible patients may reach as high as 90% in close-contact settings, giving rise to the basic reproductive number of 12 to 18. Herd immunity is achieved only if population immunity is 95% or greater. Before the introduction of the measles vaccine, most infections occurred in preschool- and elementary school-age children. Once vaccination became routine, most infected patients were infants and unvaccinated or immunocompromised children. From the licensure of the measles vaccine in 1963 until 2000, the number of measles cases steadily declined in the United States, leading to the 2000 announcement that measles had been eradicated. Globally, by the end of 2018, 89% of children had received at least 1 dose of the combined measles-mumps-rubella (MMR) vaccine by their second birthday. From 2000 through 2016, it is estimated that measles vaccinations prevented 25.5 million deaths. However, between 2016 and 2019, new cases worldwide rose by 556% to almost 870,000, with approximately 207,500 deaths. Since 2019, the COVID-19 pandemic has negatively affected public health vaccination efforts, including surveillance systems to monitor vaccine-preventable conditions, including measles. This has led to the increased risk of measles resurgence, reinforcing the importance of health care provider recognition and management of this disease.

AUTHOR DISCLOSURE: Dr Immergluck serves as principal investigator in clinical trials sponsored by Merck, Sharpe & Dohme Corp and GSK; these manufacturers make measles vaccine products. Dr Flores has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Acute measles infection can present with a variety of signs and symptoms: early disease includes cough, coryza (catarrhal inflammation of the mucous membrane in the nose), fever, and conjunctivitis, followed by a diffuse maculopapular rash that begins on the face, then trunk, and last extremities. Pathognomonic of measles, Koplik spots (small white spots, often with red edges, on the buccal mucosa) can also be found. The incubation period is 8 to 12 days (range, 7–21 days). Peak transmissibility generally occurs from 4 days before to 4 days after rash onset. Acute otitis media, pneumonia, gastroenteritis, and acute meningoencephalitis can also occur as secondary complications. Most fatal cases are from pulmonary and neurologic complications, which occur in 1 to 3 per 1000 cases. Risk factors for severe illness include young age (<5 years old), pregnancy, immunocompromised conditions, and severe malnutrition, including vitamin A deficiency.

Although rare, devastating manifestations include measles inclusion body encephalitis and subacute sclerosing panencephalitis. The former, a clinical diagnosis confirmed only with brain biopsy showing intranuclear inclusion bodies, occurs predominantly in immunocompromised patients, primarily within 1 year of infection. The usual presentation is subacute, with evidence of progressive peripheral and central neurologic dysfunction, including focal and generalized seizures, global weakness and neuropathy, cognitive dysfunction, and altered mentation. Subacute sclerosing panencephalitis, a degenerative disease of the central nervous system, initially manifests with behavioral abnormalities and progressive cognitive decline over 6 to 11 years after initial measles infection. Patients acquire permanent motor and autonomic dysfunctions, often losing the ability to ambulate, developing breathing difficulties and cardiovascular morbidity, with death usually ensuing as a complication of secondary infections or heart failure.

Diagnosis is often based on recognizing the constellation of fever, cough, coryza, and rash with or without Koplik spots. Because other viruses (eg, adenoviruses, herpesviruses, enteroviruses) may present similarly, laboratory-based tests are needed to confirm the diagnosis. Tests include identifying the presence of IgM or IgG antibodies, and real-time polymerase chain reaction, which may detect measles RNA from bodily fluid specimens collected within the first 7 days of rash onset.

Currently, no antiviral agent is approved by the Food and Drug Administration (FDA) to treat measles. In vitro studies have shown efficacy with ribavirin, but with clinical trial data lacking it is only used for severely infected or immunocompromised patients. Supplemental vitamin A for 2 days improves clinical outcomes and decreases mortality in resource-limited settings. The World Health Organization established guidelines

for vitamin A treatment in all infected children (Table 1), with a third age-specific dose recommended 2 to 6 weeks later for vitamin A-deficient children.

For patients hospitalized with measles, along with standard precautions for infection control, precautions to prevent airborne transmission should be in place from the onset of rash for 4 days in immunocompetent patients and for the entire hospitalization in immunocompromised patients. Other hospitalized patients exposed to measles who are susceptible should be placed on airborne precautions from 5 days after exposure until 21 days after the last contact with the index case.

Routine vaccination is ultimately the most important intervention to prevent acquisition and transmission of measles: the first dose of either MMR or measles-mumps-rubella-varicella (MMRV) vaccine should be given at 12 to 15 months of age, and a second dose at 4 to 6 years of age or at least 28 days after the first dose. Reported, but rare, adverse effects of MMR/MMRV vaccines include transient fever, rash, thrombocytopenia, and allergic reactions. MMRV has a higher rate of febrile seizures than MMR and should not be given to patients with human immunodeficiency virus because the vaccine has not been clinically studied in this population.

For people exposed to measles, certain predisposing conditions (eg, unvaccinated or without documented measles immunity; underlying primary or secondary immunocompromise; pregnancy) qualify them for postexposure treatment with vaccine and/or immunoglobulin (Table 2). Postexposure vaccination is most beneficial when administered within 72 hours of exposure, and immunoglobulin within 6 days of exposure.

In the setting of a measles outbreak or travel to countries with significant rates of endemic measles, infants 6 to 11 months of age should receive a dose of MMR/MMRV, recognizing that this dose does not count toward the recommended 2-dose series that is initiated at 12 to 15 months.

In unvaccinated children, MMR/MMRV should be given at least 2 weeks before administration of a blood product or intravenous immunoglobulin (IVIg) to avoid the risk of neutralizing the vaccine virus with the administered antibodies.

Table 1. Recommendations for Vitamin A Administration

AGE, mo	DOSE, IU (μ g RAE)
≥ 12	200,000 (60,000)
6–11	100,000 (30,000)
<6	50,000 (15,000)

IU=international units, RAE=retinol activity equivalent.

Table 2. Postexposure Prophylaxis (PEP) for Measles

PATIENT CATEGORY	AGE	STATUS OF MEASLES IMMUNITY ^a	TIME FROM EXPOSURE TO MEASLES		
			≤3 d	4–6 d	>6 d
Nonpregnant, immunocompetent	All ages	Yes	PEP not indicated: exposed person has documented immunity		
	<6 mo	No, due to age before vaccination	IMlg ^b		PEP not indicated ^{c,d}
	6–11 mo	No, due to age before vaccination	MMR vaccine, no quarantine needed	IMlg ^b	PEP not indicated ^{c,d}
	≥12 mo	No, zero vaccine doses, or negative IgG	MMR vaccine, no quarantine needed	PEP not indicated; ^{c,d} then give MMR to protect from future exposures after 21-d quarantine	
	≥12 mo	Partial immunity, history of 1 dose of MMR vaccine	Second dose of MMR vaccine if ≥28 d or after last dose, no quarantine needed	Household member should obtain IgG to determine immunity and home quarantine while awaiting results; if IgG negative then quarantine for 21 d after last exposure	
				Non-household members: • Age 1–3 y: less likely sick due to proximity of first MMR vaccine dose • Age ≥4 y: give 1 dose of MMR vaccine	
	Adults	Unknown	MMR vaccine, no quarantine required	Household members, or those non-household members who work in settings with children (child care, school, etc) or in a health care facility, should obtain IgG to determine immunity, home quarantine while awaiting results; if IgG negative then quarantine for 21 d after last exposure	
Severely immunocompromised ^e	<12 mo	Not applicable	IMlg ^b		Non-household members of a confirmed/suspected case who do not work in settings with children (child care, school, etc) or health care facility may collect antibody titer while in clinic/hospital or reach out to their own provider in a timely manner
	≥12 mo		IMlg ^b		PEP not indicated ^{c,d}
	All ages	Yes	PEP not indicated		
		No	IMlg ^b		PEP not indicated ^{c,d}
Pregnant		Unknown	Draw antibody titers STAT to determine immunity and proceed per above		PEP not indicated ^{c,d}

IMlg=intramuscular immunoglobulin, IVlg=intravenous immunoglobulin, MMR=measles-mumps-rubella.

^aImmune = IgG positive, 2 MMR or measles-mumps-rubella-varicella doses, or born before 1957.

^bHome quarantine for 28 days after last exposure.

^cHome quarantine for 21 days after last exposure.

^dPEP too late to be given.

^eSevere primary immunodeficiency includes bone marrow transplant within 1 year of immunosuppressant therapy; treatment for acute lymphoblastic leukemia until 6 months after last treatment dose; solid organ transplant recipients taking immunosuppressants; daily corticosteroid therapy with a dose greater than or equal to 20 mg (or >2 mg/kg per day for patients who weigh <22 lb [<10 kg]) of prednisone or equivalent for at least 14 days; receiving certain biological immune modulators, such as tumor necrosis factor α blockers or rituximab; and AIDS or human immunodeficiency virus with severe immunosuppression defined as CD4 less than 15% (all ages) or CD4 count less than 200 lymphocytes/mm³ (age >5 years).

Likewise, children treated with IVIg or corticosteroids should wait the recommended number of months before receiving MMR/MMRV (≥ 4 weeks and up to 11 months depending on the dose of IVIg or corticosteroid).

Sustained global vaccination programs against measles have spared millions of infants and children from infection with this potentially deadly virus. However, increased vaccine hesitancy and disruption of public health interventions in the setting of the recent COVID-19 pandemic have led to pockets of resurgence of what is a dangerous but vaccine-preventable disease, and the risk is real for further outbreaks. With this, it becomes that much more vital that health care professionals can identify, manage, and prevent the spread of this potentially devastating virus.

COMMENT: So common was measles before the introduction of the vaccine that most mothers (certainly mine) could diagnose the infection in their children without input from a doctor. Now, some 60 years after the advent of vaccination, most pediatricians currently in practice have likely not seen a case—a striking testament to just how effective the measles vaccine has been. Aside from how uncomfortable children with measles frequently are, reason

enough to protect them from it, the potential serious morbidities and mortality associated with the infection make it even more tragic that increasing vaccine refusal and hesitancy in the United States are bringing back a dangerous preventable disease.

Before vaccine, several thousand children in the United States died each year of measles, and worldwide, particularly in countries where most children live in poverty and suffer from malnutrition, the mortality rate with infection approaches 25%. Not to dwell on otitis, croup, and pneumonia, the neurotoxicity of measles manifests not only in the rare case of devastating subacute sclerosing panencephalitis but also with an acute encephalitis that can strike as many as 1 in 1000 infected children, often with long-lasting effects.

We have 2 objectives before us: the clinical need to recognize the disease when we see it and to manage it properly and the public health urgency to restore herd immunity by returning vaccinations to their proper place in our armament.

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