CLINICAL PRACTICE

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Measles

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 38-year-old man presents to his primary care physician with a 3-day history of fever and cough. He is a father of two children, his wife is pregnant, and he has a history of recent travel outside the United States. The physical examination is notable for a body temperature of 39°C, conjunctivitis, and rhonchi on chest auscultation. The physician suspects bronchitis and prescribes antibiotic agents. Two days later, the patient returns with a red blotchy rash over his face and trunk. The physician becomes concerned about the possibility of measles. How should this case be further evaluated and managed? How might measles have been prevented, and what can be done to prevent the spread of the disease within the patient's family and community?

THE CLINICAL PROBLEM

Measles virus is one of the most highly contagious human pathogens known. In a 100% susceptible population, a single case of measles results in 12 to 18 secondary cases, on average.[1] Two doses of measles-containing vaccine is the standard of care for the prevention of measles.[2]

MEASLES IN THE UNITED STATES

Measles vaccine was first licensed in the United States in 1963, after which the incidence of measles declined rapidly (Fig. 1). Measles was certified as eliminated in the United States (i.e., no sustained transmission for >1 year) in 2000.[3] Strategies for elimination included achieving and maintaining very high coverage with two doses of measles-containing vaccine, implementation of vaccination requirements for school attendance in every state, sensitive laboratory-supported surveillance, and rapid outbreak detection and response.[4]

Although the incidence of measles has remained lower than 1 case per million population, an analysis of confirmed cases in the United States between 2001 and 2015 showed that importations were leading to progressively more transmission in the United States, particularly among unvaccinated persons.[5] From 2001 to 2016, a median of 28 imported cases of measles were documented each year (range, 18 to 80); among the persons with imported cases, 62% were U.S. residents and 87% were unvaccinated or had an unknown vaccination status.[6] Since 2016, a year in which 86 cases of measles were confirmed in the United States, the annual number of cases has increased. The number of cases reported so far this year (1077 as of June 20, 2019) is greater than the number reported in any entire year since measles was declared eliminated in 2000 and, in fact, exceeds the number of cases in any entire year since 1992 (Fig. 1). The high number of cases in 2019 is heavily

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KEY CLINICAL POINTS

MEASLES

- Clinicians should suspect measles in persons who have a febrile illness with rash, especially if they lack documentation of measles vaccination, have recently traveled overseas, or are part of a community with low vaccine acceptance.
- Clinical specimens (e.g., serum and nasopharyngeal swab) for laboratory confirmation should be obtained from all patients suspected to have measles at their first contact with a health care provider.
- All suspected cases of measles should be reported immediately to the local or state health department without waiting for diagnostic test results.
- U.S. travelers to other countries account for a high proportion of imported cases of measles, which emphasizes the importance of measles vaccination of U.S. residents who are 6 months of age or older before international travel.
- Serious adverse events after measles–mumps–rubella vaccination are rare and much less common than those associated with natural measles infection.
- Clinicians play a critical role in managing parental concerns about vaccination and in maintaining trust in vaccines.

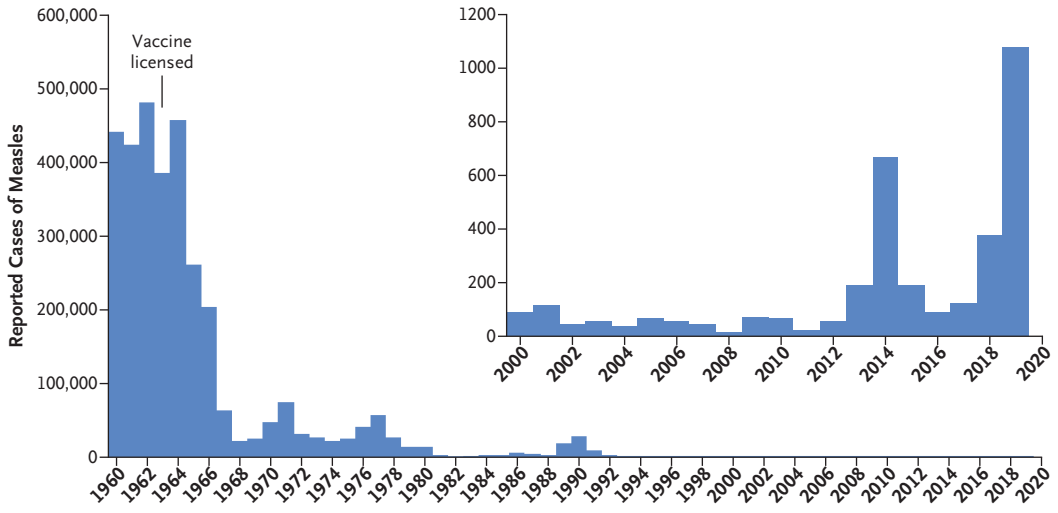

Figure 1. Numbers of Cases of Measles Reported Each Year, United States, 1960–2019.

The inset shows data from the Centers for Disease Control and Prevention (www.cdc.gov/measles/cases-outbreaks.html) on the numbers of cases of measles during the period from 2000 through June 20, 2019. In general, numbers of reported cases are an underestimate of true numbers of cases because of underdiagnosis and underreporting.

influenced by three outbreaks that started in late 2018 — one in Washington State and two in New York — in close-knit, underimmunized communities.[7] These outbreaks are linked to travelers who brought measles back from other countries such as Israel, Ukraine, and the Philippines, where large measles outbreaks are occurring. The Centers for Disease Control and Prevention (CDC) reported that an important factor contributing to the outbreaks in New York is misinformation in the communities about the safety of the measles–mumps–rubella (MMR) vaccine.[8]

MEASLES GLOBALLY

Between 2000 and 2017, the global annual incidence of reported cases of measles declined by 83%, from 145 to 25 cases per million population. In 2017, it is estimated that there were 109,000 deaths from measles worldwide, down from 545,000 in 2000; cumulatively during this period, as compared with no measles vaccination, measles vaccination prevented an estimated 21.1 million deaths.[9] Recent increases in the incidence of measles in the United States and other industrialized countries are part of a global

upswing in reported cases of measles that began in 2018 and is continuing into 2019. Countries with the largest numbers of reported cases over the most recent 6-month period include Madagascar, Ukraine, India, Brazil, Philippines, Venezuela, Thailand, Kazakhstan, Nigeria, and Pakistan.[10] Although the vast majority of cases worldwide occur in countries with weak health systems, vaccine refusal is emerging as a risk factor for measles outbreaks, and the World Health Organization (WHO) has identified vaccine hesitancy as one of the top 10 global health threats in 2019.[11]

All six WHO regions have the goal of measles elimination by or before 2020. The Americas is the only region that had been verified to be free of endemic measles. However, an outbreak of measles that started in Venezuela in 2017 is still ongoing, indicating that endemic measles transmission has been reestablished in the Americas.[12]

STRATEGIES AND EVIDENCE

CLINICAL PRESENTATION

Measles is an acute viral illness that starts with a prodromal phase, lasting 2 to 4 days, of fever and at least one of the "three Cs" (cough, coryza, and conjunctivitis), similar to any upper respiratory tract infection.[13] The characteristic measles rash — an erythematous maculopapular exanthem — appears 2 to 4 days after the onset of fever, first on the face and head and then on the trunk and extremities; it may be confluent on the face and upper body (Fig. 2). During the ensuing 3 to 5 days, the rash in different parts of the body fades in the order in which it appeared, and full recovery occurs within 7 days after rash onset in uncomplicated cases. Koplik spots, small bluish white plaques on the buccal mucosa, are present in up to 70% of cases and are considered pathognomonic of measles; they may appear 1 to 2 days before the onset of rash and may be present for an additional 1 to 2 days after rash onset (Fig. 2).[15]

Complications associated with measles infection in industrialized countries include otitis media (7 to 9% of patients), pneumonia (1 to 6%), diarrhea (8%), postinfectious encephalitis (approximately 1 per 1000), subacute sclerosing panencephalitis (a progressive degenerative disease with onset usually 5 to 10 years after acute measles; approximately 1 per 10,000), and death (approximately 1 per 1000). The risk of complications is increased among infants, adults older than 20 years of age, pregnant women, undernourished children (particularly those with vitamin A deficiency), and persons with immune suppression (e.g., cancer or human immunodeficiency virus [HIV] infection). An acute progressive encephalitis (measles inclusion-body encephalitis[16]) and a characteristic giant-cell pneumonia (Hecht's pneumonia[17]) are two especially severe complications that may occur in rare cases in persons with immune suppression.

Measles runs a more devastating course in children in developing countries, a phenomenon related to undernutrition, overcrowding, and lack of access to care, with mortality as high as 1 to 15%.[18] Measles infection during pregnancy is associated with an increased risk of complications, including miscarriage, preterm birth, neonatal low birth weight, and maternal death.[19]

DIAGNOSIS

Whereas a typical case of measles is easily recognized during outbreaks, the clinical diagnosis is challenging to many clinicians who have not seen measles and in patients who present before the onset of rash or whose rash is less apparent (e.g., infants with residual maternally acquired antibodies, previous receipt of immunoglobulin, or vaccination after exposure). The typical measles rash may be absent in persons with impaired cell-mediated immunity.[20]

The differential diagnosis includes rubella, dengue fever, parvovirus B19 infection, human herpesvirus 6 infection, and other infections, as well as reactions to measles vaccine. The measles case definition recommended by the CDC (i.e., generalized maculopapular rash, fever [body temperature, ≥38.3°C], and cough, coryza, or conjunctivitis [or a combination of these symptoms]) has a high sensitivity (75 to 90%) but a low positive predictive value in low-incidence settings, indicating the need for laboratory confirmation.[21]

The most common laboratory method for confirming measles is detection of measles virus–specific IgM antibodies in a blood specimen (sensitivity, 83 to 89%; specificity, 95 to 99%).[22] These antibodies are not detectable in approximately 25% of persons within the first 72 hours after rash onset but are almost always present after 4 days of rash. A real-time polymerase-chain-reaction (PCR) assay for measles virus RNA in urine, blood, oral fluid, or nasopharyngeal spec-

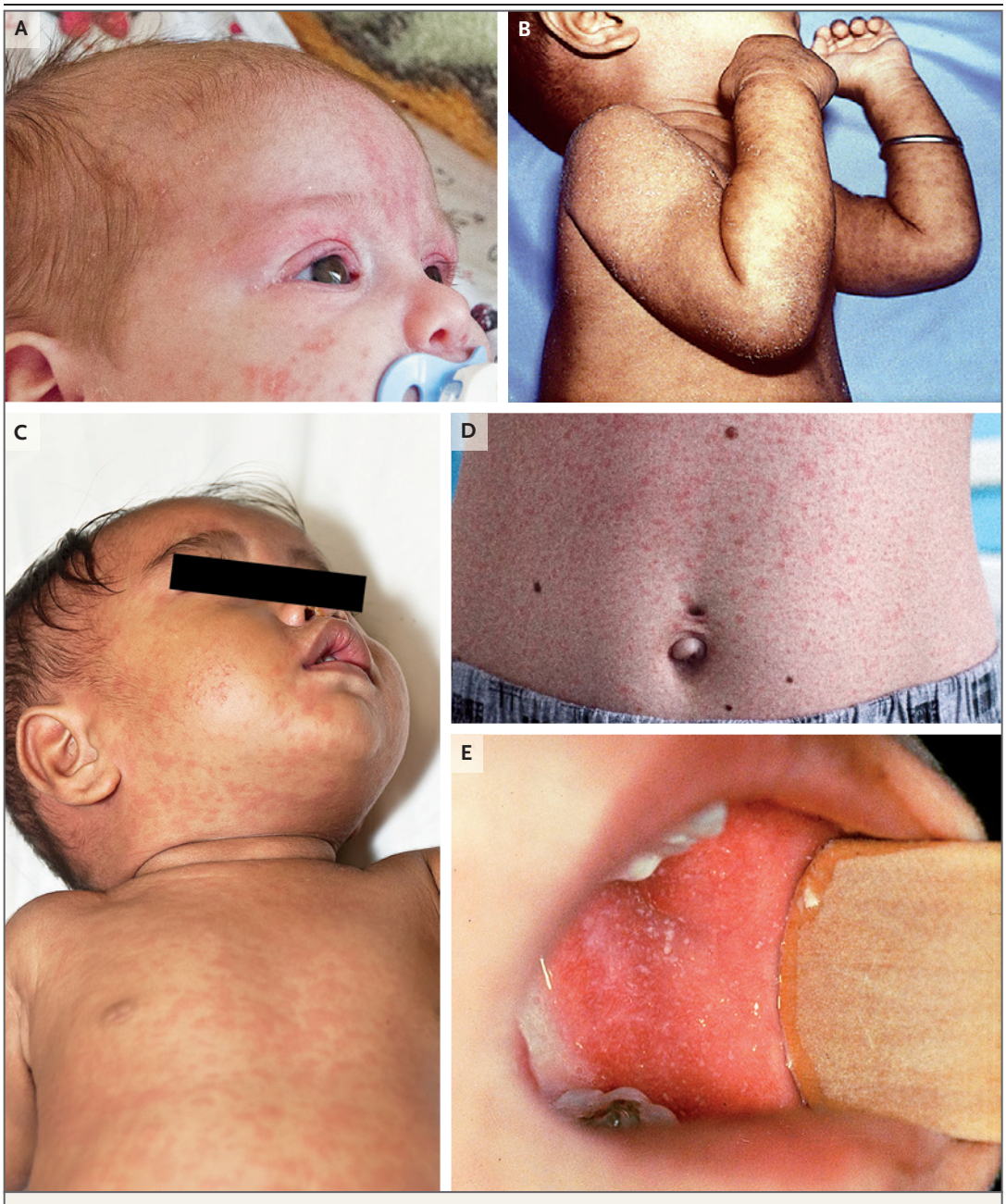

Figure 2. Manifestations of Measles in Children.

Panel A shows an infant with measles conjunctivitis and rash. Patients with measles rash are shown in Panels B, C, and D. In Panel B, pigmentation and desquamation of the measles skin rash (complications that are most often seen in undernourished children) are visible; these signs are evident approximately 5 days after the onset of rash and may continue for weeks. Panel E shows a patient with Koplik spots on the buccal mucosa. Panels A and D were provided by M. Bring of the World Health Organization (WHO), Panel B by the WHO,[14] Panel C by U. Sharapov of the Centers for Disease Control and Prevention (CDC), and Panel E by the Office of the Associate Director for Communications, Division of Public Affairs, CDC.

imens can identify infection with a sensitivity of 94% and a specificity of 99%[23] before measles IgM antibodies are detectable, and it allows genotyping of the measles virus, which is useful for tracking virus importations and spread.[24] All cases of suspected measles should be reported

immediately — without waiting for diagnostic test results — to the local or state health department, which can assist with obtaining tests and take actions to minimize spread of virus.

MANAGEMENT

Because there is no specific antiviral medication available, treatment of measles consists of supportive therapy to prevent dehydration and, in some cases, to treat nutritional deficiencies, as well as early detection and treatment of secondary bacterial infections such as pneumonia and otitis media. High doses of vitamin A have been shown to decrease mortality and the risk of complications in young children hospitalized with measles in developing countries.[25] In the United States, children with measles have been found to have low levels of serum retinol, and levels tend to be lower among those with more severe illness.[26] The American Academy of Pediatrics (AAP) recommends vitamin A administration for all children with severe measles (e.g., requiring hospitalization), with the use of the following age-specific doses: 200,000 IU for children 12 months of age or older; 100,000 IU for infants 6 to 11 months of age; and 50,000 IU for infants younger than 6 months.[27] A third age-specific dose should be given 2 to 4 weeks later to children who have clinical signs and symptoms of vitamin A deficiency. In addition, vitamin A therapy should be administered to children with measles who have immunosuppression, have clinical evidence of vitamin A deficiency, or have recently immigrated from areas with a high mortality from measles. Antibiotics, in the absence of pneumonia, sepsis, or other signs of a secondary bacterial complication, are generally not recommended.[28] To prevent nosocomial transmission, patients who are suspected to have measles should be triaged in outpatient settings, and hospitalized patients with measles should be isolated with precautions to prevent airborne transmission.[27] Patients with measles are infectious from 4 days before to 4 days after the onset of their rash.

POSTEXPOSURE PROPHYLAXIS

Measles vaccine given within 72 hours after measles exposure, or human immune globulin given up to 6 days after exposure, can prevent or attenuate disease in susceptible persons.[29] In household or classroom settings in which the timing of first exposure can be determined, prophylaxis has been shown to be highly effective (up to 90% after vaccine[30] and 95% after immune globulin[31]). Measles-containing vaccine should be considered for all exposed persons who do not have contraindications and who have not been vaccinated or have received only one dose of vaccine.

Administration of immune globulin is particularly critical for patients who are at risk for severe disease, including infants younger than 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons. The Advisory Committee on Immunization Practices recommends a dose of 0.5 ml per kilogram of body weight administered intramuscularly for persons with a body weight of up to 30 kg and a dose of 400 mg per kilogram intravenously for persons weighing more than 30 kg.[29] Because the immunity to measles conferred by administration of immune globulin is temporary, persons who receive immune globulin should subsequently receive MMR vaccine, administered no earlier than 6 months after intramuscular immune globulin or 8 months after intravenous immune globulin.

Severely immunocompromised patients (e.g., bone marrow transplant recipients, as well as persons who have acquired immunodeficiency syndrome or HIV infection with severe immunosuppression and those who have not received MMR vaccine since receiving effective antiretroviral therapy) who are exposed to measles should receive prophylaxis with intravenous immune globulin regardless of their immunologic or vaccination status, because they might not have been protected by vaccination.[29]

VACCINE EFFECTIVENESS

Field studies of the effectiveness of the measles vaccine have found high effectiveness after one dose administered at the age of 12 months or later (median effectiveness, 93%; range, 39 to 100) and even higher effectiveness after two doses (median, 97%; range, 67 to 100).[29] The WHO recommends two doses of measles-containing vaccine as the standard of care for the prevention of measles in all countries.[2] Two doses are needed to reach herd-immunity thresholds and terminate transmission. Vaccine-induced immunity is probably lifelong in the vast majority of vaccinees.[32]

Table 1. Comparison of the Risk of Complications Associated with Measles and the Risk of Serious Adverse Events after Measles Vaccination.*

Complication or Serious Adverse Event	Risk after Natural Disease†	Risk after Vaccination‡
Otitis media	7 to 9 per 100	0
Diarrhea	8 per 100	0
Pneumonia	1 to 6 per 100	0
Subacute sclerosing panencephalitis	4 to 11 per 100,000	0
Encephalitis	0.5 to 1 per 1000	<1 per 1,000,000
Death	Approximately 1 per 1000 (1 to 15 per 100 in developing countries)	0
Febrile seizure	—§	1 per 3000
Thrombocytopenic purpura	—§	1 per 30,000
Anaphylaxis	0	2 to 14 per 1,000,000

* Information is from the Institute of Medicine[35] and Pless et al.[36]
† Risk is expressed as the number of events per number of cases of measles.
‡ Risk is expressed as the number of events per number of vaccine doses administered.
§ Complication has been described in measles case reports, but the risk is not well quantified.

VACCINE SAFETY

After 50 years of licensure and with more than 100 million doses administered worldwide each year since 2000, measles-containing vaccines have a well-established safety record. The MMR vaccine has an acceptable side-effect profile. Adverse events include fever (<15% of recipients), transient rashes occurring 7 to 12 days after vaccination (5%), transient lymphadenopathy (5% of children and 20% of adults), parotitis (<1%), and aseptic meningitis (1 to 10 per million).[33,34] Serious adverse events are rare and much less common than the risks associated with natural measles infection; these include anaphylaxis (2 to 14 cases per million doses), febrile seizures (1 case per 3000 doses), thrombocytopenic purpura (1 case per 30,000 doses), and measles inclusion-body encephalitis in persons with demonstrated immunodeficiencies (Table 1).[35,36] The rubella component of MMR can cause transient arthralgia or arthritis, primarily in susceptible postpubertal female patients.

Antivaccine groups continue to postulate that the MMR vaccine may be a cause of inflammatory bowel disease and autism on the basis of a case series published in 1998 that was later retracted because of falsification of clinical information.[37] Subsequent laboratory and epidemiologic studies have not supported an association between the MMR vaccine and these conditions.[38,39]

GENERAL RECOMMENDATIONS FOR MEASLES VACCINATION

Measles-control programs throughout the world have shown that measles is eliminated if national immunization schedules are fully implemented and high vaccination coverage is achieved and maintained, whereas measles outbreaks occur when populations are not adequately vaccinated. The U.S. recommendations[29] are shown in Table 2; schedules for other countries can be found at http://apps.who.int/immunization_monitoring/globalsummary/schedules.

In addition to ongoing vaccination of new birth cohorts, prevention of measles outbreaks requires the identification and vaccination of persons who are at high risk on the basis of exposure or contact frequency (e.g., school-attending children, college students, international travelers, and health care workers) and others who are more likely to have missed both vaccination and natural infection, such as persons from underserved or geographically or socially isolated communities.

In the United States, the only measles-containing vaccines are the MMR vaccine and the combined measles–mumps–rubella–varicella (MMR-V) vaccine. The CDC recommends that the MMR and varicella vaccines be administered separately for the first dose, but they can be given as the MMR-V for the second dose.[29] MMR is the vaccine of choice for the prevention of measles in

Table 2. Summary of Measles Vaccination Recommendations in the United States.*

Age Group	Vaccination Recommendation
Preschool children	
Routine childhood schedule	First dose at 12 to 15 months (MMR vaccine); second dose at 4 to 6 years (MMR-V vaccine)
Outbreak settings or before international travel	First dose may be given as early as 6 months, with repeat of first dose at 12 months; second dose given as early as 13 months†
HIV infection	First dose at 12 months; second dose given as early as 13 months†‡
Schoolchildren and adolescents	All children in kindergarten through 12th grade should have documentation of two doses of MMR unless they have other evidence of immunity§
Adults (≥18 years of age)	Documentation of receipt of at least one dose of MMR unless they have other evidence of immunity§
High-risk settings	Students and staff in colleges and other post–high school educational institutions, persons working in health care facilities, and international travelers should have documentation of receipt of two doses of measles vaccine unless they have other evidence of immunity§

* Information is from McLean et al.[29] All recommendations exclude persons for whom measles vaccination is contraindicated. MMR denotes measles–mumps–rubella, and MMR-V measles–mumps–rubella–varicella.
† Clinicians should wait at least 28 days after any dose before giving a subsequent dose.
‡ Revaccination is recommended for persons with perinatal human immunodeficiency virus infection who were vaccinated before establishment of effective antiretroviral therapy (ART) with two appropriately spaced doses of MMR vaccine after effective ART has been established.
§ Other evidence can include birth before 1957 or laboratory confirmation of disease or laboratory evidence of immunity.

adolescents and adults and in infants 6 to 11 months of age who are at increased risk for exposure (e.g., during outbreaks or international travel) (Table 2). Recommendations regarding acceptable evidence of immunity are available to guide decisions about who should or should not be vaccinated against measles (Table 3).

AREAS OF UNCERTAINTY

Antiviral agents (e.g., ribavirin and interferon) have been used to treat severely affected and immunocompromised patients with measles, and positive outcomes have been reported.[41] However, randomized controlled trials are lacking, and ribavirin is not licensed by the Food and Drug Administration for the treatment of measles. Further research is needed to determine the benefits and risks of antiviral agents in the treatment of severe cases of measles.

Although measles meets the criteria for a disease that can be eradicated, strategies are needed to increase and maintain uptake of recommended vaccine schedules. Study is needed of new vaccine-delivery technologies (e.g., microarray patches) or new vaccines that could improve on the current two-dose strategies.

GUIDELINES

Guidelines have been published by the AAP[27] and the WHO[14] on management of measles and by the CDC[29] and the WHO[2] on the use of measles vaccine and immune globulin. The recommendations in the present article are concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

Clinicians should suspect measles in an infant, child, adolescent, or adult who has a febrile rash illness, especially if the person lacks documentation of measles vaccination, has traveled overseas (as the patient described in the vignette did) or is part of a community with low vaccine acceptance. Once measles is suspected, the clinician should immediately contact the state or local health department, which can provide advice regarding clinical specimens for laboratory diagnosis, treatment of household contacts, and follow-up of contacts to determine the need for vaccine or immune globulin. If the patient's wife, who is pregnant, lacks evidence of immunity to measles, she should receive intravenous immune globulin

Table 3. Centers for Disease Control and Prevention Recommendations for Acceptable Evidence of Immunity to Measles in the United States.*

Type of Evidence	Age Group	Comments
Written documentation of vaccination with live measles–containing vaccine	Preschool-age children (documentation of one dose) School-age children, kindergarten through 12th grade (documentation of two doses) Adults not at high risk (documentation of one dose) Adults at high risk (documentation of two doses)	Date of vaccination should appear on the vaccination card or in medical records. Adults at high risk include all students in post–high school educational institutions, health care personnel, and international travelers.
Laboratory evidence of immunity	All ages	Immunity is indicated by positivity for measles IgG.
Laboratory evidence of prior measles	All ages	A previous case of measles should have been confirmed by measles IgM positivity, IgG seroconversion or a substantial increase in measles IgG between acute- and convalescent-phase serum specimens, or a positive PCR result.
Date of birth	Born before 1957	Persons born before 1957 are assumed to have acquired measles during childhood and therefore to be immune.

* Information is from McLean et al.[29] and Gastanaduy et al.[40] Persons who do not have at least one of the criteria listed should be vaccinated. PCR denotes polymerase chain reaction.

because of the complications of measles in pregnancy and the hypothetical risk of live vaccines during pregnancy.[42] If either of the patient's children are unvaccinated or have received only one dose, they should be vaccinated with the MMR vaccine as soon as possible. To avoid further spread of measles in his community, the patient should be isolated at home for 4 days after the onset of his rash.

To minimize the risk of new cases and outbreaks, clinicians should advise patients who are planning international travel about indications for measles vaccination. With the increasing spread of inaccurate information regarding vaccine-associated risks on social media, clinicians play a key role in responding to questions from patients regarding the rationale for, and safety of, the MMR vaccine, as well as in maintaining trust in vaccination among their patients and their families. Comprehensive guidance for clinicians about managing parental concerns about vaccination is available in a recent AAP publication[43] and in online material from the CDC (www.cdc.gov/measles/index.html).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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