Curr Infect Dis Rep (2015) 17: 51
DOI 10.1007/s11908-015-0506-5

The Reemergence of Measles

C. L. Abad [1] · N. Safdar [2]

Published online: 7 October 2015

Abstract Measles, or rubeola, is a highly infectious, acute viral illness of childhood that is considered eliminated in the USA but has reemerged in the past few years. Globally, an estimated 20 million cases of measles continue to occur, and it remains a leading cause of death among young children. It is rare in the USA and other first world countries, but numerous outbreaks have occurred in the USA recently, due to a combination of factors including poor vaccine coverage and importation of cases among travelers returning from endemic areas. The diagnosis of measles is usually made clinically, when an individual presents with a constellation of symptoms including cough, coryza, conjunctivitis, high fever, and an erythematous maculopapular rash in a cephalocaudal distribution. Complications are common and include otitis media, pneumonia, encephalitis, and rarely death. A measles vaccine is available in two doses and provides excellent protection against the disease. Despite this, vaccination coverage, especially among young adults, remains poor. Given its resurgence in the USA and other countries, interventions are urgently needed to address low vaccination rates and vaccine hesitancy. Measles awareness should also be a priority among young clinicians, who may have never seen a case or are not familiar with the disease.

Keywords Acute viral illness · Acute viral illness of childhood · Measles · Measles vaccine

This article is part of the Topical Collection on *Skin, Soft Tissue, Bone and Joint Infectious Diseases*

✉ N. Safdar
ns2@medicine.wisc.edu

[1] Department of Medicine, University of the Philippines-Philippine General Hospital, Manila/The Medical City, Pasig City, Philippines

[2] William S. Middleton Memorial Veterans Hospital and the Department of Medicine, University of Wisconsin-Madison School of Medicine, Madison, WI, USA

Introduction

Measles, or rubeola—derived from "rubeo," the Latin word for red—is a highly contagious, acute viral illness caused by a single-stranded, enveloped RNA virus. It is classified as a member of the genus Morbillivirus in the paramyxoviridae family. Measles is endemic in most of the world, and an estimated 20 million cases occurs annually [1]. Measles remains a leading cause of death globally among young children, despite the availability of a safe and effective vaccine for over 40 years. Nevertheless, the vaccine has had considerable impact, with an estimated 75 % reduction in children's deaths comparing numbers from 2000 to 2012 [2]. In fact, a new goal to achieve a 95 % reduction of measles worldwide by this year has been set by World Health Organization (WHO) [3].

In the USA, ongoing transmission of the measles virus was declared eliminated (defined as interruption of continuous transmission lasting ≥12 months) in 2000, an achievement attributed to high rates of vaccination coverage [4]. However, importations from other countries where measles remains endemic continue to occur, and poor vaccine coverage has led to recent outbreaks of measles in the USA. The reemergence of measles in recent years has led to renewed interest in the virus. In this article, we discuss its epidemiology, transmission, clinical features, complications, vaccine indications, and public health implications.

Epidemiology and Transmission

Measles is one of the most contagious of the vaccine-preventable diseases, with reproduction rates (R0) estimated at 12 to 18—meaning that the average person with measles is capable of infecting 12 to 18 other people if all close contacts are susceptible [5]. It has a secondary attack rate among susceptible individuals higher than 90 %. The virus can be transmitted in the air (aerosolized) in respiratory droplets or by direct or indirect contact with the nasal and throat secretions of infected persons when an infected person breathes, coughs, or sneezes [6].

Despite being declared eliminated in the USA, there have been several measles outbreaks in the USA in the past few years. Most recently, during January 4–April 2, 2015, a total of 159 measles cases (in 155 US residents and four foreign visitors) from 18 states were reported to the Centers for Disease Control (CDC) [1]. Of those infected, 55 % were adults [58 (36 %) were aged 20–39 years, and 30 (19 %) were aged ≥40 years]. Twenty-two patients (14 %) were hospitalized, including five with pneumonia. The majority of the 159 patients with reported measles were either unvaccinated (71 [45 %]) or had unknown vaccination status (60 [38 %]). The bulk of cases (96 %) were import-associated cases, belying the importance of vaccine coverage and herd immunity (discussed later).

Unfortunately, this pattern of measles resurgence in the USA is also reflected in Europe. Since a decrease in the number of notified measles cases in Europe between 2003 and 2009 [7], there have been a number of measles outbreaks especially in Central and Western Europe, with a peak of cases reported in 2011 (32,124 cases reported). France was the most affected country, with 47 % of cases in Europe in 2011, while several other countries have also reported a considerable number of cases including Bulgaria, Germany, Italy, Romania, Spain, Ukraine, and the UK [7, 8]. More recently, over a period of 1 year, over a thousand suspected measles cases (n=1073) were reported across the UK [9]. Most confirmed and probable cases occurred within two age groups—infants (too young to be eligible for measles-mumps-rubella (MMR) vaccination) and children aged 10–19 years. This resurgence of measles in countries without endemic transmission of disease and prior control is thought to result from poor vaccination rates [9].

Clinical Presentation

Measles is considered a systemic illness. Following exposure, the incubation period before onset of the first symptoms is usually 10–12 days. The prodromal symptoms, known as the "3Cs" of measles—cough, coryza, and conjunctivitis—occur prior to onset of the rash. Fever accompanies the prodromal phase and may be as high as 105 °F. Koplik spots—small spots with white or bluish-white centers on an erythematous base on the buccal around the second molar—are transient, noted only in 50–70 % of patients, but are highly specific [10].

The rash usually appears 14 days after exposure (range 7–18 days) [11, 12]. The classic rash (Fig. 1) in patients with measles is red, blotchy, maculopapular, and develops in a cephalocaudal and centrifugal distribution—it begins on the face, becomes generalized, and lasts 4–7 days. The fever typically ends once the rash appears. Individuals with measles are considered infectious from 4 days before to 4 days after the onset of rash [11] and should be in airborne isolation precautions during this period if hospitalized.

Measles should be suspected in any patient who presents with fever, rash, and epidemiologic risk factors such as travel to endemic areas or areas known to have recent transmission.

Laboratory Diagnosis

In areas such as the USA and Europe where the incidence of measles is low, a clinical diagnosis of measles in the absence of a confirmed outbreak has a low positive predictive value, and clinical signs enumerated above are unreliable as the sole criteria for diagnosis [3]. A number of other infections such as roseola, rubella, rickettsial disease (Rocky Mountain spotted fever), and dengue fever can present with a rash resembling measles; therefore, laboratory assessment is required for accurate diagnosis.

Measles-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) are both produced during the primary immune response and can be detected in the serum within days of rash onset, using a sensitive enzyme-linked immunosorbent assay (ELISA). Approximately 70 % of measles cases are IgM-positive at 0–2 days after the rash onset, and 90 % are positive 3–5 days after rash onset. IgM antibody levels peak after 7–10 days and then decline, rarely detectable after 6–

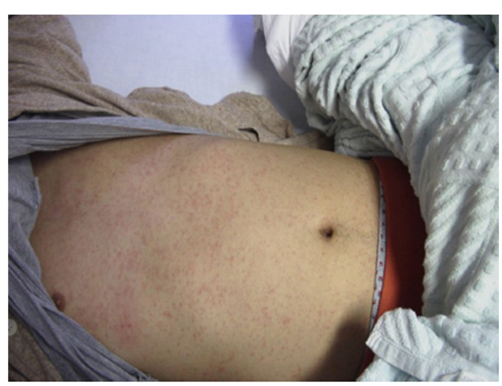

Fig. 1 An adult male with a maculopapular, truncal rash. From Hirai et al. [13] with permission

8 weeks. Reexposure to measles induces a strong anamnestic immune response with a rapid boosting of IgG antibodies, preventing clinical disease [3]. Measles virus can be isolated from conventional clinical specimens (nasopharyngeal swab, urine, or peripheral blood mononuclear cells) up to 5 days following onset of the rash and may be detected using polymerase chain reaction (PCR) assays on specimens obtained up to 7 days or more after onset of the rash [14].

Complications

Measles infects multiple systems and targets epithelial, reticuloendothelial, and white blood cells [15]. Complications, when they occur, arise largely by disruption of epithelial surfaces of different organ systems and immunosuppression [16–18]. Approximately 30 % of reported cases of measles involve one or more complications. In developed countries, these include otitis media (7–9 %), pneumonia (1–6 %), diarrhea (6 %), blindness, and post-infectious encephalitis (1 per 1000 cases). The risk of serious measles complications is higher in infants and adults [19]. A summary of complications from measles adapted from an excellent review by Perry and Halsey [20] is listed in Table 1.

Measles and its associated complications can be severe in certain populations, such as those with underlying immune deficiencies. In fact, with the rise in measles incidence, it now has to be considered among the reemerging viruses in the transplant population. The incidence of measles in transplant recipients, as well as the proportion with severe disease, is unclear. Two series identified two cases of interstitial pneumonia (one fatal) among 24 hematopoietic stem cell transplantation (HSCT) recipients diagnosed with measles [35]. Subacute measles encephalitis (SME) has also been reported in renal transplant recipients and a single HSCT recipient. The clinical course is one of deteriorating mental status and treatment-refractory seizures [35]. Four of six transplant cases of SME died [36]. Among patients with HIV, case reports validate the severity of measles and its unusual presentation. In particular, several case reports document a delayed, uncharacteristic, or absent rash and the frequent occurrence of pneumonitis in both HIV-infected children [37–41] and adults [37, 42–44] with measles.

Treatment

Like other viral illnesses, the treatment of measles is supportive. There is no specific antiviral therapy for measles. However, the WHO provides guidance for the use of vitamin A for severe measles cases among children, such as those who are hospitalized [45].

Measles Vaccine: Impact, Indications, Efficacy, and Adverse Effects

The measles vaccine is one of the most cost-effective health interventions developed. Before its discovery, infection with measles virus was nearly universal during childhood, and more than 90 % of persons had immunity from the disease by age 15 years. Measles occurred in epidemic cycles and an estimated three to four million persons acquired measles each year [46]. In the USA, approximately 500,000 persons with measles were reported each year, of whom 500 died, 48,000 were hospitalized, and another 1000 had permanent brain damage from measles encephalitis [47]. With its inception, the number of reported measles cases decreased dramatically, with the greatest decrease occurring among children aged <10 years [48, 49].

The measles vaccine, a live-attenuated vaccine, has been available for use since 1963. In that year, both an inactivated ("killed") and a live attenuated vaccine (Edmonston B strain) were licensed for use in the USA. The inactivated vaccine was withdrawn in 1967 because it was not protective, and recipients

Table 1 Complications associated with measles by organ system (adapted from [20], with permission)

Organ system, reference	Complications
Respiratory [21–23]	Otitis media, mastoiditis, croup (laryngotracheobronchitis), tracheitis, pneumonia, pneumothorax, mediastinal emphysema
Neurological [24]	Febrile convulsions, encephalitis, post-infectious encephalitis, inclusion body encephalitis in immunocompromised persons, subacute sclerosing pan encephalitis (SSPE), Guillain-Barre' syndrome, Reye's syndrome, transverse myelitis
Gastrointestinal [25–28]	Diarrhea (enteritis), mesenteric adenitis, appendicitis, hepatitis, pancreatitis, stomatitis, noma (cancrum oris)
Ophthalmic [29]	Keratitis, corneal ulceration, corneal perforation, central vein occlusion, blindness
Hematologic [30]	Thrombocytopenic purpura, disseminated intravascular coagulation (DIC)
Cardiovascular [31, 32]	Myocarditis, pericarditis
Dermatologic [27, 28]	Severe desquamation, cellulitis
Other [33, 34]	Hypocalcemia, myositis, nephritis, renal failure, malnutrition, death

frequently developed a unique syndrome, called atypical measles. Over time, there have been further modifications to the original Edmonston B strain to reduce adverse effects, and the Edmonston-Enders strain is currently in use [50].

The measles vaccine was first recommended as a single-dose vaccine. However, measles outbreaks among school-aged children who received one dose of measles vaccine prompted changes in recommendations from a single-dose vaccine to two doses of measles-containing vaccine, preferably as MMR [51]. To date, it is recommended that all US residents born after 1956 should ensure that they receive MMR vaccine or have serologic evidence of measles immunity (Table 2). Vaccine recommendations for those born after 1956 and travelling out of the USA who do not have serologic evidence of immunity include the following: two doses of MMR given subcutaneously, separated by at least 28 days for adults and children aged ≥12 months. Infants age 6–11 months who receive one dose of MMR vaccine should still receive a second dose at ≥1 year [50]. The vaccine is contraindicated in anyone with a history of anaphylactic reactions to neomycin, history of severe allergic reaction to any component of the MMR vaccine, pregnancy, and immunosuppression. A thorough discussion of the contraindications is available in the Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP) [50].

Given as a single dose, the measles-containing vaccine administered at age ≥12 months is approximately 94 % effective in preventing measles (range 39–98 %) [52, 53]. The effectiveness of two doses of measles-containing vaccine was ≥99 % in two studies conducted in the USA and 67, 85–≥94, and 100 %, in three studies in Canada [52, 54–57]. Vaccine effectiveness was higher among children given the vaccine at age ≥15 months compared to 12 months [54], belying the importance of timing. Similar estimates of vaccine effectiveness have been reported from Australia and Europe [53]. The measles vaccine induces long lasting immunity in most persons, based on serologic and immunologic data [58]. Approximately 95 % of vaccinated persons examined 11 years after initial vaccination and 15 years after the second dose of MMR (containing the Enders-Edmonston strain) vaccine had detectable antibodies to measles [59–62].

Apart from the MMR vaccine, an aerosolized vaccine against measles is also available and has been used by more than four million children in Mexico since 1980 [63]. However, its efficacy compared to the subcutaneous vaccine has been questioned. A randomized controlled trial published recently in the New England Journal [64] showed that the aerosolized vaccine is immunogenic, but based on predetermined margins, was inferior to the MMR vaccine in terms of antibody seropositivity.

MMR vaccine is generally well tolerated and is rarely associated with serious adverse events. It may cause fever (<15 %), transient rashes (5 %), lymphadenopathy (5 % of children and 20 % of adults), or parotitis (<1 %) [65–69]. The majority of persons vaccinated are otherwise asymptomatic. A recent Cochrane review validates these findings [70]. In persons with immune deficiencies, that are inadvertently given the vaccine, there is evidence that supports a causal relation between MMR vaccination and anaphylaxis, febrile seizures, thrombocytopenic purpura, transient arthralgia, and measles inclusion body encephalitis [71–75], although these are rare. The concern that measles vaccine is causally

Table 2 Acceptable presumptive evidence of immunity to measles (adapted from [50])

Routine	High school	Health care providers	International travelers
Documentation of age-appropriate vaccination with a live measles virus-containing vaccine[a]: A. Preschool-aged children: one dose B. School-aged children (grades K-12): two doses C. Adults not at high risk[d]: one dose	Documentation of vaccination with two doses of live measles virus-containing vaccine[a]		Documentation of age-appropriate vaccination with a live measles virus-containing vaccine: A. Infants aged 6–11 months[c]: one dose B. Persons aged ≥12 months[a]: two doses
OR, Laboratory evidence of immunity[b]			
OR, Laboratory confirmation of disease			
OR, Born before 1957[e]			

[a] The first dose of MMR vaccine should be administered at age ≥12 months; the second dose of measles- or mumps-containing vaccine should be administered no earlier than 28 days after the first dose

[b] Measles, rubella, or mumps immunoglobulin G (IgG) in serum; equivocal results should be considered negative

[c] Children who receive a dose of MMR vaccine at age <12 months should be revaccinated with two doses of MMR vaccine: the first of which should be administered when the child is aged 12 through 15 months and the second at least 28 days later. If the child remains in an area where disease risk is high, the first dose should be administered at age 12 months

[d] Adults at high risk include students in post-high school educational institutions, health care personnel, and international travelers

[e] For unvaccinated health care personnel born before 1957 who lack laboratory evidence of measles, rubella, or mumps immunity or laboratory confirmation of disease, health care facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval (for measles and mumps) and one dose of MMR vaccine (for rubella), respectively

associated with autism spectrum disorders is not borne out by science [76–78] although the myth continues to be pervasive.

Reemergence of Measles

In the last few years, measles has resurfaced in areas where it is considered rare, or eliminated. These measles outbreaks are alarming, and the reasons behind them must be thoroughly evaluated. Often, outbreaks of vaccine-preventable diseases occur when vaccination rates fall below a certain threshold, placing the community at risk. This so-called threshold theorem [74, 79] underlies the concept of "herd immunity." Herd immunity can be thought of as a threshold level of immunity in the population above which a disease no longer spreads. For measles, the level of immunity needed to interrupt transmission is higher than the thresholds for almost all other vaccine-preventable diseases—to prevent sustained spread of the measles virus, 92 to 94 % of the community must be protected [80].

Vaccine coverage among certain populations both in the USA and Europe has waned over the last several years. Parental concerns about vaccine safety issues, such as the association between vaccines and autism, though not supported by a credible body of scientific evidence [81–84], have led increasing numbers of parents to refuse or delay their children's vaccination [85, 86]. This is alarming, as children with nonmedical exemptions are at increased risk for acquiring and transmitting vaccine-preventable diseases [87]. In a retrospective cohort study, for example, children who were unvaccinated were 35 times as likely to contract measles as nonexempt children (relative risk, 35; 95 % confidence interval [CI], 34 to 37) [88]. Other studies [87, 89] have confirmed that areas with high rates of vaccine refusal are at increased risk of outbreaks (2–22 times higher risk of disease outbreak, depending on the disease).

Outbreaks of vaccine-preventable disease often start among persons who refuse vaccination, then spread rapidly within unvaccinated populations (the herd), and subsequently involve other subpopulations. To illustrate, the most recent multistate outbreak of measles in the USA began with an unvaccinated person at Disneyland in California. Among 110 patients, 49 (45 %) were unvaccinated and another 43 % had unknown or undocumented vaccination status [90]. An article from the New England Journal [80] emphasizes that to prevent measles from reestablishing itself as an endemic disease in the USA, the vaccine must be accessible to all who need it—especially to people traveling to and from countries with circulating disease—and hesitant patients and families must be convinced the vaccine is safe and effective.

Carrillo-Santisteve and Lopalco [91] provide some insight regarding the difficulty in convincing patients about the importance of vaccination. They introduce the concept of vaccine paradox, in which vaccines are the victims of their own success. When vaccination coverage increases, a dramatic decrease in the incidence of disease follows, in turn, leading to a decrease in the perceived risk of the disease and its complications. As the disease (such as measles) is no longer remembered as dangerous, real or alleged vaccine adverse events become disproportionately highlighted. These vaccine risks are emphasized and propagated by a relatively few, yet very loud antivaccination proponents, who use several methods [92] to create fear and doubt about vaccine safety. In fact, the most frequent reason for nonvaccination, in a survey among parents of school-aged children, was concern that the vaccine might cause harm [93].

In order to curb the rise of measles and other vaccine-preventable diseases, some health care providers have considered terminating their provider relationship with families that refuse vaccines [94, 95]. In a national survey of members of the American Academy of Pediatrics (AAP), almost 40 % of respondents said that they would not provide care to a family that refused all vaccines, and 28 % said that they would not provide care to a family that refused some vaccines [94]. However, the academy's Committee on Bioethics advises against discontinuing care for families that decline vaccines and has recommended that pediatricians "share honestly what is and is not known about the risks and benefits of the vaccine in question [96]."

So what can be done to help prevent the reestablishment of measles as an endemic disease? Health care providers play a pivotal role in parental decision-making with regard to immunization. Health care providers are cited by parents, including parents of unvaccinated children, as the most frequent source of information about vaccination [93]. In fact, in a study of the knowledge, attitudes, and practices of primary care providers, a high proportion of those providing care for children whose parents refused vaccination and those providing care for appropriately vaccinated children were both found to have favorable opinions of vaccines [97]. However, those providing care for unvaccinated children had less confidence in vaccine safety and less likely to perceive vaccines as benefitting individuals and communities, underscoring the importance of the provider's advocacy for and knowledge regarding vaccination.

From a public health perspective, improving the quality of vaccine supply, advocacy activities among vaccine decision makers, and activities involving the general public, should be put in place in order to increase the demand for measles vaccination and immunization in general [91]. Campaigns to increase awareness about the disease itself are likewise paramount—early recognition of measles by clinicians is key in making sure that appropriate infection control procedures are followed to prevent disease spread.

Conclusion

Measles remains a leading cause of death among young children worldwide despite the availability of a very effective vaccine. It is a highly contagious disease, and early recognition of the classic presentation of a febrile illness preceded by cough, coryza, and conjunctivitis is necessary to help prevent spread. The multiple outbreaks that have occurred in certain regions of the world where measles is no longer endemic are very alarming and are likely from poor vaccine coverage. Interventions to address low vaccination rates and vaccine hesitancy are urgently needed. Efforts to increase awareness about the disease and strengthening vaccine advocacy are imperative in order to prevent it from reestablishing itself as an endemic disease.

Compliance with Ethics Guidelines

Conflict of Interest Nasia Safdar and Cybele Abad have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

1. Clemmons NS, Gastanaduy PA, Fiebelkorn AP, Redd SB, Wallace GS. Measles—United States, January 4–April 2, 2015. MMWR Morb Mortal Wkly Rep. 2015;64:373–6.
2. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet. 2012;379:2173–8.
3. World Health Organization. Global measles and rubella strategic plan: 2012–2020. Geneva, 2012.
4. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. J Infect Dis. 2004;189 Suppl 1: S43–7.
5. Plotkin SA OW, Offit PA, eds. Vaccines. 6th ed. Philadelphia: Elsevier, 2012; 2012.
6. Centers for Disease Control and Prevention. Measles (rubeola): for healthcare professionals. 2014. http://www.cdc.gov/measles/hcp/index.html.
7. World Health Organization (WHO) Regional Office for Europe. Guidelines for measles and rubella outbreak investigation and response in the WHO European Region. Copenhagen: WHO. 2013. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/217164/OutbreakGuidelines-updated.pdf.
8. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report: Reporting on 2011 surveillance data and 2012 epidemic intelligence data. Stockholm: ECDC. 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf.
9. Pegorie M, Shankar K, Welfare WS, et al. Measles outbreak in Greater Manchester, England, October 2012 to September 2013: epidemiology and control. Euro Surveill. 2014;19.
10. Mason WH. Measles. In: Kliegman RMBR, Jenson HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007. p. 1331–7.
11. United States Centers for Disease Control and Prevention. Measles. In: Atkinson W, editor. Epidemiology and prevention of vaccine-preventable diseases. 12th ed. Washington, DC: Public Health Foundation; 2011. p. 173–92.
12. Strebel PM. Measles vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. Philadelphia: Saunders-Elsevier; 2008. p. 353–98.
13. Hirai Y, Asahata S, Ainoda Y, Fujita T, Kawashima M, Totsuka K. Truncal rash in adult measles. Int J Infect Dis. 2014;20:80–1.
14. WHO Expanded Programme on Immunization. Manual for the laboratory diagnosis of measles and rubella virus infection, 2nd ed. Geneva, World Health Organization, 2006 (http://www.who.int/immunization_monitoring/LabManualFinal.pdf).
15. Roberts GB, Bain AD. The pathology of measles. J Pathol Bacteriol. 1958;76:111–8.
16. Atabani SF, Byrnes AA, Jaye A, et al. Natural measles causes prolonged suppression of interleukin-12 production. J Infect Dis. 2001;184:1–9.
17. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles virus infection: an hypothesis for altered immune responses. J Infect Dis. 1994;170 Suppl 1:S24–31.
18. Schneider-Schaulies S, ter Meulen V. Pathogenic aspects of measles virus infections. Arch Virol Suppl. 1999;15:139–58.
19. Strebel PM. Measles vaccine. In: Plotkin SAOW, Offit PA, editors. Vaccines. 5th ed. Philadelphia: Saunders-Elsevier; 2008. p. 353–98.
20. Perry RT, Halsey NA. The clinical significance of measles: a review. J Infect Dis. 2004;189 Suppl 1:S4–16.
21. Crosse BA. Subcutaneous and mediastinal emphysema complication of measles. J Infect. 1989;19:190.
22. Markowitz LE, Nieburg P. The burden of acute respiratory infection due to measles in developing countries and the potential impact of measles vaccine. Rev Infect Dis. 1991;13 Suppl 6:S555–61.
23. Sharma A. A rare complication of measles: subcutaneous and mediastinal emphysema. J Trop Med Hyg. 1993;96:169–71.
24. Johnson RT. Inflammatory and demyelinating diseases. In: Johnson RT, editor. Viral infections of the nervous system. 2nd ed. Philadelphia: Lippincott-Raven; 1998. p. 227–64.
25. Cohen N, Golik A, Blatt A, et al. Pancreatic enzyme elevation in measles. J Clin Gastroenterol. 1994;19:292–5.
26. Koster FT, Curlin GC, Aziz KM, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bull World Health Organ. 1981;59:901–8.
27. Morley DC. Measles in the developing world. Proc R Soc Med. 1974;67:1112–5.
28. Cherry JD. Measles. In: Feigin RD, Cherry JD, editors. Textbook of pediatric infectious diseases. 4th ed. Philadelphia: WB Saunders; 1988. p. 2054–74.
29. Sommer A. Xerophthalmia, keratomalacia and nutritional blindness. Int Ophthalmol. 1990;14:195–9.
30. Hudson JB, Weinstein L, Chang TW. Thrombocytopenic purpura in measles. J Pediatr. 1956;48:48–56.
31. Gavish D, Kleinman Y, Morag A, Chajek-Shaul T. Hepatitis and jaundice associated with measles in young adults. An analysis of 65 cases. Arch Intern Med. 1983;143:674–7.
32. Leibovici L, Sharir T, Kalter-Leibovici O, Alpert G, Epstein LM. An outbreak of measles among young adults. Clinical and laboratory features in 461 patients. J Adolesc Health Care. 1988;9:203–7.
33. Casanova-Cardiel LJ, Hermida-Escobedo C. Measles in the young adult. Clinical features of 201 cases. Rev Investig Clin. 1994;46:93–8.
34. Wairagkar NS, Gandhi BV, Katrak SM, et al. Acute renal failure with neurological involvement in adults associated with measles virus isolation. Lancet. 1999;354:992–5.
35. Waggoner J, Deresinski S. Rare and emerging viral infection in the transplant population. In: Safdar A, editor. Principles and practice of transplant infectious diseases. Berlin: Springer Medizin; 2013.
36. Turner A, Jeyaratnam D, Haworth F, et al. Measles-associated encephalopathy in children with renal transplants. Am J Transplant. 2006;6:1459–65.

37. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA. 1992;267:1237–41.
38. Krasinski K, Borkowsky W. Measles and measles immunity in children infected with human immunodeficiency virus. JAMA. 1989;261:2512–6.
39. Nadel S, McGann K, Hodinka RL, Rutstein R, Chatten J. Measles giant cell pneumonia in a child with human immunodeficiency virus infection. Pediatr Infect Dis J. 1991;10:542–4.
40. Palumbo P, Hoyt L, Demasio K, Oleske J, Connor E. Population-based study of measles and measles immunization in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 1992;11:1008–14.
41. Rudy BJ, Rutstein RM, Pinto-Martin J. Responses to measles immunization in children infected with human immunodeficiency virus. J Pediatr. 1994;125:72–4.
42. Forni AL, Schluger NW, Roberts RB. Severe measles pneumonitis in adults: evaluation of clinical characteristics and therapy with intravenous ribavirin. Clin Infect Dis. 1994;19:454–62.
43. Ross LA, Kim KS, Mason Jr WH, Gomperts E. Successful treatment of disseminated measles in a patient with acquired immunodeficiency syndrome: consideration of antiviral and passive immunotherapy. Am J Med. 1990;88:313–4.
44. Stogner SW, King JW, Black-Payne C, Bocchini J. Ribavirin and intravenous immune globulin therapy for measles pneumonia in HIV infection. South Med J. 1993;86:1415–8.
45. WHO guidelines for epidemic preparedness and response to measles outbreaks. 1999. Accessed 1 June 2015, at http://www.who.int/csr/resources/publications/measles/WHO_CDS_CSR_ISR_99_1/en/.
46. Moss WJ, Griffin DE. Measles. Lancet. 2012;379:153–64.
47. Bloch AB, Orenstein WA, Stetler HC, et al. Health impact of measles vaccination in the United States. Pediatrics. 1985;76:524–32.
48. Hinman AR, Brandling-Bennett AD, Nieburg PI. The opportunity and obligation to eliminate measles from the United States. JAMA. 1979;242:1157–62.
49. Hinman AR, Orenstein WA, Papania MJ. Evolution of measles elimination strategies in the United States. J Infect Dis. 2004;189 Suppl 1:S17–22.
50. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62:1–34.
51. Measles prevention. MMWR Morb Mortal Wkly Rep 1989;38 Suppl 9:1–18.
52. De Serres G, Boulianne N, Defay F, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12–14 months versus 15 months of age. Clin Infect Dis. 2012;55:394–402.
53. Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. J Infect Dis. 2011;204 Suppl 1:S133–48.
54. De Serres G, Boulianne N, Meyer F, Ward BJ. Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. Epidemiol Infect. 1995;115:315–23.
55. Sutcliffe PA, Rea E. Outbreak of measles in a highly vaccinated secondary school population. CMAJ. 1996;155:1407–13.
56. Vitek CR, Aduddell M, Brinton MJ, Hoffman RE, Redd SC. Increased protections during a measles outbreak of children previously vaccinated with a second dose of measles-mumps-rubella vaccine. Pediatr Infect Dis J. 1999;18:620–3.
57. Yeung LF, Lurie P, Dayan G, et al. A limited measles outbreak in a highly vaccinated US boarding school. Pediatrics. 2005;116:1287–91.
58. Markowitz LE, Preblud SR, Fine PE, Orenstein WA. Duration of live measles vaccine-induced immunity. Pediatr Infect Dis J. 1990;9:101–10.
59. Davidkin I, Jokinen S, Broman M, Leinikki P, Peltola H. Persistence of measles, mumps, and rubella antibodies in an MMR-vaccinated cohort: a 20-year follow-up. J Infect Dis. 2008;197:950–6.
60. LeBaron CW, Beeler J, Sullivan BJ, et al. Persistence of measles antibodies after 2 doses of measles vaccine in a postelimination environment. Arch Pediatr Adolesc Med. 2007;161:294–301.
61. Markowitz LE, Albrecht P, Orenstein WA, Lett SM, Pugliese TJ, Farrell D. Persistence of measles antibody after revaccination. J Infect Dis. 1992;166:205–8.
62. Ward BJ, Boulianne N, Ratnam S, Guiot MC, Couillard M, De Serres G. Cellular immunity in measles vaccine failure: demonstration of measles antigen-specific lymphoproliferative responses despite limited serum antibody production after revaccination. J Infect Dis. 1995;172:1591–5.
63. Fernandez-de Castro J, Kumate-Rodriguez J, Sepulveda J, Ramirez-Isunza JM, Valdespino-Gomez JL. Measles vaccination by the aerosol method in Mexico. Salud Publica Mex. 1997;39:53–60.
64. Low N, Bavdekar A, Jeyaseelan L, et al. A randomized, controlled trial of an aerosolized vaccine against measles. N Engl J Med. 2015;372:1519–29.
65. Dos Santos BA, Ranieri TS, Bercini M, et al. An evaluation of the adverse reaction potential of three measles-mumps-rubella combination vaccines. Rev Panam Salud Publica. 2002;12:240–6.
66. Gatchalian S, Cordero-Yap L, Lu-Fong M, et al. A randomized comparative trial in order to assess the reactogenicity and immunogenicity of a new measles mumps rubella (MMR) vaccine when given as a first dose at 12–24 months of age. Southeast Asian J Trop Med Public Health. 1999;30:511–7.
67. Grillner L, Hedstrom CE, Bergstrom H, Forssman L, Rigner A, Lycke E. Vaccination against rubella of newly delivered women. Scand J Infect Dis. 1973;5:237–41.
68. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. Lancet. 1986;1:939–42.
69. Weibel RE, Carlson Jr AJ, Villarejos VM, Buynak EB, McLean AA, Hilleman MR. Clinical and laboratory studies of combined live measles, mumps, and rubella vaccines using the RA 27/3 rubella virus. Proc Soc Exp Biol Med. 1980;165:323–6.
70. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2012;2, CD004407.
71. Evidence concerning rubella vaccines and arthritis, radiculoneuritis, and thrombocytopenic purpura. Adverse effects of pertussis and rubella vaccines: a report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. In: Howson CP, Howe CJ, HVF, editors. Institute of Medicine. Washington, DC: National Academy Press; 1991:187–205.
72. Measles and mumps vaccines. Adverse events associated with childhood vaccines evidence bearing on causality. In: Stratton KR, Howe CJ, Johnston RBJ, editors. Institute of Medicine. Washington, DC: National Academy Press; 1994:118–86.
73. Immunization safety review: measles-mumps-rubella vaccine and autism. In: Stratton K, Gable A, Shetty P, M M, editors. Institute of Medicine. Washington, DC: National Academy Press; 2001.
74. Immunization safety review: vaccines and autism Institute of Medicine. Washington, DC: National Academy Press; 2004.
75. Measles, mumps, and rubella vaccine. Adverse effects of vaccines: evidence and causality Institute of Medicine Washington, DC; The National Academies Press; 2012.
76. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or

developmental regression in children with autism: population study. BMJ. 2002;324:393–6.
77. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351:637–41.
78. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med. 2002;347:1477–82.
79. Daley DJ, Gani J. Epidemic modelling: an introduction Cambridge. United Kingdom: Cambridge University Press; 1999.
80. Orenstein W, Seib K. Mounting a good offense against measles. N Engl J Med. 2014;371:1661–3.
81. DeStefano F. Vaccines and autism: evidence does not support a causal association. Clin Pharmacol Ther. 2007;82:756–9.
82. Doja A, Roberts W. Immunizations and autism: a review of the literature. Can J Neurol Sci. 2006;33:341–6.
83. Fombonne E. Are measles infections or measles immunizations linked to autism? J Autism Dev Disord. 1999;29:349–50.
84. Fombonne E, Cook EH. MMR and autistic enterocolitis: consistent epidemiological failure to find an association. Mol Psychiatry. 2003;8:133–4.
85. Offit PA. Vaccines and autism revisited—the Hannah Poling case. N Engl J Med. 2008;358:2089–91.
86. Smith MJ, Ellenberg SS, Bell LM, Rubin DM. Media coverage of the measles-mumps-rubella vaccine and autism controversy and its relationship to MMR immunization rates in the United States. Pediatrics. 2008;121:e836–43.
87. Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. JAMA. 2000;284:3145–50.
88. Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. JAMA. 1999;282:47–53.
89. Omer SB, Enger KS, Moulton LH, Halsey NA, Stokley S, Salmon DA. Geographic clustering of nonmedical exemptions to school immunization requirements and associations with geographic clustering of pertussis. Am J Epidemiol. 2008;168:1389–96.
90. Zipprich J, Winter K, Hacker J, Xia D, Watt J, Harriman K. Measles outbreak—California, December 2014-February 2015. MMWR Morb Mortal Wkly Rep. 2015;64:153–4.
91. Carrillo-Santisteve P, Lopalco PL. Measles still spreads in Europe: who is responsible for the failure to vaccinate? Clin Microbiol Infect. 2012;18 Suppl 5:50–6.
92. Kata A. Anti-vaccine activists, Web 2.0, and the postmodern paradigm—an overview of tactics and tropes used online by the anti-vaccination movement. Vaccine. 2012;30:3778–89.
93. Salmon DA, Moulton LH, Omer SB, DeHart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case–control study. Arch Pediatr Adolesc Med. 2005;159:470–6.
94. Flanagan-Klygis EA, Sharp L, Frader JE. Dismissing the family who refuses vaccines: a study of pediatrician attitudes. Arch Pediatr Adolesc Med. 2005;159:929–34.
95. Freed GL, Clark SJ, Hibbs BF, Santoli JM. Parental vaccine safety concerns. The experiences of pediatricians and family physicians. Am J Prev Med. 2004;26:11–4.
96. Diekema DS. Responding to parental refusals of immunization of children. Pediatrics. 2005;115:1428–31.
97. Salmon DA, Pan WK, Omer SB, et al. Vaccine knowledge and practices of primary care providers of exempt vs. vaccinated children. Hum Vaccin. 2008;4:286–91.