SUPPLEMENT ARTICLE

The Clinical Significance of Measles: A Review

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Forty years after effective vaccines were licensed, measles continues to cause death and severe disease in children worldwide. Complications from measles can occur in almost every organ system. Pneumonia, croup, and encephalitis are common causes of death; encephalitis is the most common cause of long-term sequelae. Measles remains a common cause of blindness in developing countries. Complication rates are higher in those <5 and >20 years old, although croup and otitis media are more common in those <2 years old and encephalitis in older children and adults. Complication rates are increased by immune deficiency disorders, malnutrition, vitamin A deficiency, intense exposures to measles, and lack of previous measles vaccination. Case-fatality rates have decreased with improvements in socioeconomic status in many countries but remain high in developing countries.

Before the introduction of measles vaccines, measles virus infected 95%–98% of children by age 18 years [1–4], and measles was considered an inevitable rite of passage. Exposure was often actively sought for children in early school years because of the greater severity of measles in adults.

CHARACTERISTIC ILLNESS

After an incubation period of 8–12 days, measles begins with increasing fever (to 39°C–40.5°C) and cough, coryza, and conjunctivitis [5, 6]. Symptoms intensify over the 2–4 days before the onset of rash and peak on the first day of rash [7]. The rash is usually first noted on the face and neck, appearing as discrete erythematous patches 3–8 mm in diameter. The lesions increase in number for 2 or 3 days, especially on the trunk and the face, where they frequently become confluent (figure 1). Discrete lesions are usually seen on the distal extremities, and with careful observation, small numbers of lesions can be found on the palms of 25%–50% of those infected. The rash lasts for 3–7 days and then fades in the same manner as it appeared, sometimes ending with a fine desquamation that may go unnoticed in children who are bathed daily. An exaggerated desquamation is commonly seen in malnourished children [6, 9, 10]. Fever usually persists for 2 or 3 days after the onset of the rash, and the cough may persist for as many as 10 days.

Koplik's spots usually appear 1 day before the onset of rash and persist for 2 or 3 days. These bluish-white, slightly raised, 2- to 3-mm-diameter lesions on an erythematous base appear on the buccal mucosa, usually opposite the first molar, and occasionally on the soft palate, conjunctiva, and vaginal mucosa [11, 12]. Koplik's spots have been reported in 60%–70% of persons with measles but are probably present in most persons who develop measles [13]. An irregular blotchy enanthem may be present in other areas of the buccal mucosa. Photophobia from iridocyclitis, sore throat, headache, abdominal pain, and generalized mild lymphadenopathy are also common.

Measles is transmitted by the respiratory route and is highly infectious. Infectivity is greatest in the 3 days before the onset of rash, and 75%–90% of susceptible household contacts develop the disease [14–16]. The early prerash symptoms are similar to those of other common respiratory illnesses, and affected persons often participate in routine social activities, facilitating

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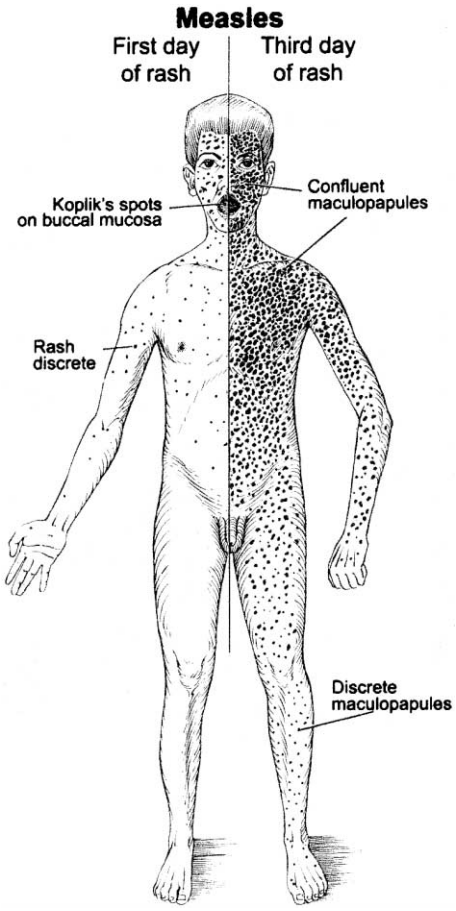

Figure 1. Development and distribution of measles rash. Reprinted with permission from [8].

transmission. Numerous outbreaks of disease in highly vaccinated populations occur when children in the first few days of illness attend sporting events as participants or spectators, especially indoor events such as basketball and wrestling tournaments [17–21]. Outbreaks also occur when ill children are brought to a doctor's office or emergency room for evaluation for fever, irritability, or rash [22, 23].

MILD, MODIFIED, AND ATYPICAL MEASLES

Milder forms of measles occur in children and adults with preexisting partial immunity. Infants who have low levels of passively acquired maternal antibody and persons who receive blood products that contain antibody often have subclinical infections or minimal symptoms that may not be diagnosed as measles [24–26]. Vaccination protects >90% of recipients against disease, but after exposure to natural measles, some vaccinees develop boosts in antibody associated with mild symptoms and may have rash with little or no fever or nonspecific respiratory symptoms [27–32]. People with inapparent subclinical measles virus infections are not known to transmit measles virus to household contacts [33].

Atypical measles occurred in children who received formalin-inactivated (killed) measles vaccine that was in use in the United States from 1963 to 1968 [34]. These children developed high fever, a rash that was most prominent on the extremities and often included petechiae, and a high rate of pneumonitis [34–36]. Recent studies in monkeys indicate that this illness was caused by antigen-antibody immune complexes resulting from incomplete maturation of the antibody response to the vaccine [37, 38].

COMPLICATIONS

Measles virus infects multiple organ systems and targets epithelial, reticuloendothelial, and white blood cells, including monocytes, macrophages, and T lymphocytes [39]. Pathological studies of children dying during acute measles have found multinucleated giant cells typical of measles virus infection throughout the respiratory and gastrointestinal tracts and in most lymphoid tissues [40–51]. Measles virus infection leads to a decline in CD4 lymphocytes, starting before the onset of rash and lasting for up to 1 month, and resulting in suppression of delayed-type hypersensitivity as measured by anergy to skin test antigens, including tuberculosis antigen [52–56]. Whether measles predisposes to reactivation of latent *Mycobacterium tuberculosis* infections has been a subject of debate [57].

Complications from measles have been reported in every organ system (table 1). Many of these complications are caused by disruption of epithelial surfaces and immunosuppression [70–72]. Rates of complications from measles vary by age (table 2) and underlying conditions.

RESPIRATORY COMPLICATIONS

Otitis media. Otitis media is the most common complication of measles reported in the United States and occurs in 14% of children <5 years old (table 2). Presumably, inflammation of the epithelial surface of the eustachian tube causes obstruction and secondary bacterial infection. Lower rates of otitis media are noted with increasing age, most likely a function of the increasing diameter of the eustachian tube and the decreasing risk of obstruction.

Laryngotracheobronchitis. Laryngotracheobronchitis or "measles croup" was noted in 9%–32% of US children hospitalized with measles [73–78]. The majority of affected children were <2 years old. In one-third to one-half of such cases, culture of samples from the trachea yields positive results for bacterial pathogens, with a purulent exudate and evidence of secondary bacterial tracheitis, pneumonia, or both. The most commonly cultured organism is *Staphylococcus aureus,* although *Strepto-*

Table 1. Complications associated with measles by organ system.

Organ system, reference	Complications
Respiratory [58–60]	Otitis media, mastoiditis, croup (laryngotracheobronchitis), tracheitis, pneumonia, pneumothorax, mediastinal emphysema
Neurological [61]	Febrile convulsions, encephalitis, postinfectious encephalitis, inclusion body encephalitis in immunocompromised persons, subacute sclerosing pan encephalitis, Guillain-Barré syndrome, Reye's syndrome, transverse myelitis
Gastrointestinal [10, 39, 62, 63]	Diarrhea (enteritis), mesenteric adenitis, appendicitis, hepatitis, pancreatitis, stomatitis, noma (cancrum oris)
Ophthalmic [64]	Keratitis, corneal ulceration, corneal perforation, central vein occlusion, blindness
Hematologic [65]	Thrombocytopenic purpura, disseminated intravascular coagulation
Cardiovascular [39, 66, 67]	Myocarditis, pericarditis
Dermatologic [10]	Severe desquamation, cellulitis
Other [68, 69]	Hypocalcemia, myositis, nephritis, renal failure, malnutrition, death

coccus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Escherichia coli, and *Enterobacter* species have also been identified [74, 76–79]. In a series of 6 children intubated because of measles croup, viral cultures revealed that 1 child was coinfected with adenovirus and another with herpes simplex virus (HSV) [74]. Laryngotracheobronchitis was the second most common cause of death in US children hospitalized with measles, after pneumonia [73–79].

Pneumonia. Measles infects the respiratory tracts of nearly all affected persons. Pneumonia is the most common severe complication of measles and accounts for most measles-associated deaths [80]. In studies of unselected hospitalized children with measles, 55% had radiographic changes of bronchopneumonia, consolidation, or other infiltrates; 77% of children with severe disease and 41% of children with mild disease had radiographic changes [81]. In recent years, pneumonia was present in 9% of children <5 years old with measles in the United States (table 2), in 0%–8% of cases during outbreaks [82–87], and in 49%–57% of adults [88, 89].

Pneumonia may be caused by measles virus alone, secondary viral infection with adenovirus or HSV, or secondary bacterial infection [39, 80, 90]. Measles is one cause of Hecht's giant cell pneumonia, which usually occurs in immunocompromised persons but can occur in otherwise normal adults and children [46, 91–94]. Studies that included culture of blood, lung punctures, or tracheal aspirations revealed bacteria as the cause of 25%–35% of measles-associated pneumonia. *S. pneumoniae, S. aureus,* and *H. influenzae* were the most commonly isolated organisms [39, 80]. Other bacteria (e.g., *Pseudomonas* species, *Klebsiella pneumoniae,* and *E. coli*) are less common causes of severe pneumonia associated with measles. In studies of young adult military recruits with pneumonia associated with measles, *Neisseria meningitidis* was a probable cause in some cases [85, 95].

Pneumomediastinum and mediastinal emphysema have been reported as complications of measles in several countries [58, 60, 90, 96]. Some children have the clinical pattern of bronchiolitis [39]. Because viral cultures are not always done, the possibility of coinfection with other respiratory viruses cannot be ruled out.

Measles pneumonia in immunocompromised patients. Among immunocompromised persons, diffuse progressive pneumonitis caused by the measles virus is the most common cause of death [97–104]. These patients may first have typical measles with pneumonia, or they may have a nonspecific illness without rash followed by pneumonitis without a rash. In general, signs of pneumonitis develop in the 2 weeks after the first onset of symptoms [90, 96, 105]. Other patients have had reappearance of rash and pneumonitis after long intervals following "classical" measles [97, 106].

GASTROINTESTINAL COMPLICATIONS

Measles probably infects the intestinal tracts of most persons with measles. A gastric biopsy obtained the day before rash onset from a 44-year-old man revealed characteristic giant cells that were positive for measles by immunologic staining, and 8 of 10 children exposed to the man subsequently developed measles [51]. Several cases of appendicitis have developed before and during measles rash, and characteristic giant cells typical for measles have been found in appendix tissue [42, 43, 45, 107–109].

Diarrhea. In the United States, 8% of all reported measles cases during 1987–2000 were complicated by diarrhea. Rates were higher in those <5 or >30 years old (table 2). Among hospitalized persons with measles in the United States, 30%–70% had diarrhea [73–78, 88, 89]. Feachem and Koblinsky [110] found that 15%–63% of measles cases from community-based studies from developing countries in the prevaccine era were complicated by diarrhea and that 9%–77% of all diarrheal deaths were measles-associated. Stools of children with measles-associated diarrhea usually have the same bacteria as those of children with diarrhea not associated with measles [111–113]. Measles-associated diarrhea typically begins just before rash onset [63], suggesting that measles virus is responsible for most of the

Table 2. Complications by age for reported measles cases, United States, 1987–2000.

Complication	Overall (67,032 cases with age information)	No. (%) of persons with complication, by age group				
		<5 years (n = 28,730)	5–9 years (n = 6492)	10–19 years (n = 18,580)	20–29 years (n = 9161)	>30 years (n = 4069)
Any	19,480 (29.1)	11,883 (41.4)	1173 (18.1)	2369 (12.8)	2656 (29.0)	1399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5482 (8.2)	3294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)
Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7470 (26.0)	612 (9.4)	1612 (8.7)	2075 (22.7)	1107 (27.2)
Otitis media	4879 (7.3)	4009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3959 (5.9)	2480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

Source: Centers for Disease Control and Prevention.

diarrhea episodes but that secondary bacterial or viral infections may contribute to the severity and duration of illness.

Dehydration was found in 32% of hospitalized patients in California [114]. Morley [10, 115] first described the high rates of gastrointestinal complications that occurred after measles in developing countries: mouth sores, decreased food intake, protracted diarrhea, weight loss, and precipitation of severe protein calorie malnutrition [63]. Noma (cancrum oris), a progressive oral lesion that destroys orofacial tissue, has been noted after measles in Africa [116–118] and India [119]. In young adults, measles is associated with hepatitis, hypocalcemia, and elevation of creatinine phosphokinase levels [66, 67, 85, 89, 120–123].

NEUROLOGICAL COMPLICATIONS

Febrile seizures. Febrile seizures occur in 0.1%–2.3% of children with measles in the United States and England [75, 77, 124–127] and are usually benign and not associated with residual damage. Most children with uncomplicated measles have changes visible on electroencephalography, but these changes are most likely due to fever and other metabolic changes [128–130]. **Postinfectious encephalomyelitis** (PIE) occurs in 1–3 per 1000 infected persons, usually 3–10 days after onset of rash [39, 131]. Higher rates of PIE due to measles occur in adolescents and adults than in school-aged children (table 2 [124, 132, 133]). PIE usually begins with the abrupt onset of new fever, seizures, altered mental status, and multifocal neurological signs [131, 134]. Although measles virus was found in cerebrovascular endothelial cells in a person who died during the first few days of rash [135], the virus usually is not found in the central nervous systems of persons with PIE. PIE appears to be caused by an abnormal immune response that affects myelin basic protein [61, 136]. As many as 25% of people with PIE due to measles die, and ~33% of survivors have lifelong neurological sequelae, including severe retardation, motor impairment, blindness, and sometimes hemiparesis [39, 131].

Subacute sclerosing panencephalitis (SSPE). SSPE is caused by persistence of measles virus in central nervous system tissue for several years, followed by a slowly progressive infection and demyelination affecting multiple areas of the brain [39, 137]. The initial SSPE symptoms, usually decreased school performance and behavioral disorders, are often misdiagnosed as psychiatric problems. Subsequently, myoclonic seizures develop, and a characteristic burst-suppression pattern may be seen on electroencephalography. Measles antibody is present in the cerebrospinal fluid. The disease slowly progresses until affected persons are in a vegetative state. Wild-type measles viruses, but not measles vaccine viruses, have been found in brain tissue [138]. SSPE occurs on average in 1 per 8.5 million persons who develop measles in the United States [139–141], but the rate appears to be higher in some other countries [141–144]. Factors responsible for persistence of measles virus in these persons are not known, nor is it known whether measles virus persists in otherwise normal hosts. Geographic clustering of SSPE occurs in several countries, and there is an increased incidence in children residing in rural areas. In 2 studies, children with SSPE had more close exposure to birds than did control subjects [140, 141]. These data suggest that as-yet-undefined environmental factors, most likely another infectious agent, contribute to this disease.

Measles encephalitis in immunocompromised patients. A progressive central nervous system measles virus infection, termed "measles inclusion body encephalitis," occurs in immunocompromised persons with disorders such as human immunodeficiency virus (HIV) infection or leukemia. Onset is usually 5 weeks to 6 months after acute measles. The illness begins with mental-status changes and seizures in the absence of fever; >80% of deaths occur within weeks [145–148].

OCULAR COMPLICATIONS

Conjunctivitis occurs in most persons with measles, and inflammation of the cornea (keratitis) is common. In a study of 61 Turkish military personnel with measles, 57% had keratitis detected by slit lamp examination [149]. In well-nourished persons, these lesions usually heal without residual damage. How-

ever, secondary bacterial (e.g., *Pseudomonas* or *Staphylococcus*) or viral infections (e.g., HSV or adenovirus) can lead to permanent scarring and blindness [150]. Vitamin A deficiency predisposes to more severe keratitis, corneal scarring, and blindness [151]. Measles associated with vitamin A deficiency is one of the most common causes of acquired blindness in children in developing countries [68, 69]. Blindness can also result from cortical damage from measles encephalitis.

OTHER ASSOCIATIONS

Measles has been hypothesized to cause or contribute to multiple sclerosis, but available evidence is weak and inconclusive [152]. Measles or measles vaccines have been suggested to contribute to or induce autism, but available data favor rejection of these hypotheses [153–155]. Studies from different laboratories have had conflicting evidence for persistence of measles virus nucleocapsid in affected tissue from patients with otosclerosis [156, 157], Paget's disease [158], and inflammatory bowel disease [153, 159, 160].

FACTORS AFFECTING MEASLES MORBIDITY AND MORTALITY RATES

Sex. Historically, males have had higher case-fatality rates than did females [13, 161]. An analysis of vital statistics data from several countries (primarily in the Americas and Europe) for the years 1950–1989 suggests that women and girls may have slightly higher mortality rates after measles than do men and boys [162], but recent surveillance data from the United States and United Kingdom show equal rates of complications for men and women (table 3[124, 163]). Pregnant women have an increased risk of complications, including death, following measles [164].

Age. Complication rates, including mortality, from measles are highest in children <5 years and adults (table 2). Most infants are protected during the first months of life via maternally derived antibodies. However, when immunity is lacking, measles can be severe [165–168]. Adults more commonly have encephalitis, hepatitis, hypocalcemia, or pancreatitis after measles. The increased severity of measles in adults most likely reflects the decline in cell-mediated immunity that begins in adulthood [169, 170]. Okada et al. [55] found that young infants and adults have more severe and a longer duration of lymphopenia after measles than do children.

Crowding. Several studies from West Africa [171, 172] and Europe [173, 174] show that children who develop measles after within-household exposure have higher case-fatality rates than do children who are exposed to measles outside the household. This phenomenon is most likely secondary to a higher inoculum from more intensive and prolonged exposure compared with more casual exposures outside the home. In Bangladesh, Koenig et al. [175] found that children who lived in a house of <18.6 m^2 had 2.6 times the risk of dying from measles as that of children who lived in houses of >37 m^2. In the United States, however, no relationship between crowding and measles case-fatality rates has been found [176, 177].

Immunosuppression. Children with defects in macrophage function only (e.g., chronic granulomatous disease) do not have increased rates of complications from measles [178–180]. Suppression of lymphocyte function, resulting from congenital defects in T lymphocyte function, bone marrow transplantation [104], chemotherapy for cancer, or immunosuppressive doses of steroids, is associated with increased severity of measles [39]. In a review of 40 measles cases in children with malignancies, 58% of children had pneumonitis, 20% had encephalitis, and 8% had both [99]. Only 60% of the case-patients had typical measles rash [99]. The fatality rate was 55% overall [99]. In some immunosuppressed patients with measles, multiple organ systems are affected [39, 40, 181–183]. Measles has developed after bone marrow transplantation even when both donor and recipient have histories of measles vaccination [104]. Patients with B cell immune deficiency syndromes without T cell ab-

Table 3. Complication rates by sex for reported measles cases, United States, 1987–2000.

Complication	Overall (n = 66,800 with information available)	No. (%) of persons with complication, by sex	
		Males (n = 33,898)	Females (n = 32,902)
Any	19,443 (29.1)	9740 (28.7)	9703 (29.5)
Death	177 (0.3)	93 (0.3)	84 (0.3)
Diarrhea	5473 (8.2)	2831 (8.4)	2642 (8.0)
Encephalitis	96 (0.1)	49 (0.1)	47 (0.1)
Hospitalization	12,854 (19.2)	6381 (18.8)	6473 (19.7)
Otitis media	4872 (7.3)	2542 (7.5)	2330 (7.1)
Pneumonia	3948 (5.9)	1986 (5.9)	1962 (6.0)

Source: Centers for Disease Control and Prevention.

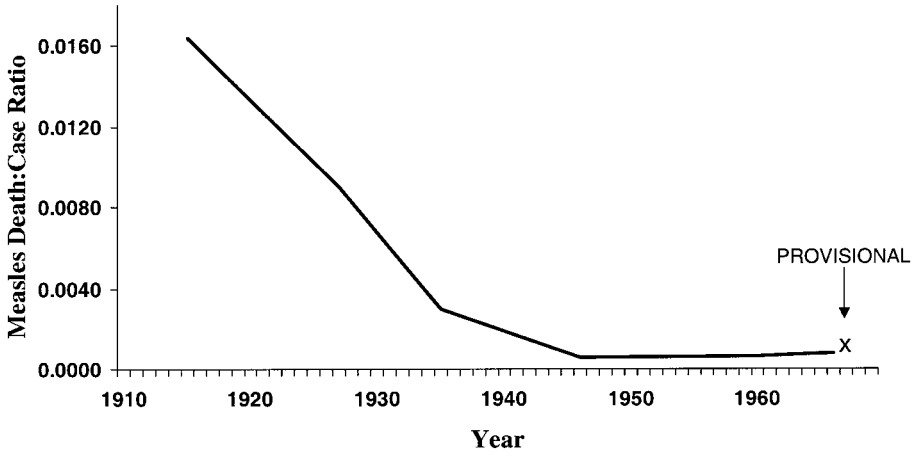

Figure 2. Measles death:case ratios, New York State, 1910–1969, by decade. Reprinted with permission from [212].

normalities do not appear to have increased rates of complications associated with measles.

Children born to HIV-infected women become susceptible to measles at an earlier age than do children born to HIV-negative women because the former transmit reduced amounts of antibodies to their infants [184–186]. HIV-infected infants not taking highly active antiretroviral therapy (HAART) have decreased responses to measles vaccination and a faster decline in vaccine-induced immunity [186]. In New York City during a 1989 measles outbreak, 6 of the 12 measles deaths were in persons likely infected with HIV [187]; in 1990 and 1991, 60% of all measles-related deaths in New Jersey occurred in HIV-infected children [188]. However, a study of hospitalized children with measles in Kinshasa, Zaire, found similar rates of pneumonia, diarrhea, and death after measles in HIV-seronegative and -seropositive young children [189]. There have been no studies of HIV-infected children undergoing HAART to determine how they handle measles virus infection, but survival rates would be expected to be higher than in untreated children, because children undergoing HAART have good immune responses to measles vaccination [190, 191].

Malnutrition. Malnourished children have impairments in multiple aspects of the immune system, prolonged excretion of measles virus, and higher measles case-fatality rates [9, 63, 192–194]. Measles contributes to the development of malnutrition because of protein-losing enteropathy, increased metabolic demands, and decreased food intake. Children who have measles early in life have significantly lower mean weights for age than do children of the same age who do not develop measles [183, 195].

Vitamin A deficiency. Children with clinical or subclinical vitamin A deficiency in many developing countries have increased case-fatality rates [196, 197]. Measles and other illnesses are associated with reductions in serum retinol concentrations and may induce overt vitamin A deficiency [197, 198]. Hospitalized US measles patients frequently have deficiencies in vitamin A; these children are more likely to have pneumonia or diarrhea after measles [73, 199, 200]. In countries with high measles mortality, treatment with vitamin A once daily for 2 days (200,000 IU for children $\geq$12 months of age or 100,000 IU for infants <12 months) is associated with an ~50% reduction in mortality [196, 201–203]. The World Health Organization recommends vitamin A therapy for all children with measles [204]. For hospitalized children <2 years old with measles in the United States, the American Academy of Pediatrics recommends a single dose of vitamin A (200,000 IU for children $\geq$12 months; 100,000 IU for those <12 months) [205].

BURDEN OF MEASLES

Developed countries. Measles case-fatality rates have declined in association with economic development and associated decreased crowding, older age at infection, improved nutrition, and treatment for secondary pneumonia [206, 207]. One hundred years ago in Scotland, the measles case-fatality rate was 30–40 deaths per 1000 cases [208]. In the United States, mortality from measles decreased from 25 per 1000 reported cases in 1912 [209, 210] to 1 per 1000 reported cases in 1962 [211]. In New York State, measles mortality decreased by >15-fold long before the introduction of measles vaccination (figure 2) [212]. US and UK case-fatality rates were ~1 per 1000 reported measles cases from the 1940s through the 1980s [3, 124, 133, 211]. During the past 13 years in the United States, the case-fatality rate has averaged 3 per 1000 reported measles cases (table 2). This increase is most likely due to more complete reporting of measles as a cause of death, HIV infections, and a higher proportion of cases among preschool-aged children and adults. Annual US measles deaths have declined from 408 in 1962 to 0 from 1993–present [213].

Developing countries. Measles remains a leading cause of

death and disability-adjusted life-years lost [214]. Community-based studies during the 1970s and 1980s revealed measles case-fatality rates of 3%–34% [215–217], 10–20 times those in industrialized countries. In 2000, the World Health Organization estimated that 30–40 million persons developed measles, resulting in 777,000 deaths, most in sub-Saharan Africa [218]. This estimate was based on expected case fatality rates. Another approach based on verbal autopsies gives a lower estimate of the number of measles-associated deaths [219, 220].

High case-fatality rates in developing countries are due to a young age at infection, crowding, underlying immune deficiency disorders, vitamin A deficiency, and lack of access to medical care. Before the introduction of measles vaccines, one-third of children in many developing countries were infected in the first and second years of life, and most children were infected before age 5 years [195, 221, 222]. An estimated 125 million preschool-aged children are estimated to have vitamin A deficiency, placing them at high risk for death, severe infection, or blindness as a result of measles [197]. In recent years, the use of vitamin A therapy for children with measles, prompt antibiotic therapy for pneumonia, and older age at time of infections have contributed to the lower case-fatality rates (≤1%) in some developing countries (figure 3) [223–228]. In Latin America [229] and southern Africa [230], achieving high vaccination rates has reduced measles mortality in these regions to near zero.

Mortality from measles increases during times of war or famine. In Ethiopia in 2000, measles was responsible for 22% of deaths in children <5 years of age and 17% of deaths in children aged 5–14 years [231]. In Afghanistan, measles case-fatality rates have been as high as 28% [232]. In 2000, there were at least 1200 measles-related deaths in Afghanistan, and the case-fatality rate was 8%–13% [233]. Case-fatality rates for people hospitalized with measles in Sydney, Australia, increased during years of economic depression but were followed by lower rates in the 1940s (figure 4) [234].

IMPACT OF MEASLES VACCINE

Measles vaccination is one of the most cost-effective health interventions ever developed. Without the vaccine, 5 million children would die each year from measles—assuming an estimated case-fatality rate of 2%–3%. Without measles vaccination, the costs of caring for those with measles in the United States would be ~$2.2 billion annually, and the indirect costs would be an additional $1.6 billion [235]. Each dollar spent on measles vaccine saves $12–$17 in direct and indirect costs [235–237].

Measles vaccination was associated with a 36% decline in overall death rate and a 57% reduction in the rate of death directly attributable to measles or diarrhea, respiratory illness, or malnutrition in Bangladesh [238]. Koenig et al. [175] found that unvaccinated children of low socioeconomic status were

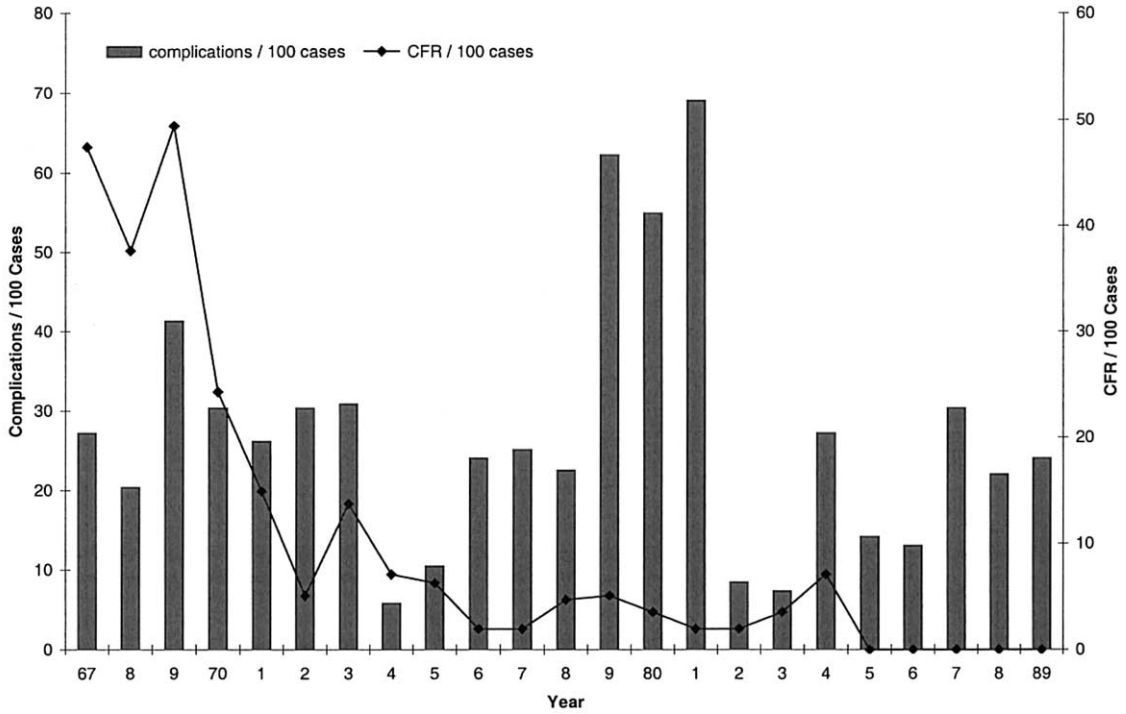

Figure 3. Measles case-fatality rates (CFR) versus rates of complications for children with measles in Gweru, Zimbabwe, 1967–1989. Reprinted with permission from [223].

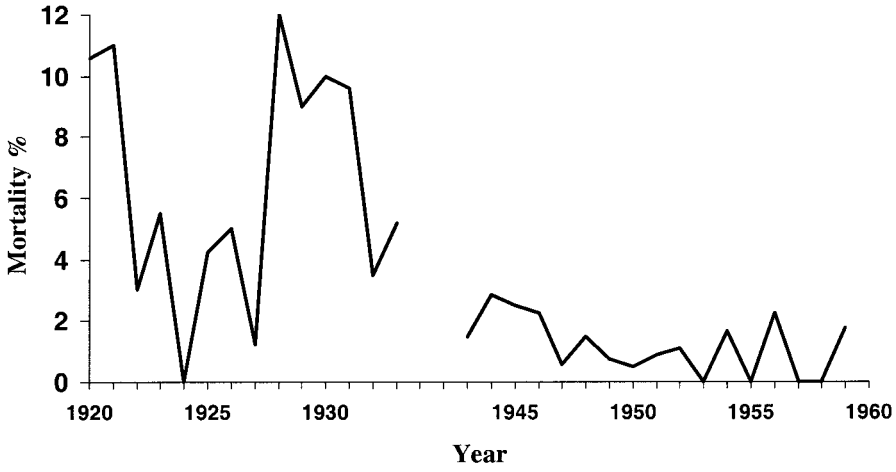

Figure 4. Percentage of mortality from measles among patients admitted to Coast Hospital, Sydney, Australia, 1920–1959. Reprinted with permission from [234].

2.5 times more likely than children of high socioeconomic status to die of measles. In vaccinated populations, children of low socioeconomic status had a risk of death only 50% higher than that of children of high socioeconomic status [175]. Holt et al. [239] found that vaccinated children in households of lower socioeconomic status had a markedly higher chance of surviving to age 39 months than did unvaccinated children in households of lower socioeconomic status. Measles vaccination had a lesser effect on overall child survival in households of higher socioeconomic status.

In Haiti, Bangladesh, and sub-Saharan Africa, measles vaccination was associated with an overall reduction in mortality of 30%–86% [240]. Aaby and colleagues [240, 241] have hypothesized that measles vaccination is associated with a reduction in mortality resulting from nonspecific beneficial effects on the immune system; however, the data are not conclusive.

SUMMARY

Measles is an important cause of serious complications and death. Pneumonia is the most frequent severe complication, and croup, diarrhea, and malnutrition precipitated by measles contribute to mortality. Encephalitis occurs in ~1 of every 1000 children with measles. Concurrent vitamin A deficiency increases rates of complications. Children <5 years of age, adults, and persons with malnutrition or immunodeficiency disorders are at increased risk of complications. In developing countries, measles case-fatality rates are 10- to 100-fold higher than in developed countries; ~770,000 children died of measles in 2000. Older age at infection, vitamin A supplementation, and antibiotic therapy for secondary bacterial infections have reduced measles-associated deaths in the developing world. Eradication of measles would be a major public health accomplishment.

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