8.5.6 Measles 772

8.5.6 Measles 772

772 section 8 Infectious diseases In the normal infant, maternal IgG passes to the fetus and seems to protect the infant against mumps during the first year of life. The typical disease of mumps in infants is a rare clinical finding, even in populations with no previous experience of the disease. MuV may be isolated in vague respiratory infections in infants. Laboratory diagnosis In patients without parotitis, especially meningitis, and in the absence of contact history, serological tests and RT-PCR are the only means of reaching a firm diagnosis. MuV isolation is an insensitive method and now rarely used. MuV contains several different antigenic compo- nents, which provoke distinct antibodies that are useful for laboratory confirmation. Antibody to the N protein rises in the first 2 weeks of in- fection but then declines rapidly. Antibody to the HN protein appears at the end of the first week, usually in high titre: it may persist for years and indicates past infection. Neutralizing antibodies also develop, but titres are a poor correlate of protection. Nowadays, sensitive enzyme immunoassays allow early diagnosis by detection of mumps-specific IgM and IgA. In recent outbreaks in the United States of America and in the United Kingdom, IgM-negative cases have been identified. IgA can be detected in saliva or mouth washings on about the fourth day after infection, and in the serum early in the disease. Measurement of antibodies in acute and convalescent sera is a reliable method for diagnosis, especially in patients who have no parotitis. RT-PCR meth- odology targeting the detection of mumps RNA in nose and throat swabs has been developed and is replacing and adding to serology- based techniques in routine laboratory diagnosis and confirmation. Treatment There is no specific antiviral treatment. Symptomatic treatment in- cludes simple analgesics, but for the severe pain of orchitis, morphine (15–30 mg) may be required for a day or two. Corticosteroids are worth trying in severe cases of parotitis, more especially in orchitis. An adult dose of 60 mg prednisolone daily for 2 or 3 days sometimes gives dramatic relief from pain, though it may not reduce the swelling. Prevention and control The mainstay of prevention is vaccination of susceptible individ- uals. Isolation is not effective as the patient has been infectious for days before parotitis occurs and subclinical cases are frequent. Attenuated live vaccine gives 95% seroconversion, and protection lasts for at least 15 years. In developed countries, mumps vaccine is currently given between 14 and 16 months of age as one compo- nent of a live attenuated trivalent mumps/measles/rubella (MMR) vaccine. A two-dose schedule with follow-up at 4–5 years of age is now recommended. This has suppressed the incidence of mumps by more than 98% in the United States of America and in the United Kingdom. Nevertheless, both countries have had recent outbreaks of mumps in college age populations in both unvaccinated individuals as well as those with a documented vaccination history. It is not clear whether this is due to primary vaccine failure or waning immunity in the absence of frequent challenge. Identification of patients in several outbreaks who had received two doses of mumps

vaccine indicates that waning immunity is the most likely explanation for recurrent outbreaks. Recommendation of a third dose of vaccine is being considered. The ability of new variant wild-type virus strains to break thought the protective immunity established by older vac- cines which are largely based on genotype A strains, appears a less likely cause of the current outbreaks. Mumps vaccination is contra- indicated in pregnant women and patients with immunodeficiency due to immunosuppressive therapy or disease. However, HIV sero- positive children should be vaccinated with the MMR vaccine. FURTHER READING Christie AB (1980). Infectious diseases: epidemiology and clinical prac- tice, 3rd edition. Churchill Livingstone, Edinburgh. Duprex WP, Rima BK (2011). Mumps virus. In: eLS. John Wiley & Sons, Ltd, Chichester. http://www.els.net/. Rima BK, Duprex WP (2008). Mumps virus. In: Mahy BWJ, van Regenmortel MHV (eds) Encyclopedia of virology, 3rd edition. Academic Press, London. Rubin SA, Sauder CJ, Carbone KM (2013). Mumps virus. In: Knipe DM, Howley PM (eds) Fields virology, 6th edition, Ch. 35, pp. 1024–41. Wolters Kluwer, Lippinocott Williams & Wilkins, Philadelphia, PA. Wright KE (2006). Mumps. In: Newton VA, Vallely PJ (eds) Infection and hearing loss, pp. 109–26. John Wiley and Sons Ltd, Chichester. 8.5.6 Measles Hilton C. Whittle and Peter Aaby ESSENTIALS Measles is a single-stranded RNA virus that is spread by aerosolized droplets and is highly transmissible. It causes a spectrum of disease ranging from mild in the well-nourished to severe in the malnour- ished or immunosuppressed: mortality is 3–10% in Africa. Clinical features—10 to 14 days after infection, the viral prodrome typically consists of runny nose and fever, sometimes also diarrhoea or convulsions; signs include mild conjunctivitis, red mucosae, and (on the buccal mucosa) Koplik’s spots. After 14–18 days a morbilliform rash first appears on the forehead and neck, then spreads to involve the trunk and finally the limbs. Other manifestations include severe con- junctivitis (especially in those who are vitamin A deficient), pneumonitis and enteritis (which may cause profuse diarrhoea). Early complications include (1) pneumonia—caused by secondary bacterial infection and responsible for most deaths; (2) stomatitis—caused by herpes sim- plex virus and/or candidal infection; (3) enteritis—due to candidal or bacterial superinfection; (4) eye infection—corneal ulceration may be caused by some combination of measles itself, herpes simplex infec- tion, vitamin A deficiency, and use of traditional eye medicines; more than half of childhood blindness in Africa is related to measles; (5) skin and other infections (e.g. pyoderma); (6) encephalitis—occurs in 0.1– 0.2% of cases; probably attributable to a neuroimmunologic process;

8.5.6 Measles 773 mortality is 10–15%, and 25% of children are left with permanent neurological disability. Late complications include malnutrition, giant cell pneumonia, and subacute sclerosing panencephalitis. Diagnosis and treatment—diagnosis is primarily clinical, but signs might be less clear-cut in vaccinated subjects. Detection of measles-specific IgM antibody or detection of measles antigen in saliva or urine can clinch the diagnosis if the rash is mild or atyp- ical. Management is supportive, including administration of vitamin A, and with prompt treatment of secondary infections. Prophylactic antibiotics such as amoxyicillin to prevent pneumonia might be war- ranted in settings with limited access to clinical services. Prevention—(1) Passive immunization—human immunoglobulin is highly effective if given within 5 days of exposure and should be administered to those in whom vaccination is contraindicated. (2) Active immunization—live vaccine is often given in the developed world as one component of a trivalent measles–mumps–rubella vac- cine at 12 to 18 months of age. However, this is not appropriate for children in developing countries, who are infected by measles at a much earlier age, where substantial successes in controlling the dis-ease has been obtained with a strategy combining (a) catch-up—a one-time mass campaign

covering everybody aged 9 months to 14 years, regardless of previous measles or immunization; (2) keep- up—achieving a high coverage with routine measles vaccination for each birth cohort; (3) follow-up—subsequent mass campaigns covering all children every 3–5 years; and (4) mop-up—campaigns that target children who are difficult to reach or during outbreaks. This strategy has eliminated measles from Latin America. Introduction Measles is an acute, highly transmissible RNA viral infection of humans that is spread by aerosolized droplets. It causes much death and suffering, especially among poor children in developing countries. Its severity varies according to host and socioeconomic factors, not to antigenic variation or alteration in virulence of the virus. There is no reservoir of infection other than in humans and no evidence of a carrier state and as there is an effective vaccine, global eradication is possible but daunt- ingly high vaccine coverage of more than 95% will be needed. The virus causes a generalized infection coupled with severe damage to the immune system due to destruction of T lympho- cytes, disturbance of the Th1/Th2 cytokine balance, and im- paired antigenic presentation. The chief clinical features result from infection of the skin, mucous membranes, and respiratory tract. Death, which occurs in up to 15% of hospitalized chil- dren in Africa, results from secondary infections and immuno- suppression. Attack rates in unimmunized home contacts are very high (of the order of 90%) and long-life immunity follows the disease but not vaccination. Supplemental immunization activities allowing repeated vaccination every 3 to 5 years in endemic countries have lowered measles deaths dramatically. Although the coverage for the first dose of measles vaccine has reached 85% (Fig. 8.5.6.1a) and measles mortality declined by 79% between 2000 and 2014, an estimated 114 900 people still die annually of measles (Fig. 8.6.5.1b). Epidemiology Measles has been the archetypical childhood infection, known and feared by all parents. Nearly everybody contracted this most infec- tious of childhood diseases. Measles was the single biggest cause of childhood deaths. In the prevaccination era, 6 million children might have died annually of measles. With advances in coverage during the last 25 years is still one of the most important of the vaccine-preventable infections. The severity and age of infection varies mark- edly between poor and rich countries. In the West, most children were infected between 3 and 6 years of age, when they attended nur- sery and primary schools. Mortality was low (<0.05%) and morbidity, although considerable when compared to many other common viral infections, was limited. Most cases occurred in the winter and spring, with a biannual epidemic pattern. Widespread immunization has dramatically reduced both the number of cases and complications in high-income countries but coverage, which needs to be over 95%, has seldom been high enough to eliminate measles except in the Americas. Thus, measles still persists in most regions of the world showing marked annual variation (Fig. 8.5.6.1c). In low-income countries, measles is still severe and behaves dif- ferently. It kills between 3 and 10% of children in the community and some 10–20% of those admitted to hospital. Mortality from mea- sles is considerably higher in Africa (3–10%) than in Asia or South America (1%). West Africa has the highest case fatality rates. There are many reasons for this increase in severity in the tropics: children are infected at 1–2 years of age; severe malnutrition leads to prolonged, severe measles. Overcrowding is another strong determinant, for secondary and tertiary cases in large families are at great risk of death. Exposure to a large dose of the virus when in close contact with the index case might be the critical factor. The severity of measles depends on the severity of disease in the index case. The high mortality found in West Africa is due to this region having the largest polygamous and extended families, which in- crease the risk of intense exposure. When females stay at home and are constrained in their social contacts, mortality is higher in girls than boys. There is also a high case fatality in children with chronic disease, including kwashiorkor, tuberculosis, and HIV infection. Hospital wards, refugee camps, and

clinics in developing countries have been important centres of disease transmission. Though measles can have permanent sequelae, recent research has provided limited support for the previous belief in long-term excess morbidity and mortality after the first 6 weeks of measles infection. Long-term consequences might also depend on intensity of ex- posure. Index cases apparently have better long-term survival than secondary cases, suggesting a beneficial effect of mild measles infec- tion. Long-term morbidity is most likely to be experienced by young children who have severe measles following intensive exposure. Although measles immunization has dramatically decreased the number of cases and deaths, vaccinated cases are not infrequent as immunity wanes with time. These cases are characterized by a pro- longed incubation period, a short prodrome, mild symptoms, and a favourable outcome. The mild measles of immunized cases leads to less risk of transmission or transmission of less severe disease. Immunization reduces the number of children being susceptible in the same household and hence reduces the risk of intensive ex- posure (Table 8.5.6.1).

section 8 Infectious diseases 774 However, immunization might have negative consequences on herd immunity for an increasing number of unvaccinated children, or children who have responded poorly to the vaccine will reach adulthood without having been exposed to measles. Thus, vaccinated people will have lower antibody levels than naturally infected people, which is particularly important because young immun- ized mothers will transfer lower antibody levels to their offspring. In West Africa, children of immunized mothers have only half the antibody levels of children of naturally infected mothers and they become susceptible as early as 3 to 5 months of age. 5 (a) 0 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014 0.5 1 1.5 2 2.5 3 3.5 4 4.5 100 0 10 MCV Coverage* (%) No. of reported cases Millions 20 30 40 50 60 70 80 Campaigns 90 Number of cases MCV1 Coverage* MCV2 Coverage* 0 2000 2013 2012 2011 2010 2009 2008 2007 2006 Year 2005 2004 2003 2002 2001 1.6 (b) 1.4 1.2 Estimated no. of deaths (millions) 1 0.8 0.6 0.4 0.2 Estimated no. of measles deaths in absence of vaccination Estimated no. of measles deaths with vaccination 95% confidence limits for no. of measles deaths with vaccination Estimated no. of deaths averted by measles vaccination Fig. 8.5.6.1 (a) Global annual reported cases of measles and coverage of first (MCV1) and second (MCV2) doses of measles vaccines, 1980–2014. (b) Estimated number of measles deaths and number of deaths averted by measles vaccination-worldwide 2000–2014. (c) Measles case distribution by month and WHO regions, 2008–2018. (a) Source WHO/IVB database, 2015. (b) Reproduced from CDC (2015). Progress towards regional measles elimination. MMWR, 64,1246–51. (c) Source data from WHO measles surveillance data 2018.

8.5.6 Measles 775 It has been argued that measles vaccines only saved ‘weak’ children who were likely to die anyway. However, many epidemiological studies, including randomized trials, have shown remarkable reductions in all- cause mortality after standard measles vaccine. In Bangladesh, measles vaccination was associated with a 49% reduction in all-cause mortality from the age of 9 months, even though acute measles accounted for only 10–12% of deaths. This unexpected benefit was not related to prevention of measles. In most studies, this nonspecific benefit is particularly marked for girls. The World Health Organization (WHO)’s Strategic Advisory Group of Experts on Immunization (SAGE) re- viewed the potential non-specific effects of measles vaccine in 2014 and confirmed these observations. Recent studies have also shown that the combination of measles vaccine with other vaccines or vitamin A sup- plements may negatively influence the nonspecific effects on child survival. The first study from a high-income country has also shown

that in Denmark, USA, and Italy measles–mumps–rubella (MMR) vaccine is associated with a nonspecific benefit by reducing hospital admissions for infectious diseases, particularly respiratory infections. There is also evidence that the second dose of MMR has beneficial ef- fects on prolonged hospital admissions for infections. Popular beliefs In most cultures, measles has a specific local name and is a much- feared disease. Popular understanding is centred around the rash, which if it stays within the body will lead to severe disease. This belief has some basis in truth for the prodrome is prolonged in se- vere cases, and a proportion of deaths reportedly occur before the appearance of the rash during very severe epidemics. Therapeutic practices, such as rubbing the skin with palm oil or kerosene, are aimed at eliciting the rash quickly. Popular beliefs can also hamper vaccine uptake, leading to local outbreaks of measles. In the United Kingdom, after the publication of a fallacious medical article in 1998, the myth has arisen that the measles–mumps–rubella (MMR) vaccine can cause autism. Driven by an irresponsible press and the antivaccine lobby, measles vac- cine coverage fell from 93% to 79% and has yet to fully recover. In Germany some parents believe children benefit from measles and thus shun vaccination. In the Bible Belt of the Netherlands, strong religious beliefs preclude all vaccinations. Marginalized 40000 (c) 35000 30000 25000 20000 15000 10000 5000 Month of onset Measles cases (Lab+Epi+Clinical) 2014-01 2014-02 2014-03 2014-04 2014-05 2014-06 2014-07 2014-08 2014-09 2014-10 2014-11 2014-12 2015-01 2015-02 2015-03 2015-04 2015-05 2015-06 2015-07 2015-08 2015-09 2015-10 2015-11 2015-12 2016-01 2016-02 2016-03 2016-04 2016-05 2016-06 2016-07 2016-08 2016-09 2016-10 2016-11 2016-12 2017-01 2017-02 2017-03 2017-04 2017-05 2017-06 2018-01 2018-02 2018-03 2018-04 2018-05 2018-06 2017-07 2017-08 2017-09 2017-10 2017-11 2017-12 0 WPR SEAR EUR EMR AMR AFR Fig. 8.5.6.1 Continued Table 8.5.6.1 Impact of measles immunization on the transmission and severity of measles Outcome measurements Bissau 1980–1982 Senegal 1983–1990 Bissau 1991 Case fatality ratio: vaccinated / unvaccinated (95% CI) Acute mortality within 1 month 0.39 (0.13–1.14) 0.0 (0–0.92) 0.30 (0.13–0.72) Delayed mortality from 1 month to 3 years 0.44 (0.22–0.90) Secondary attack rate ratio according to vaccinated/ unvaccinated index cases 0.28 (0.10–0.79) 0.36 (0.15–0.87) Based on data from Aaby P, et al. (1986). Vaccinated children get milder measles infection: a community study from Guinea-Bissau. J Infect Dis, 154, 858–63, and Samb B, et al. (1997). Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. Am J Epidemiol, 145, 51–7.

776 section 8 Infectious diseases communities like the Roma shun medical and other authorities, and many are unvaccinated. Thus it is difficult to eliminate measles in Europe. In northern Nigeria, a predominantly Muslim area, re- ligious and political leaders have warned of the dangers of Western vaccines: coverage fell, and large outbreaks of polio and measles have ensued. The virus and its antigens Measles mainly infects humans, but like the other closely related morbilliviruses (such as rinderpest or canine distemper virus) it is able to cross species to infect other primates, but these outbreaks have not proved to be reservoirs of infection for humans. The virus contains a single strand of RNA, is highly pleomorphic, and ranges from 100 to 300 nm in diameter. It propagates by budding from the cell membrane, from which it acquires an envelope. The membrane of infected cells and the virion envelope contain two surface glyco- proteins, the haemagglutinin (H) and fusion (F) proteins, and a nonglycosylated matrix (M) protein, which forms the inner layer. The H protein, which allows attachment of the wild type virus to cells, via the CDw150 and nectin-4 receptors, is the main target for neutralizing antibodies. The CDw150 receptor is expressed on im- mature lymphocytes and on effector memory T cells, and is rapidly induced on T and B cells after activation; the nectin-4 or poliovirus receptor-like 4 is expressed on

epithelial cells. The F protein is re- sponsible for fusion and syncytium formation of infected cells. The internal components or nucleocapsid consist of RNA, the nu- cleoprotein (N), which is the major protein, the phosphoprotein (P), and the large protein (L). The F protein is remarkably stable, the H protein shows minor antigenic variation, but the N protein, which contains a variable region in the C-terminal, is highly divergent among different strains of virus. Genetic analysis of Haemagglutinin and Nucleoprotein genes allowed molecular surveillance of the mea- sles virus to track the international spread of the virus. There is also variation in the M protein, which some claim is related to persistent infection. The virus and its antigens are shown in Fig. 8.5.6.2. Pathogenesis and the immune response The course of infection and the immune response to this invasion are shown in Fig. 8.5.6.3. The measles virus, which is thermolabile and survives best at low humidities, is spread to susceptible contacts in droplets during sneezing and coughing. First, it infects and multi- plies in lymphoid cells in the mucosa of the upper respiratory tract or the conjunctivae. Some 4–6 days later, the virus is found in the reticuloendothelial tissue of the liver and the spleen after passage through lymph nodes and spread via the blood. Here it multiplies, causing fusion of cells to form giant cells with many nuclei. Viral antigens, which can be found by immunofluorescent techniques in and on the surface of both these cells and lymphocytes, now induce the immune response. First, natural killer cells and cytotoxic T cells mount a cell-mediated reaction that contains the virus and limits its spread within cells. Later, B cells are primed to produce antibody. Defects in the cellular immune system, as in severe malnutrition, cancer, or primary and secondary immunodeficiencies, allow wide- spread multiplication of the virus to cause fatal giant cell pneumonia. Fusion (F) Haemagglutinin (H) Lipid bilayer RNA Large protein (L) Phosphoprotein (P) Nucleocapsid (N) Matrix (M) Fig. 8.5.6.2 The virus and its antigens. Reprinted by permission from Macmillan Publishers Ltd: Moss WJ, and Griffen DE (2006). Global measles elimination. Nat Rev Microbiol, 4, 900–8, copyright © 2006. Measles Stage Day Infection 0 Invasion 6 12 Rash 16 21 Recovery Epithelia Lymph node Blood Induction ab c.m.i. Allergy Immune response Lymphoid tissue Secondary infections Secondary anergy Persistent immunity Epithelia Fig. 8.5.6.3 Pathogenesis of measles. + Denotes, amount of virus; ab, antibody. Reproduced with permission from Parry EHOP (ed) (1984). Principles of medicine in Africa, 2nd edition. Oxford University Press, Oxford.

8.5.6 Measles 777 Around day 8, the measles virus is carried by the blood, either free or in mononuclear cells, to the target tissues, which are epithelia of the skin, eye, lung, and gut. Again, the agent multiplies to cause a bright erythema of the mucosae and Koplik’s spots (see next), which are foci of viral multiplication. At this stage, measles virus may be cultured from nasopharyngeal secretions, and antigen can be de- tected by immunofluorescent techniques or PCR in the character- istic giant cells of the buccal mucosa, in epithelial cells, and in both B and T lymphocytes in the blood. The rash, appearing around days 14–16, is the sign of a strong and complicated allergic reaction to the virus in epithelia. The ex- tent and severity of the rash, which reflects the clinical severity of the disease, is determined by the number of target cells infected. Histological examination shows virus in the disrupted epidermis, in the corium, and in capillary endothelium. These tissues are infil- trated by mononuclear cells together with antibody, immune com- plexes, and complement. An intact cell-mediated immune response is essential to generate the rash and clear the virus, for if impaired, as in the case of children with leukaemia, or occasionally in severe kwashiorkor, the virus multiplies unchecked and no rash appears. Some 2 or 3 days after the start of the rash, around day 17 or 18, the virus can no longer be cultured from epithelia, for infected cells have been disrupted and the free virus neutralized by antibody. The first

antibody to appear is to the nucleoprotein antigens. The second to appear, which is largely responsible for neutralization of the virus, is to the haemagglutinin. Finally, the antibody to the fusion glycoprotein appears in a low titre. This antibody stops cell-to-cell spread of the virus. At this stage the child is markedly immunosup- pressed and thus susceptible to secondary infections of the eyes, mouth, gut, and lungs. Latent viruses, such as herpes simplex or cytomegalovirus, may be reactivated and in turn cause further damage to the immune system. The delayed hypersensitivity reac- tion, as measured by skin tests to old tuberculin or candida antigen, is absent or severely impaired. By the third week, day 21, as the patient recovers, antibody is in full production. Levels remain elevated for the rest of the patient's life, ei- ther because of repeated subclinical infections or because the virus persists in latent form in the spleen and other organs, so stimulating antibody. Occasionally, the virus persists in the brain in a damaging form to cause subacute sclerosing panencephalitis (see next). Immunosuppression The mechanisms of immunosuppression are complex (Fig. 8.5.6.4). The CD4 + and CD8 + cytotoxic T-cell response, which is exuberant, may result in the destruction of infected T cells and dendritic cells thus leading to their depletion, deficient antigen processing, and generalized immunosuppression. Cross-binding of the CD46 cel- lular receptor down-regulates interleukin 12 (IL-12), a crucial cytokine in the development of Th1 and delayed hypersensitivity responses. Infection of CDw150+ lymphocytes, in particular ac- tivated CD45RA- memory lymphocytes, results in suppression of lymphoproliferation and cell death and loss of cell-mediated immunity. Thus, measles ultimately dampens the Th1 response, resulting in a skewing towards a Th2 cytokine response and suscep- tibility to intracellular and other pathogens for 4–6 weeks. This im- munosuppression might be in the interest of the host by limiting further autoallergic damage of infected tissues. However, the recent claim that this immunological amnesia may last for 2–3 years is not supported by long-term follow-up studies of mortality after measles in both W. Africa and Bangladesh. Pathogenesis in the underprivileged, in the malnourished, and in the HIV-infected Measles is severe, prolonged, and carries a high case fatality rate due to secondary infections in children of the developing world, as it was formerly in the underprivileged in Europe. Two explanations are offered. Crowding leads to a high dose of measles virus and also in- creases the chances of secondary infection. The period of incubation T Cell ↑ IL-10 ↑ IL-4 ↓ IL-12 ↓ Differentiation Lymphocyte apoptosis Impaired lymphoproliferation Immunomodulatory cytokines Interleukin-12 downregulation Impaired antigen presentation T Cell T Cell Monocyte DC Fig. 8.5.6.4 Potential mechanisms of immune suppression following measles virus infection. Reprinted from Moss WJ, Ota MO, and Griffen DE (2004). Measles: immune suppression and immune responses.
Int J Biochem Cell Biol, 36, 1380–5, copyright © 2004, with permission from Elsevier.

 has been found to be short, around 10–12 days, in severe and fatal cases, consistent with the concept of infecting dose as a mechanism of severe disease. Alternatively, or in tandem, malnutrition dimin- ishes the immune response to the virus, allowing great proliferation of virus and subsequent damage to the host. The immune response follows, which generates a severe and widespread rash followed by prolonged immunosuppression. Secondary bacterial infections with, for example, Streptococcus pneumoniae, or latent infections such as herpes simplex or Mycobacterium tuberculosis occur in the wake of this intense damage to the immune system, often killing or maiming the child. Virus persists in lymphocytes and epithelial cells for up to 30 days after the start of the rash. Anorexia, increased catab- olism, protein loss from the gut, and further malnutrition exaggerate the problem, which is worst in the weanling child (Fig. 8.5.6.5). The death rate after measles in hospitalized infants is higher in severely

malnourished and HIV-infected children, and prolonged viral shedding occurs in these children. Thus, in regions of high prevalence, HIV-infected children may be unrecognized trans- mitters of the virus but to date there is no evidence that this has hampered measles control. Asymptomatic HIV-infected children respond suboptimally to vaccination; those with AIDS are even less likely to respond and may be threatened by persistent measles infec- tion (see prevention). Clinical features There is a spectrum of severity ranging from mild in the privileged and well-nourished to severe in the blatantly malnourished or im- munosuppressed. However, the rule is not inviolate and other fac- tors such as the age and dose of infection are probably as important in determining the severity of disease. Measles, often severe, occa- sionally infects unvaccinated young adults or those who have lived in isolated communities. The clinical features of measles and some complications are shown in Fig. 8.5.6.6 and discussed next. Prodrome (days 10–14) A diagnosis of measles is often missed at this stage, when fever coupled with a runny nose, and sometimes complicated by con- vulsions, is the main feature. Other signs are mild conjunctiv- itis, red mucosa, Koplik's spots, and diarrhoea. Koplik's spots Impaired immunity Secondary infection Malnutrition Acute measles infection Fig. 8.5.6.5 The complex interaction between infection, nutrition, and impaired immunity seen in measles. Reproduced with permission from Greenwood BM (1996). The host's response to infection. In: Weatherall DJ, Ledingham JGGL, Warrell DA (eds) (1996). Oxford textbook of medicine, 3rd edition, p. 282. Oxford University Press, Oxford. Measles Incubation Prodrome Allergic Secondary infections Late complications Systemic Respiratory Skin Eye Mouth Gut Nutritional 0 10 14 19 28 4 5 6 Days after infection Weeks Tuberculosis Pneumocystis Blindness Gut infected Fever Fever Cough Cough Pneumonitis Rash Pyoderma, ulcers Conjunctivitis Keratitis, perf Kopliks Diarrhoea Herpes Anorexia Protein loss Loss of weight Marasmus Kwashiorkor Gut infected Pneumonia Infection Diarrhoea-bacterial Candida Fig. 8.5.6.6 Clinical features of measles and some of its complications. Reproduced with permission from Parry EHOP (ed) (1984). Principles of medicine in Africa, 2nd edition, Oxford University Press, Oxford.

 are found in the buccal mucosa (Fig. 8.5.6.7). They are small, irregular, bright-red spots with a minute bluish-white speck in the centre of each of them. The prodrome is prolonged in severe cases, and reduced in individuals with modified measles due to maternal antibodies, previous immunization, or the prophylactic use of immunoglobulin. Rash (days 14–18) The morbilliform rash first appears on the forehead and neck and then spreads, over a period of 3–4 days, to involve the trunk and fi- nally the limbs (Fig. 8.5.6.8). In children in Africa and other parts of the developing world the rash is often red, confluent, raised (Fig. 8.5.6.9), very extensive, and sometimes accompanied by bleeding into the skin and gut. Later, the rash blackens (postmeasles 'staining', see Fig. 8.5.6.10), then the skin peels causing extensive desquamation (Fig. 8.5.6.11). Other epithelial surfaces are inflamed, the severity matching that of the rash. Cough may be hoarse and coupled with inspiration difficulty if the larynx and trachea are inflamed. Signs of pneumonitis are ap- parent, which in severe cases can cause cyanosis or be complicated by mediastinal and subcutaneous emphysema. Conjunctivitis, espe- cially in those who are vitamin A deficient, can be severe. Enteritis might cause profuse diarrhoea with a resulting loss of protein, and malabsorption of food and water. The mouth is painful and red, which adds to the misery of the child, who becomes anorexic and may even refuse to suck the breast. In the uncomplicated case, as is usual in the West, the convalescent period is short, usually lasting less than a week. Complications should be suspected if fever persists while the rash is fading or desquamating. Complications Early complications (days 18–30) As a result of the widespread, severe allergic reaction to the measles virus signified by the rash, the patient is left severely immunosup- pressed

and is susceptible to infection. Pneumonia This causes the most deaths (Table 8.5.6.2) and is heralded by a rise in fever, leucocytosis, and respiratory difficulties. Lobar pneumonia is usually caused by S. pneumoniae, but bronchopneumonia, which is more common, results from other bacteria, such as Staphylococcus aureus, or secondary viral infections with, for example, herpes simplex or adenovirus. A variety of other organisms such as Gram-negative bacteria, cytomegalovirus, fungi, M. tuberculosis, and Pneumocystis jirovecii should be considered as potential lung pathogens in the malnourished or immunocompromised child. Stomatitis and enteritis Chronic diarrhoea and a sore mouth caused by candidal infection are common complications of measles in children in the develop ing world. The gut is often superinfected with Bacteroides spp., Escherichia coli, Pseudomonas spp., and S. aureus, which results in malabsorption and protein loss. Deep ulcers caused by herpes sim- plex virus erode the corners of the mouth, gums, and inner surface of the lips causing much misery, illness, and pain (Fig. 8.5.6.12). Fig. 8.5.6.7 Koplik's spots on the buccal mucosa. Courtesy of the late Dr B. E. Juel-Jensen. (a) (b) Fig. 8.5.6.8 (a, b) The morbilliform rash first appears on the forehead and neck and then spreads, over a period of 3–4 days, to involve the trunk and finally the limbs. Copyright D. A. Warrell.

780 section 8 Infectious diseases Eye infections Corneal ulceration leading to impaired vision or blindness is common after measles, especially in malnourished and vitamin A deficient children (Fig. 8.5.6.13). Several studies from Africa have shown that more than half of childhood blindness is related to mea- sles. The mechanisms are still under discussion. In northern Nigeria, herpes simplex was found in 47% of active corneal ulcers after mea- sles, and measles virus in 12%: the children often had evidence of oral herpes. In a study in Tanzania, blindness precipitated by mea- sles was associated with vitamin A deficiency (50%), herpes simplex infection (21%), and the use of traditional eye medicine (17%). Skin and other infections Pyoderma is common after measles. In the malnourished patient, deep eroding ulcers can bore through the skin, even into bone. When originating in the mouth they are known as cancrum oris or noma (Fig. 8.5.6.14). Otitis media is also common. Encephalitis This is a rare, but much feared, complication found in approximately 1 to 2 per 1000 cases. The onset is usually between 4 and 7 days after the start of the rash, but, rarely, it might occur within 48 h or up to 2 weeks from the onset. In addition to seizures, there is often fever, irritability, headache, and a disturbance in consciousness that can progress to profound coma. The disorder is probably attributable to a neuroallergic process. Lymphocytes from the cerebrospinal fluid have been shown to respond to myelin basic protein, as in experi- mental allergic encephalomyelitis. The virus cannot be isolated from cerebrospinal fluid, which contains lymphocytes and raised levels of IgG but normal levels of measles antibody. Mortality and morbidity Fig. 8.5.6.9 Measles rash in an African child. Fig. 8.5.6.10 Darkening measles rash after several days ('measles staining'). Courtesy of the late Dr B. E. Juel-Jensen. Fig. 8.5.6.11 Desquamating measles rash in an African child. Table 8.5.6.2 Complications and mortality in inpatients with measles, northern Nigeria, July–December 1978 No. Died Percentage dead Pneumonia 169 32 18.9 Gastroenteritis 65 9 13.8 Marasmic kwashiorkor 25 6 24.0 Laryngotracheobronchitis 21 4 19.0 Encephalitis 10 4 40.0 Reproduced with permission from Parry EHOP (ed) (1984). Principles of medicine in Africa, 2nd edition. Oxford University Press, Oxford. Fig. 8.5.6.12 Deep ulcers caused by herpes simplex virus. Copyright D. A. Warrell.

8.5.6 Measles 781 are high: 10–15% of patients die and 25% of children are left with permanent brain damage. Treatment is supportive; dexamethasone has no convincing beneficial effect. Late

complications Malnutrition This is the most frequent complication, for children of the developing world often lose a lot of weight during measles and may take many weeks to regain it. Those originally underweight, who have had severe measles, are at greatest risk, for anorexia in these children is prolonged, much protein is lost from the gut, and secondary in- fections, which lead to marasmus or marasmic kwashiorkor, are frequent. Measles has been shown to persist in the epithelia and lymphocytes of the severely malnourished for 30 or more days after the rash. Persistent infection Pneumonitis Giant cell pneumonia is found in patients with defects in cell-mediated immunity. Children with leukaemia or kwashiorkor are particularly vulnerable, as are those with symptomatic HIV in- fection. The lung disease might develop weeks after measles, and in most cases the rash of measles has been absent and thus the diagnosis may not be suspected. The diagnosis is made by viro- logical and/or histological examination of lung tissue. Most of these children die. Subacute sclerosing panencephalitis Persistent measles virus infection in the brain is responsible for this rare, progressive disease of the brain, which is found in 1 in 10 000 to 100 000 children after measles. The child with subacute sclerosing panencephalitis has usually experienced normal measles, albeit at a young age, 5–10 years earlier. The first indication is a disturbance in intellect and personality. Behavioural disorders and deterioration in school work are frequently mentioned. There then follow, over a period of weeks and months, myoclonus-like seizures, signs of extrapyramidal and pyramidal disease, and finally a state of decere- brate rigidity followed by death. The electroencephalogram shows a characteristic regular series of high-amplitude, spike-like waves. Very high titres of measles complement-fixing and haemagglutinin- inhibiting antibody are present both in serum and cerebrospinal fluid. Treatments for subacute sclerosing panencephalitis have in- cluded the use of transfer factor, plasmapheresis, and antiviral drugs, but to no avail. Multiple sclerosis, autism, and Crohn’s disease There is no convincing evidence that measles virus or immune re- sponses to it have a causative role in these diseases. The alleged as-sociation between the measles–mumps–rubella (MMR) vaccine, autism, and Crohn’s disease was based on weak science and has now been convincingly refuted by larger and stronger epidemiological studies. Subsequent molecular studies have failed to confirm the ori- ginal finding of measles virus and genomic RNA in diseased bowel. The false alarm raised by this report caused a substantial reduction in the number of children vaccinated against measles in the United Kingdom. Diagnosis This is primarily clinical, although signs might be less clear-cut in vaccinated subjects. Thus, in areas of high vaccine coverage the detection of measles-specific IgM antibody by enzyme-linked im- munoassay or, better still, the detection of measles by polymerase chain reaction in blood or urine can clinch the diagnosis if the rash is mild or atypical. Subclinical measles, which boosts immunity, is common in vaccinated children after exposure to measles: the Fig. 8.5.6.13 Corneal ulceration leading to impaired vision or blindness after measles, especially in malnourished and vitamin A deficient children. Copyright D. A. Warrell. Fig. 8.5.6.14 Cancrum oris, or noma, following measles.

 diagnosis is made by detecting a fourfold or greater rise in measles antibody within 2–6 weeks of exposure. It is not clear if such cases are infectious. Treatment of measles and its complications No effective antimeasles drug exists, yet some children do benefit from treatment in hospital. The following criteria indicate severe measles and a need for hospital admission: a widespread, confluent rash darkening to deep red or purple; signs of laryngeal obstruc- tion; subcutaneous emphysema; marked dehydration; blood in the stool or more than five stools a day; convulsion or loss of con- sciousness; severe secondary pneumonia; corneal ulceration; se- vere ulceration of the mouth and skin. These signs should be taken particularly

seriously when the child is underweight or frankly malnourished. Hydrate the child orally or intravenously. Treat lobar pneu- monia with benzylpenicillin, and bronchopneumonia with amoxicillin. If severe, or if there is coexisting HIV infection or severe malnutrition, use combined antibiotics such as ampicillin and gen- tamicin. If staphylococcal infection is suspected use flucloxacillin plus gentamicin. Antibiotic eye ointments relieve discomfort and possibly prevent secondary infections of measles conjunctivitis. Antibiotics (topical and systemic) and vitamin A should be given routinely for the treatment of eye ulcers. If herpes simplex virus is the cause, use aciclovir topically or, when severe, systemically. Candida infections of the mouth or gut often respond dramatically to nystatin. Feeding, by tube if necessary, needs careful planning and presentation, for the anorexic infected child will be in severe negative energy balance due to a greatly increased catabolic rate. Case fatality rates are 30–50% lower in those children in hospital treated with vitamin A. This should be given orally at the time of diagnosis and on the next day in a dose of 50 000 IU for children less than 6 months of age, 100 000 IU for children between 6 and 12 months of age and in a dose of 200 000 IU for older children. If eye signs of vitamin A deficiency are present, if the child is mal- nourished or the measles severe the initial dose should be repeated 2 to 3 weeks later. The prophylactic use of antibiotics such as amoxicillin or co-trimoxazole to prevent secondary infections after measles is a widespread practice based on slender evidence. The only community randomized, placebo-controlled trial was small: those children who received co-trimoxazole had less pneumonia and conjunctivitis and had a significantly higher weight gain (see Table 8.5.6.3). Prevention Passive immunization with human immunoglobulin is highly effective if given within 5 days of exposure, in a dose for children of 0.2 ml/kg. Immunoglobulin should be given to those in whom vac- cination is contraindicated such as severely immunocompromised children with cancer, AIDS, or congenital immunodeficiencies. For children with severe malnutrition, WHO recommends measles vac- cination in the acute phase followed by a second dose on recovery as the immune response is suboptimal. This is widely practised in hospitals in developing countries and in refugee camps where there are practical difficulties in providing immunoglobulin. Although live vaccines are theoretically undesirable in these immunocomprom- ised children, no head-to-head trials of these two preventions have been conducted. The currently used vaccines are live strains, attenuated by culture in chick fibroblasts. The Edmonston–Zagreb strain, which has been cultured in human diploid cells, is also widely used. It is more ef- fective than other vaccines in the presence of antibody, and should be used in a standard dose if vaccinating infants below 9 months of age, or if a booster dose is required. The complications of vaccin- ation are few and generally mild. Fever of moderate severity is infrequent, and a mild rash with some signs of upper respiratory tract infection occurs rarely. Underweight children respond normally to the vaccine, as do ill children attending the outpatient department and those on the ward. As clinics and hospitals are major sites of transmission of the virus in the developing world, all susceptible children in these places should be vaccinated unless severely im- munocompromised. Asymptomatic HIV-infected children are ini- tially protected by measles vaccine but antibody wanes more quickly than in uninfected children. WHO recommends early vaccination at 6 months of age followed by additional vaccinations at 9 months and another later in childhood. The measles vaccination policy for low income countries has seen major changes in the last 25 years. The optimal age for vaccin- ation in the developed world is between 14 and 16 months, when Table 8.5.6.3 Prophylactic antibiotic to prevent complications after measles in Guinea-Bissau Outcome Co-trimoxazole (n = 46) Placebo (n = 38) Adjusted odds ratio (95% CI) Pneumonia 1 (2%) 6 (16%) 0.14 (0.01–1.50) Hospitalization 0 3 – Diarrhoea 3 (7%) 5 (13%) 0.17 (0.01–1.55) Severe fever 6 (13%) 11 (29%) 0.36 (0.09–1.43) Stomatitis 4 (9%) 7 (18%) 0.43

(0.08–2.26) Conjunctivitis 12 (26%) 17 (45%) 0.31 (0.10–1.03) Weight gain (g/day) 32 15 – Adapted and reproduced from Garly M-L, et al. (2006). Prophylactic antibiotics to prevent pneumonia and other complications after measles: community based randomised double blind placebo controlled trial in Guinea-Bissau. BMJ, 333, 1245–50, copyright © 2006, with permission from BMJ Publishing Group Ltd.

8.5.6 Measles 783 maternal antibody has disappeared and the children will have the highest antibody response. However, this recommendation could not be applied to children in developing countries, because there measles infects at a much earlier age. In 1970s, the World Health Organization recommended vaccination at 9 months of age but, by then, 5 to 15% of children may have had measles in endemic areas. This policy was not based on good evidence; it is still not known if vaccination at 9 months is better for saving children than vaccination at 7, 8, or 10 months of age, or a two- dose regime in infancy. Intriguingly, all studies from developing countries suggest that the benefit of measles vaccine on overall survival is greater when given early and studies from randomized trials where the children were tested for prevaccination antibody levels have indicated that children vaccinated in the presence of maternal antibody have a much stronger nonspecific benefit from the vaccine. Through the 1990s it became clear that several doses of measles vaccines were needed to improve measles control. The developed countries have used two-dose strategies with a second dose being given at school entry or to young teenagers. Latin America has obtained major successes with a combination of improved vaccin- ation coverage and regular immunization campaigns providing a second opportunity for measles vaccination. The strategy has the following elements: (1) catch-up—a one-time mass campaign covering everybody between 9 months and 14 years of age regard- less of previous measles or immunization; (2) keep-up—achieving a high coverage for routine measles vaccination at 9 months of age for each birth cohort; (3) follow-up—subsequent mass cam- paigns covering all children every 3–5 years; and (4) mop-up— campaigns that target children who are difficult to reach or during outbreaks. As a result of this strategy, Latin America was declared free of internal measles transmission. Since there is no immediate risk of measles infection, the age of routine vaccination has been raised to 12 months as this is associated with higher antibody responses. The Latin American model has been transferred to other re- gions. Rebranded as SIA (supplementary immunization activ- ities), it has assured a spectacular success in reducing measles mortality in Africa. The goal of reducing global measles deaths by 90% by 2010 compared to 2000 has been met. Furthermore, WHO is now recommending a second dose of measles vaccine in the second year of life and more than half of the world's chil- dren are now receiving a second routine measles vaccination (see Fig. 8.5.6.1a) However, these campaigns, which are donor driven, are expensive and should not be seen as a substitute for an in- adequate immunization service. Recently, following the credit crunch, international financial support for this initiative has decreased and many countries have not been able to raise suffi- cient money for SIAs. The world has not met the global targets for 2015: a higher than 90% coverage for the first routine measles vaccine in every country, a measles incidence of under five cases/ million, 95% reduction of measles deaths and elimination of mea- sles in four WHO regions. Unfortunately, it is donor policy only to measure the coverage for the first measles vaccination by 12 months of age and there- fore some countries are no longer providing routine measles vaccination after 12 months of age. Although it is WHO policy that any unvaccinated child coming to a clinic should receive the measles vaccine, there is a drive to reduce wastage and not to open a vial of measles vaccine unless 5–7 children are present for vaccination. Such policies make it difficult to achieve high coverage and some countries have seen a decline in the measles vaccination coverage. Elimination or

eradication? Global measles eradication has yet to be made official policy but as polio eradication approaches there will be increasing interest in continuing with programmes to eradicate measles and rubella. The Americas have attained elimination (i.e. no internal transmission of the virus), and other regions are pursuing such a policy. Measles satisfies the criteria for eradication for there is no animal reservoir, it is only transmitted between humans, it is easy to diagnose, and vaccines are available. Measles elimination can be accomplished for prolonged periods in defined geographical regions provided there is sufficient funding and political will. This was obtained for the first time in the Gambia in the mid-1960s as part of the smallpox eradication and measles vaccination campaigns. Rinderpest, a virus closely related to measles that decimated cattle and wild game populations over the centuries, was eradicated in 2010. Now a WHO panel has declared that measles can and should be eradicated by 2020. It stressed that eradication activities should be carried out as part of routine immunization services and estimated it would cost $US 7.8 billion. However, eradicating measles will be a daunting task for, despite global coverage of 85%, the infection is still rife in many countries (see Fig. 8.5.6.1c) First, it is the most infectious of diseases and will require vaccine coverage of greater than 95%. When there is little risk of infection, it will be increasingly difficult for parents to ap- preciate the necessity for vaccination especially as risk, although small, needs to be perceived. Secondly, herd immunity will be- come a problem as with less exposure to the virus, vaccine-induced immunity will wane more rapidly. Thirdly, some countries like Pakistan or Afghanistan and many countries in Africa will be stern tests since political instability, wars, and natural disasters make it difficult to maintain sufficiently high coverage. Fourthly, but most demanding, will be to assure long-term funding as donors have a tradition of changing priorities. The international health community is split over whether eradi- cation can be attained with the Latin American strategy using existing vaccines or whether new vaccines and delivery systems such as aerosolization are needed. New vaccines, which can be given in early infancy, or two-dose strategies using the standard Edmonston–Zagreb vaccine at 4 and 9 months of age, might be necessary to contain measles in the developing world. The latter strategy has the advantage that it might confer beneficial non specific effects on child survival in countries with high childhood mortality. In Guinea-Bissau, per protocol analysis of a trial of two doses of Edmonston–Zagreb measles vaccine in infancy revealed a mortality rate 30% lower than in the controls who received a single dose of measles vaccine at 9 months of age. Coverage of at least 95% of all susceptible children, including those between 3 and 9 months of age, with a vaccine that is at least 95% effective

---

Revision #1
Created 2026-01-22 16:45:28 UTC by Omar Ayman
Updated 2026-01-22 16:45:28 UTC by Omar Ayman