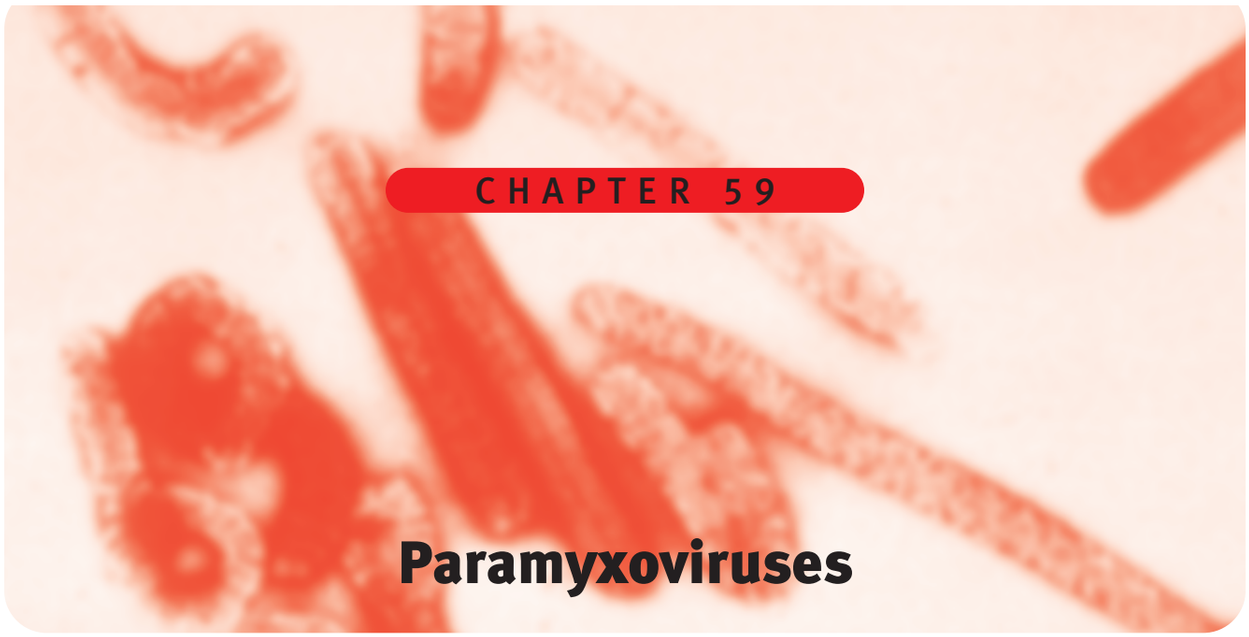


CHAPTER 59

Paramyxoviruses

The Paramyxoviridae include the following genera: *Morbillivirus, Paramyxovirus,* and *Pneumovirus* (Table 59–1). Human pathogens within the morbilliviruses include the **measles** virus; within the paramyxoviruses, the **parainfluenza** and **mumps** viruses; and within the pneumoviruses, the **respiratory syncytial virus** (RSV) and newly discovered, but relatively common, **metapneumovirus.** Their virions have similar morphologies and protein components, and they share the capacity to induce **cell-cell fusion** (syncytia formation and multinucleated giant cells). A new group of highly pathogenic paramyxoviruses, including two zoonosis-causing viruses, **Nipah virus** and **Hendra virus,** was identified in 1998 after an outbreak of severe encephalitis in Malaysia and Singapore.

These agents cause some well-knownmajor diseases. Measles virus causes a potentially serious generalized infection characterized by a maculopapular rash (**rubeola**). Parainfluenza viruses cause upper and lower respiratory tract infections, primarily in children, including pharyngitis, croup, bronchitis, bronchiolitis, and pneumonia. Mumps virus causes a systemic infection whose most prominent clinical manifestation is parotitis. RSV causes mild upper respiratory tract infections in children and adults but can cause life-threatening pneumonia in infants.

Measles and mumps viruses have *only one serotype,* and protection is provided by an effective **live vaccine.** In the United States and other developed countries, successful vaccination programs using the live attenuated measles and mumps vaccines have made measles and mumps rare. In particular, these programs have led to the virtual elimination of the serious sequelae of measles.

Structure and Replication

Paramyxoviruses consist of **negative-sense, single-stranded ribonucleic acid (RNA)** (5 to 8×10^6 Da) in a helical nucleocapsid surrounded by a pleomorphic **envelope** of approximately 156 to 300 nm (Figure 59–1). They are similar in many respects to orthomyxoviruses but are larger and do not have the segmented genome of the influenza viruses (Box 59–1). Although significant homology exists among paramyxovirus genomes, the order of the protein-coding regions differs for each genus. The gene products of the measles virus are listed in Table 59–2.

The nucleocapsid consists of the negative-sense, single-stranded RNA associated with the nucleoprotein (**NP**), polymerase phosphoprotein (**P**), and large (**L**) protein. The L protein is the RNA polymerase, the P protein facilitates RNA synthesis, and the NP protein helps maintain genomic structure. The nucleocapsid associates with the matrix (**M**) protein lining the inside of the virion envelope. The envelope contains two glycoproteins, a fusion (**F**) protein, which promotes fusion of the viral and host cell membranes, and a viral attachment protein (hemagglutinin-neuraminidase [**HN**], hemagglutinin [**H**], or **G** protein) (see Box 59–1). The F protein must be activated by proteolytic cleavage, which produces F_1 and F_2 glycopeptides held together by a disulfide bond, to express membrane-fusing activity.

Replication of the paramyxoviruses is initiated by the binding of the HN, H, or G protein on the virion envelope to sialic acid on the cell surface glycolipids. The measles virus binds to a protein, CD46 (membrane cofactor protein, MCP). This receptor is present on most cell types,

TABLE 59–1. Paramyxoviridae

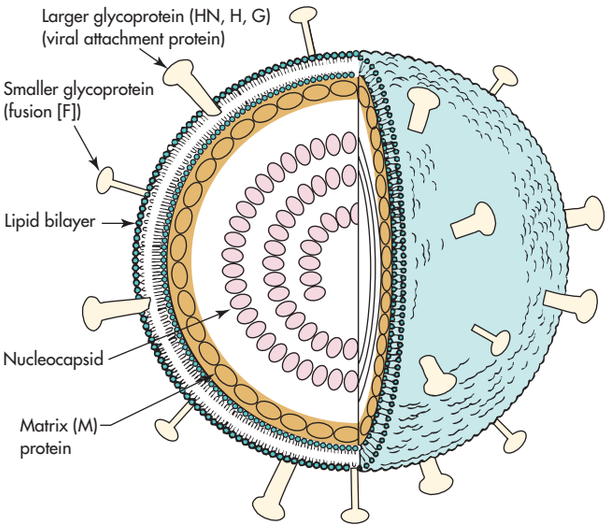
Genus	Human Pathogen
Morbillivirus	Measles virus
Paramyxovirus	Parainfluenza viruses 1 to 4 Mumps virus
Pneumovirus	Respiratory syncytial virus Metapneumovirus

BOX 59–1. Unique Features of the Paramyxoviridae

- Large virion consists of a negative RNA genome in a helical nucleocapsid surrounded by an envelope containing a viral attachment protein (hemagglutinin-neuraminidase [HN], parainfluenza virus and mumps virus; hemagglutinin [H], measles virus; and glycoprotein [G], respiratory syncytial virus [RSV]) and a fusion glycoprotein (F).
- The three genera can be distinguished by the activities of the viral attachment protein: HN of parainfluenza virus and mumps virus has hemagglutinin and neuraminidase, and H of measles virus has hemagglutinin activity, but G of RSV lacks these activities.
- Virus replicates in the cytoplasm.
- Virions penetrate the cell by fusion with and exit by budding from the plasma membrane.
- Viruses induce cell-cell fusion, causing multinucleated giant cells.
- Paramyxoviridae are transmitted in respiratory droplets and initiate infection in the respiratory tract.
- Cell-mediated immunity causes many of the symptoms but is essential for control of the infection.

protects the cell from complement by regulating complement activation, and is also the receptor for human herpes virus 6 and some strains of adenovirus. The F protein promotes fusion of the envelope with the plasma membrane. Paramyxoviruses are also able to induce cell-cell fusion, thereby creating multinucleated giant cells (syncytia).

The replication of the genome occurs in a manner similar to that of other negative-strand RNA viruses (i.e., rhabdoviruses). The RNA polymerase is carried into the cell as part of the nucleocapsid. Transcription, protein synthesis, and replication of the genome all occur in the host cell's cytoplasm. The genome is transcribed into individual messenger RNAs (mRNAs) and a full-length positive-sense RNA template. New genomes associate with the L, N, and NP proteins to form nucleocapsids, which associate with the M proteins on viral glycoprotein–modified plasma membranes. The glycoproteins are synthesized and processed like cellular glycoproteins. Mature virions then bud from the host cell plasma membrane and exit the cell. Replication of the paramyxoviruses is represented by the RSV infectious cycle shown in Figure 59–2.



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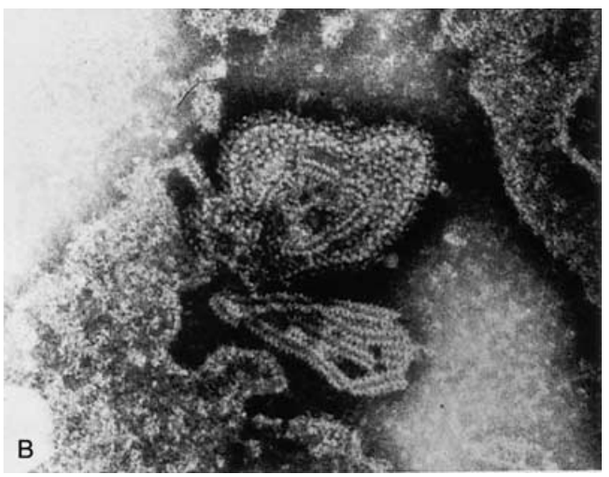

FIGURE 59–1. A, Model of paramyxovirus. The helical nucleocapsid–consisting of negative-sense, single-stranded RNA and the P protein, nucleoprotein (NP), and large (L) protein—associates with the matrix (M) protein at the envelope membrane surface. The nucleocapsid contains RNA transcriptase activity. The envelope contains the viral attachment glycoprotein (hemagglutinin-neuraminidase [HN], hemagglutinin [H], or G protein [G]) and the fusion (F) protein. **B,** Electron micrograph of a disrupted paramyxovirus showing the helical nucleocapsid. (**A** redrawn from Jawetz E, Melnick JL, Adelberg EA: *Review of medical microbiology,* ed 17, Norwalk, Conn, 1987, Appleton & Lange; **B** courtesy Centers for Disease Control and Prevention, Atlanta.)

Measles Virus

Measles is one of the five classic childhood exanthems, along with rubella, roseola, fifth disease, and chickenpox. Historically, measles was one of the most common and unpleasant viral infections with potential sequelae. Before 1960, more than 90% of the population younger than 20 years had experienced the rash, high fever, cough,

TABLE 59–2. Viral-Encoded Proteins of Measles Virus

Gene Products*	Virion Location	Function
Nucleoprotein (NP)	Major internal protein	Protection of viral RNA
Polymerase phosphoprotein (P)	Association with nucleoprotein	Possible part of transcription complex
Matrix (M)	Inside virion envelope	Assembly of virions
Fusion factor (F)	Transmembranous envelope glycoprotein	Factor active in fusion of cells, hemolysis, and viral entry
Hemagglutinin-neuraminidase (HN): hemagglutinin (H); glycoprotein (G)	Transmembranous envelope glycoprotein	Viral attachment proteins
Large protein (L)	Association with nucleoprotein	Polymerase

Modified from Fields BN, editor: *Virology,* New York, 1985, Raven.
*In order of transcription.

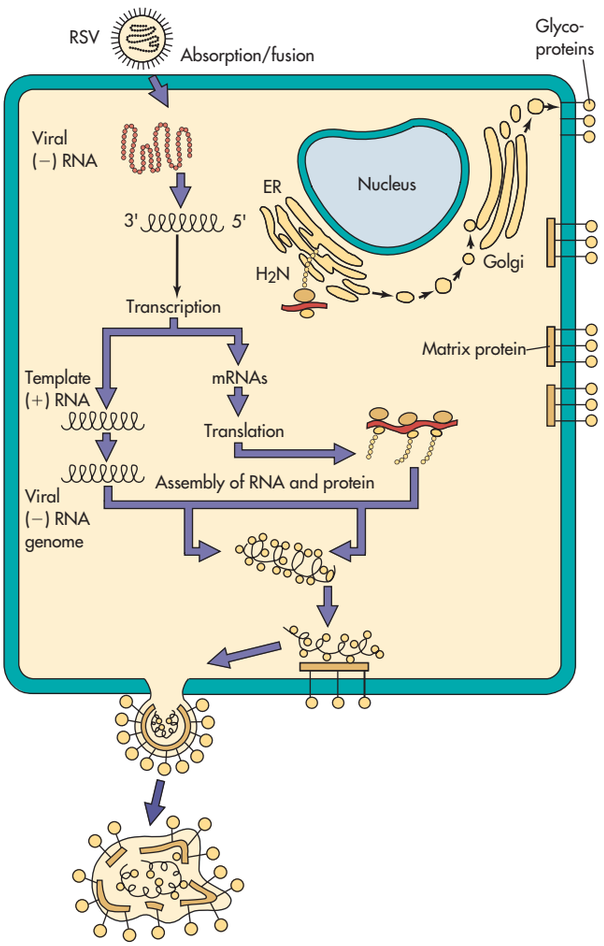

FIGURE 59–2. Replication of paramyxoviruses. The virus binds to glycolipids or proteins and fuses with the cell surface. Individual mRNAs for each protein and a full-length template are transcribed from the genome. Replication occurs in the cytoplasm. The nucleocapsid associates with matrix and glycoprotein-modified plasma membranes and leaves the cell by budding. (–), Negative sense; (+), positive sense; ER, endoplasmic reticulum; RSV, respiratory syncytial virus. (Redrawn from Balows A, Hausler WJ Jr, Lennette-EH: *Laboratory diagnosis of infectious diseases: Principles and practice,* New York, 1988, Springer-Verlag.)

conjunctivitis, and coryza of measles. Since the use of the live vaccine began in 1993, fewer than 1000 cases have been reported in the United States. Measles is still one of the most prominent causes of disease (30 to 40 million cases per year) and death (1 to 2 million per year) worldwide in unvaccinated populations.

PATHOGENESIS AND IMMUNITY

Measles is known for its propensity to cause cell fusion, leading to the formation of giant cells (Box 59–2). As a result, the virus can pass directly from cell to cell and escape antibody control. Inclusions occur most commonly in the cytoplasm and are composed of incomplete viral particles. Infection usually leads to cell lysis, but persistent infections without lysis can occur in certain cell types (e.g., human brain cells).

Measles is **highly contagious** and is transmitted from person to person by **respiratory droplets** (Figure 59–3). Local replication of virus in the respiratory tract precedes its spread to the lymphatic system and cell-associated viremia. The wide dissemination of the virus causes infection of the conjunctiva, respiratory tract, urinary tract, small blood vessels, lymphatic system, and the central nervous system. During the incubation period, measles causes a decrease in eosinophils and lymphocytes, including B and T cells, and a depression of their response to activation (mitogens). *The characteristic* ***maculopapular*** *measles rash is caused by immune T cells targeted to measles-infected endothelial cells lining small blood vessels.* Recovery follows the rash in most patients, who then have **lifelong immunity** to the virus. The time course of measles infection is shown in Figure 59–4.

Measles can cause encephalitis in three ways: (1) direct infection of neurons, (2) a postinfectious encephalitis, which is believed to be immune mediated, and (3) subacute sclerosing panencephalitis (SSPE) caused by a defective variant of measles generated during the acute disease.

BOX 59–2. Disease Mechanisms of Measles Virus

Virus infects epithelial cells of respiratory tract.
Virus spreads systemically in lymphocytes and by **viremia.**
Virus replicates in cells of conjunctivae, respiratory tract, urinary tract, lymphatic system, blood vessels, and central nervous system.
Rash is caused by T-cell response to virus-infected epithelial cells lining capillaries.
Cell-mediated immunity is essential to control infection; antibody is not sufficient because of measles' ability to spread cell to cell.
Sequelae in central nervous system may result from immunopathogenesis (postinfectious measles encephalitis) or development of defective mutants (subacute sclerosing panencephalitis).

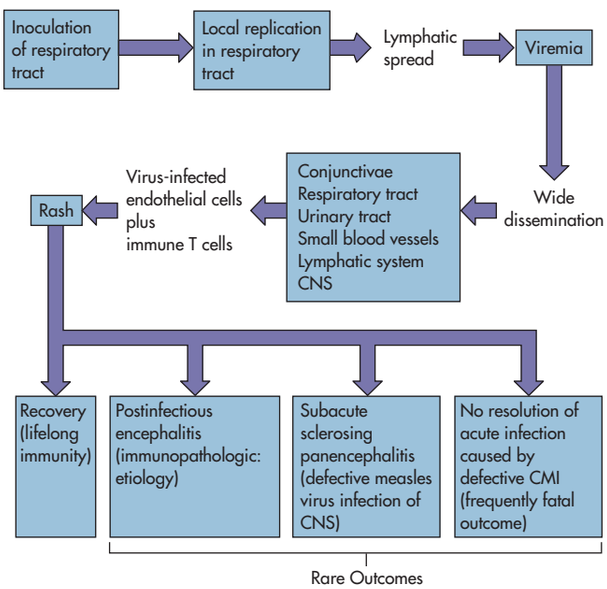

FIGURE 59–3. Mechanisms of spread of the measles virus within the body and the pathogenesis of measles. CMI, Cell-mediated immunity; CNS, central nervous system.

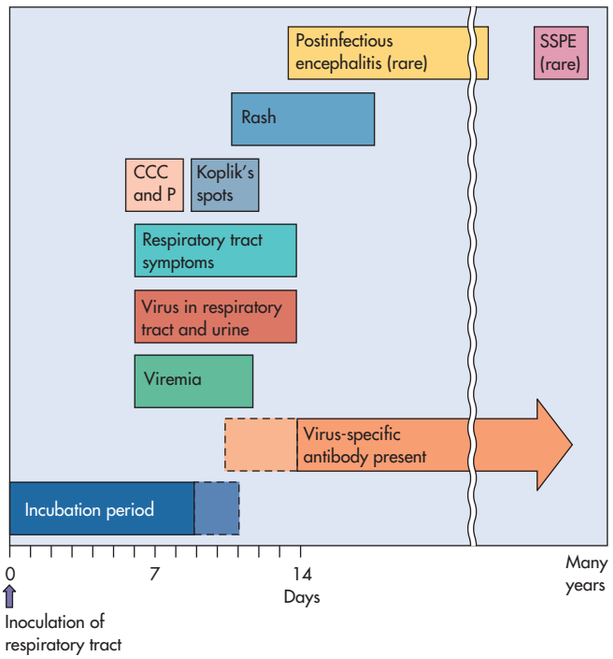

FIGURE 59–4. Time course of measles virus infection. Characteristic prodrome symptoms are cough, conjunctivitis, coryza, and photophobia (CCC and P), followed by the appearance of Koplik's spots and rash. SSPE, Subacute sclerosing panencephalitis.

The SSPE virus acts as a slow virus and causes cytopathologic effect in neurons and symptoms many years after acute disease.

Cell-mediated immunity is responsible for most of the symptoms and is essential for the control of measles infection. T-cell–deficient children who are infected with measles have an atypical presentation consisting of **giant cell pneumonia without a rash.** During measles infection, and for weeks after, the virus depresses the immune response by directly infecting monocytes, T and B cells and by promoting a switch to T cell production of TH2-associated cytokines, especially interleukin 4 (IL4), IL5, IL10, and IL13. These cytokines reduce the host's ability to mount protective cell–mediated immune and DTH-type responses. Despite this condition, protection from reinfection is lifelong.

EPIDEMIOLOGY

The development of effective vaccine programs has made measles a rare disease in the United States. In areas without a vaccine program, epidemics tend to occur in 1- to 3-year cycles, when a sufficient number of susceptible people have accumulated. Many of these cases occur in preschool-age children who have not been vaccinated and who live in large urban areas. The incidence of infection peaks in the winter and spring. Measles is still common in people living in developing countries and is the most significant cause of death in children 1 to 5 years of age in several countries. Immunocompromised and malnourished people with measles may not be able to resolve the infection, resulting in death.

Measles, which can be spread in respiratory secretions before and after the onset of characteristic symptoms, is one of the most contagious infections known (Box 59–3). In a household, approximately 85% of exposed susceptible people become infected, and 95% of these people develop clinical disease.

The measles virus has only one serotype and infects only humans, and infection usually manifests as

symptoms. These properties facilitated the development of an effective vaccine program. Once vaccination was introduced, the yearly incidence of measles dropped dramatically in the United States, from 300 to 1.3 per 100,000 (U.S. statistics for 1981 to 1988). This change represented a 99.5% reduction in the incidence of the infection from that in the prevaccination period from 1955 to 1962.

Poor compliance with vaccination programs and the prevaccinated population (<2 years old) provide susceptible individuals to measles. The virus may surface from within the community or can be imported by immigration from areas of the world lacking an effective vaccine program. An outbreak of measles in a daycare center (10 infants, too young to have been vaccinated, and two adults) was traced to an infant from the Philippines.

BOX 59–3. Epidemiology of Measles

Disease/Viral Factors
Virus has large enveloped virion that is easily inactivated by dryness and acid.
Contagion period precedes symptoms.
Host range is limited to humans.
Only one serotype exists.
Immunity is lifelong.

Transmission
Inhalation of large-droplet aerosols.

Who Is at Risk?
Unvaccinated people.
Immunocompromised people, who have more serious outcomes.

Geography/Season
Virus is found worldwide.
Virus is endemic from autumn to spring, possibly because of crowding indoors.

Modes of Control
Live attenuated vaccine (Schwartz or Moraten variants of Edmonston B strain) can be administered.
Immune serum globulin can be administered after exposure.

CLINICAL SYNDROMES

Measles is a serious febrile illness (Table 59–3). The incubation period lasts 7 to 13 days, and the prodrome starts with **high fever** and CCC and P—**cough, coryza, conjunctivitis,** and **photophobia.** The disease is most infectious during this time.

After 2 days of illness, the typical mucous membrane lesions, known as **Koplik's spots** (Figure 59–5), appear. They are seen most commonly on the buccal mucosa across from the molars, but they may appear on other mucous membranes as well, including the conjunctivae and the vagina. The lesions, which last 24 to 48 hours, are usually small (1 to 2 mm) and are best described as grains of salt surrounded by a red halo. Their appearance in the mouth establishes with certainty the diagnosis of measles.

Within 12 to 24 hours of the appearance of Koplik's spots, the **exanthem** of measles starts below the ears and

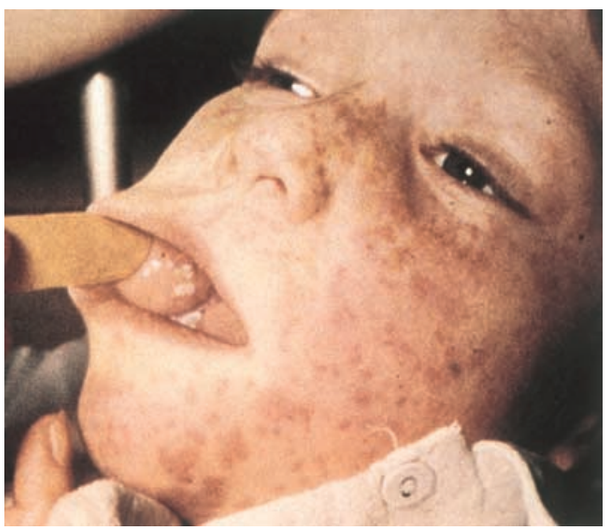

FIGURE 59–5. Koplik's spots in the mouth and exanthem. Koplik's spots usually precede the measles rash and may be seen for the first day or two after the rash appears. (Courtesy Dr. J.I. Pugh, St. Albans; from Emond RTD, Rowland HAK: *A color atlas of infectious diseases,* ed 3, London, 1995, Mosby.)

TABLE 59–3. Clinical Consequences of Measles Virus Infection

Disorder	Symptoms
Measles	Characteristic maculopapular rash, cough, conjunctivitis, coryza, photophobia, Koplik's spots *Complications:* Otitis media, croup, bronchopneumonia, and encephalitis
Atypical measles	More intense rash (most prominent in distal areas); possible vesicles, petechiae, purpura, or urticaria
Subacute sclerosing panencephalitis	Central nervous system manifestations (e.g., personality, behavior, and memory changes; myoclonic jerks; spasticity; and blindness

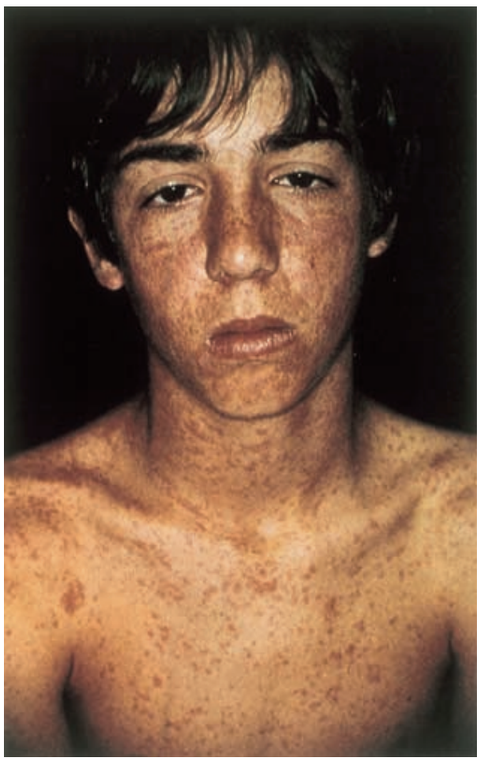

FIGURE 59–6. Measles rash. (From Habif TP: *Clinical dermatology: Color guide to diagnosis and therapy,* St Louis, 1985, Mosby.)

spreads over the body. The **rash is maculopapular** and usually very extensive, and often the lesions become confluent. The rash, which takes 1 or 2 days to cover the body, fades in the same order in which it appeared over the body. The fever is highest and the patient is sickest on the day the rash appears (Figure 59–6).

Pneumonia, which can also be a serious complication, accounts for 60% of the deaths caused by measles. The mortality associated with pneumonia, like the incidence of the other complications associated with measles, is higher in the malnourished and for the extremes of age. **Bacterial superinfection** is common in patients with pneumonia caused by the measles virus.

One of the most feared complications of measles is **encephalitis,** which may occur in as many as 0.5% of those infected and may be fatal in 15% of cases. Encephalitis can rarely occur during acute disease, but usually begins 7 to 10 days after the onset of illness. **This postinfectious encephalitis** is caused by immunopathologic reactions, is associated with demyelination of neurons, and occurs more often in older children and adults.

Atypical measles occurred in people who received the older inactivated measles vaccine and were subsequently exposed to the wild measles virus. It may also rarely occur in those vaccinated with the attenuated virus vaccine. Prior sensitization with insufficient protection enhances the immunopathologic response to the challenge by wild measles virus. The illness begins abruptly and is a more intense presentation of measles. 1

Subacute sclerosing panencephalitis is an extremely serious, very late neurologic sequela of measles that afflicts approximately seven of every 1 million patients. The incidence of SSPE has decreased markedly as the result of the measles vaccination programs.

This disease occurs when a defective measles virus persists in the brain and acts as a slow virus. The virus can replicate and spread directly from cell to cell but is not released. SSPE is most prevalent in children who were initially infected when younger than 2 years and occurs approximately 7 years after clinical measles. The patient demonstrates changes in personality, behavior, and memory, followed by myoclonic jerks, blindness, and spasticity. Unusually high levels of measles antibodies are found in the blood and cerebrospinal fluid of patients with SSPE.

The immunocompromised and malnourished child is at highest risk for severe outcome of measles. **Giant cell pneumonia without rash** occurs in children lacking T-cell immunity. Severe bacterial superinfection and pneumonia occur in malnourished children, with up to 25% mortality.

LABORATORY DIAGNOSIS

The clinical manifestations of measles are usually so characteristic that it is rarely necessary to perform laboratory tests to establish the diagnosis. The measles virus is difficult to isolate and grow, although it can be grown in primary human or monkey cell cultures. Respiratory tract secretions, urine, blood, and brain tissue are the recommended specimens. It is best to collect respiratory and blood specimens during the prodromal stage and up until 1 to 2 days after the appearance of the rash.

Measles antigen can be detected with immunofluorescence in pharyngeal cells or urinary sediment or the measles genome by reverse transcriptase polymerase chain reaction (RT-PCR) in any of the aforementioned specimens. Characteristic cytopathologic effects, including multinucleated giant cells with cytoplasmic inclusion bodies, can be seen in Giemsa-stained cells taken from the upper respiratory tract and urinary sediment.

Antibody, especially immunoglobulin (Ig)M, can be detected when the rash is present. Measles infection can be confirmed by the finding of seroconversion or a fourfold increase in the titer of measles-specific antibodies between sera obtained during the acute stage and the convalescent stage.

BOX 59–4. Measles-Mumps-Rubella (MMR) Vaccine

Composition: Live attenuated viruses
Measles: Schwartz or Moraten substrains of Edmonston B strain
Mumps: Jeryl Lynn strain
Rubella: RA/27-3 strain
Vaccination schedule: At age 15-24 months and at age 4-6 years or before junior high school (12 years of age)
Efficiency: 95% lifelong immunization with a single dose

*Data from update on adult immunization, *MMWR Morb Mortal Wkly Rep* 40(RR-12), 1991.

BOX 59–5. Disease Mechanisms of Parainfluenza Viruses

There are four serotypes of viruses.
Infection is **limited to respiratory tract;** upper respiratory tract disease is most common, but significant disease can occur with lower respiratory tract infection.
Parainfluenza viruses do *not* cause viremia or become systemic
Diseases include **coldlike** symptoms, **bronchitis** (inflammation of bronchial tubes), and **croup** (laryngotracheobronchitis).
Infection induces protective immunity of short duration.

TREATMENT, PREVENTION, AND CONTROL

A live attenuated measles vaccine, in use since 1963, has been responsible for a significant reduction in the incidence of measles in the United States. The current Schwartz or Moraten attenuated strains of the original Edmonston B vaccine are being used in the United States. Live attenuated vaccine is given to all children at 2 years of age, in combination with mumps and rubella (**MMR vaccine**) and the varicella vaccines (Box 59–4). Although immunization is successful in more than 95% of vaccinees, revaccination is required in much of the United States for children before grade school or junior high school. As noted earlier, a killed measles vaccine, which was introduced in 1963, was not protective, and its use was subsequently discontinued because recipients were at risk for the more serious atypical measles presentation on infection. Although measles is a good candidate for eradication, because it is strictly a human virus and there is only one serotype, this is prevented by difficulties in distributing the vaccine to regions that lack proper refrigeration facilities (e.g., Africa) and distribution networks.

Hospitals in areas experiencing endemic measles may wish to vaccinate or check the immune status of their employees to decrease the risk of nosocomial transmission. Exposed susceptible people who are immunocompromised should be given immune globulin to lessen the risk and severity of clinical illness. This product is most effective if given within 6 days of exposure. No specific antiviral treatment is available for measles.

Parainfluenza Viruses

Parainfluenza viruses, which were discovered in the late 1950s, are respiratory viruses that usually cause **mild coldlike symptoms** but can also cause **serious respiratory tract disease.** Four serologic types within the parainfluenza genus are human pathogens. Types 1, 2, and 3 are second only to RSV as important causes of severe lower respiratory tract infection in infants and young children. They are especially associated with **laryngotracheobronchitis** (**croup**). Type 4 causes only mild upper respiratory tract infection in children and adults.

PATHOGENESIS AND IMMUNITY

Parainfluenza viruses infect epithelial cells of the upper respiratory tract (Box 59–5). The virus replicates more rapidly than measles and mumps viruses and can cause giant cell formation and cell lysis. Unlike measles and mumps viruses, the parainfluenza viruses rarely cause viremia. The viruses generally stay in the upper respiratory tract, causing only coldlike symptoms. In approximately 25% of cases the virus spreads to the lower respiratory tract, and in 2% to 3%, disease may take the severe form of laryngotracheobronchitis.

The cell-mediated immune response both causes cell damage and confers protection. IgA responses are protective but short-lived. Parainfluenza viruses manipulate cell-mediated immunity to limit development of memory. Multiple serotypes and the short duration of immunity after natural infection make reinfection common, but the reinfection disease is milder, suggesting at least partial immunity.

EPIDEMIOLOGY

Parainfluenza viruses are ubiquitous, and infection is common (Box 59–6). The virus is transmitted by person-to-person contact and respiratory droplets. Primary infections usually occur in infants and children younger than 5 years. Reinfections occur throughout life, indicating short-lived immunity. Infections with parainfluenza viruses 1 and 2, the major causes of croup, tend to occur in the autumn, whereas parainfluenza virus 3 infections occur throughout the year. All of these viruses spread readily within hospitals and can cause outbreaks in nurseries and pediatric wards.

CLINICAL SYNDROMES

Parainfluenza viruses 1, 2, and 3 may cause respiratory tract syndromes ranging from a **mild coldlike upper respiratory tract infection** (coryza, pharyngitis, mild bronchitis, wheezing, and fever) to **bronchiolitis** and **pneumonia.** Older children and adults generally experience milder infections than those seen in young children, although pneumonia may occur in the elderly.

A parainfluenza virus infection in infants may be more severe than infections in adults, causing bronchiolitis, pneumonia, and, most notably, croup (laryngotracheobronchitis). **Croup** results in subglottal swelling, which may close the airway. Hoarseness, a "seal bark" cough, tachypnea, tachycardia, and suprasternal retraction develop in infected patients after a 2- to 6-day incubation period. Most children recover within 48 hours. The principal differential diagnosis is epiglottitis caused by *Haemophilus influenzae.*

LABORATORY DIAGNOSIS

Parainfluenza virus is isolated from nasal washings and respiratory secretions and grows well in primary monkey kidney cells. Like other paramyxoviruses, the virions are labile during transit to the laboratory. The presence of virus-infected cells in aspirates or in cell culture is indicated by the finding of syncytia and is identified with immunofluorescence. Like the hemagglutinin of the influenzaviruses, the hemagglutinin of the parainfluenza viruses promotes hemadsorption and hemagglutination. The serotype of the virus can be determined through the use of specific antibody to block hemadsorption or hemagglutination (hemagglutination inhibition). Rapid RT-PCR techniques are becoming the method of choice to detect and identify parainfluenza viruses from respiratory secretions.

BOX 59–6. Epidemiology of Parainfluenza Virus Infections

Disease/Viral Factors
Virus has large enveloped virion that is easily inactivated by dryness and acid.
Contagion period precedes symptoms and may occur in absence of symptoms.
Host range is limited to humans.
Reinfection can occur later in life.

Transmission
Inhalation of large-droplet aerosols.

Who Is at Risk?
Children: At risk for mild disease or croup.
Adults: At risk for reinfection with milder symptoms.

Geography/Season
Virus is ubiquitous and worldwide.
Incidence is seasonal.

Modes of Control
There are no modes of control.

TREATMENT, PREVENTION, AND CONTROL

Treatment of croup consists of the administration of nebulized cold or hot steam and careful monitoring of the upper airway. On rare occasions, intubation may become necessary. No specific antiviral agents are available.

Vaccination with killed vaccines is ineffective, possibly because they fail to induce local secretory antibody and appropriate cellular immunity. No live attenuated vaccine is available.

Mumps Virus

Mumps virus is the cause of acute, benign viral **parotitis** (painful swelling of the salivary glands). Mumps is rarely seen in countries that promote use of the live vaccine, which is administered with the measles and rubella live vaccines.

Mumps virus was isolated in embryonated eggs in 1945 and in cell culture in 1955. The virus is most closely related to parainfluenza virus 2, but there is no cross-immunity with the parainfluenza viruses.

PATHOGENESIS AND IMMUNITY

The mumps virus, of which only one serotype is known, causes a lytic infection of cells (Box 59–7). The virus initiates infection in the epithelial cells of the upper respiratory tract and infects the parotid gland either by way of Stensen's duct or by means of a viremia. The virus is spread by the viremia throughout the body to the testes, ovary, pancreas, thyroid, and other organs. Infection of the central nervous system, especially the meninges, with symptoms (meningoencephalitis) occurs in as many as

BOX 59–7. Disease Mechanisms of Mumps Virus

Virus infects epithelial cells of respiratory tract.
Virus spreads systemically by viremia.
Infection of parotid gland, testes, and central nervous system occurs.
Principal symptom is swelling of parotid glands caused by inflammation.
Cell-mediated immunity is essential for control of infection and is responsible for causing some of the symptoms. Antibody is not sufficient because of virus' ability to spread cell to cell.

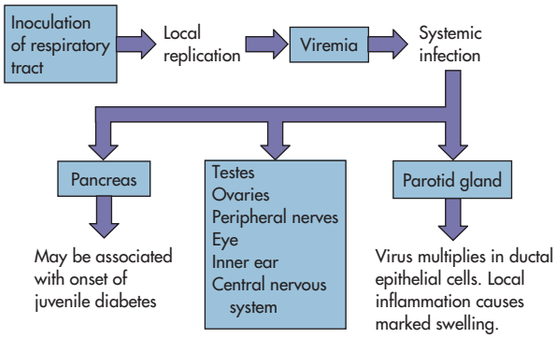

FIGURE 59–7. Mechanism of spread of mumps virus within the body.

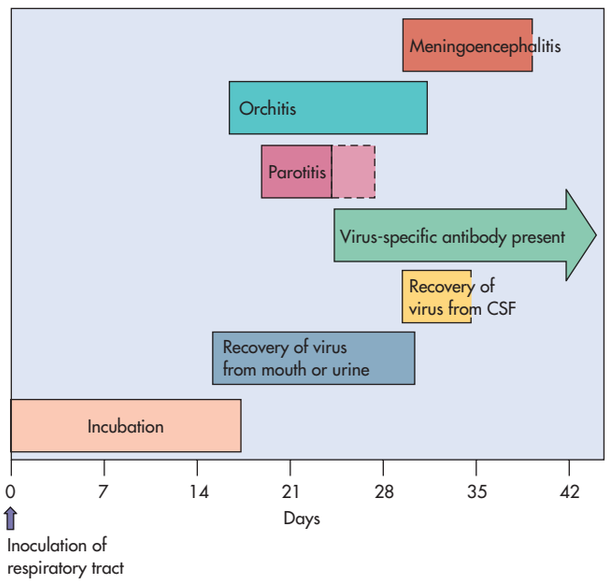

FIGURE 59–8. Time course of mumps virus infection.

50% of those infected (Figure 59–7). Inflammatory responses are mainly responsible for the symptoms. The time course of human infection is shown in Figure 59–8. Immunity is lifelong.

EPIDEMIOLOGY

Mumps, like measles, is a very communicable disease with only one serotype, and it infects only humans (Box 59–8). In the absence of vaccination programs, infection occurs in 90% of people by the age of 15. The virus spreads by direct person-to-person contact and respiratory droplets. The virus is released in respiratory secretions from patients who are asymptomatic and during the 7-day period before clinical illness, so it is virtually impossible to control the spread of the virus. Living or working in close quarters promotes the spread of the virus, and the incidence of the infection is greatest in the winter and spring.

BOX 59–8. Epidemiology of Mumps Virus

Disease/Viral Factors
Virus has large enveloped virion that is easily inactivated by dryness and acid.
Contagion period precedes symptoms.
Virus may cause asymptomatic shedding.
Host range is limited to humans.
Only one serotype exists.
Immunity is lifelong.

Transmission
Inhalation of large-droplet aerosols.

Who Is at Risk?
Unvaccinated people.
Immunocompromised people, who have more serious outcomes.

Geography/Season
Virus is found worldwide.
Virus is endemic in late winter and early spring.

Modes of Control
Live attenuated vaccine (Jeryl Lynn strain) is part of MMR vaccine.

CLINICAL SYNDROMES

Mumps infections are often asymptomatic. Clinical illness manifests as a parotitis that is almost always bilateral and accompanied by fever. Onset is sudden. Oral examination reveals redness and swelling of the ostium of Stensen's (parotid) duct. The swelling of other glands (epididymo-orchitis, oophoritis, mastitis, pancreatitis, and thyroiditis) and meningoencephalitis may occur a few days after the onset of the viral infection but can occur in the absence of parotitis. The swelling that results from mumps orchitis may cause sterility. Mumps virus involves the central nervous system in approximately 50% of patients; and 10% of those affected may exhibit clinical evidence of such an infection.

LABORATORY DIAGNOSIS

Virus can be recovered from saliva, urine, the pharynx, secretions from Stensen's duct, and cerebrospinal fluid. Virus is present in saliva for approximately 5 days after the onset of symptoms and in urine for as long as 2 weeks. Mumps virus grows well in monkey kidney cells, causing the formation of multinucleated giant cells. The hemadsorption of guinea pig erythrocytes also occurs on virus-infected cells, due to the viral hemagglutinin.

A clinical diagnosis can be confirmed by serologic testing. A fourfold increase in the virus-specific antibody level or the detection of mumps-specific IgM antibody

indicates active infection. Enzyme-linked immunosorbent assay, immunofluorescence tests, and hemagglutination inhibition can be used to detect the mumps virus, antigen, or antibody.

TREATMENT, PREVENTION, AND CONTROL

Vaccines provide the only effective means for preventing the spread of mumps infection. Since the introduction of the live attenuated vaccine (Jeryl Lynn vaccine) in the United States in 1967 and its administration as part of the MMR vaccine, the yearly incidence of the infection has declined from 76 to 2 per 100,000. Antiviral agents are not available.

Respiratory Syncytial Virus

RSV, first isolated from a chimpanzee in 1956, is a member of the *Pneumovirus* genus. Unlike the other paramyxoviruses, RSV lacks hemagglutinin and neuraminidase activities. It is the most common cause of **fatal acute respiratory tract infection** in infants and young children. It infects virtually everyone by 2 years of age, and reinfections occur throughout life, even among elderly persons.

PATHOGENESIS AND IMMUNITY

RSV produces an infection that is localized to the respiratory tract (Box 59–9). As the name suggests, RSV induces syncytia. The pathologic effect of RSV is mainly caused by direct viral invasion of the respiratory epithelium, which is followed by immunologically mediated cell injury. Necrosis of the bronchi and bronchioles leads to the formation of "plugs" of mucus, fibrin, and necrotic material within smaller airways. The narrow airways of young infants are readily obstructed by such plugs. Natural immunity does not prevent reinfection, and vaccination with killed vaccine appears to enhance the severity of subsequent disease.

BOX 59–9. Disease Mechanisms of Respiratory Syncytial Virus

Virus causes localized infection of respiratory tract.
Virus does not cause viremia or systemic spread.
Pneumonia results from cytopathologic spread of virus (including syncytia).
Bronchiolitis is most likely mediated by host's immune response.
Narrow airways of young infants are readily obstructed by virus-induced pathologic effects.
Maternal antibody does not protect infant from infection.
Natural infection does not prevent reinfection.
Improper vaccination increases severity of disease.

EPIDEMIOLOGY

RSV is very prevalent in young children; almost all children have been infected by 2 years of age (Box 59–10) with global annual infection rates of 64 million and mortality of 160,000. As many as 25% to 33% of these cases involve the lower respiratory tract, and 1% are severe enough to necessitate hospitalization (occurring in as many as 95,000 children in the United States each year).

RSV infections almost always occur in the winter. Unlike influenza, which may occasionally skip a year, RSV epidemics occur every year.

The virus is very contagious, with an incubation period of 4 to 5 days. The introduction of the virus into a nursery, especially into an intensive care nursery, can be devastating. Virtually every infant becomes infected, and the infection is associated with considerable morbidity and, occasionally, death. The virus is transmitted on hands, by fomites, and to some degree by respiratory routes.

As already noted, RSV infects virtually all children by the age of 4 years, especially in urban centers. Outbreaks may also occur among the elderly population (e.g., in nursing homes). Virus is shed in respiratory secretions for many days, especially by infants.

BOX 59–10. Epidemiology of Respiratory SyncytialVirus

Disease/Viral Factors
Virus has large enveloped virion that is easily inactivated by dryness and acid.
Contagion period precedes symptoms and may occur in absence of symptoms.
Host range is limited to humans.

Transmission
Inhalation of large-droplet aerosols.

Who Is at Risk?
Infants: Lower respiratory tract infection (bronchiolitis and pneumonia).
Children: Spectrum of disease—mild to pneumonia.
Adults: Reinfection with milder symptoms.

Geography/Season
Virus is ubiquitous and found worldwide.
Incidence is seasonal.

Modes of Control
Immune globulin is available for infants at high risk.
Aerosol ribavirin is available for infants with serious disease.

BOX 59–11. Clinical Summaries

Measles: An 18-year-old woman returned had been home 10 days from a trip to Haiti when she developed a fever, cough, runny nose, mild redness of her eyes, and now has a red, slightly raised rash over her face, trunk, and extremities. There are several 1-mm white lesions inside her mouth. She was never immunized for measles because of an "egg allergy."

Mumps: A 30-year-old man returning from a trip to Russia began with a 1- to 2-day period of headache and decreased appetite, followed by swelling over both sides of his jaw. The swelling extends from the bottom of the jaw to in front of the ear. Five days after the jaw swelling appeared, the patient began complaining of nausea and lower abdominal and testicular pain.

Croup: A grumpy 2-year-old toddler with little appetite has a sore throat, fever, hoarse voice, and coughs with the sound of a barking seal. A high-pitched noise (stridor) is heard on inhalation. Flaring of the nostrils indicates difficulty breathing.

TABLE 59–4. Clinical Consequences of Respiratory Syncytial Virus Infection

Disorder	Age Group Affected
Bronchiolitis, pneumonia, or both	Fever, cough, dyspnea, and cyanosis in children younger than 1 year
Febrile rhinitis and pharyngitis	Children
Common cold	Older children and adults

CLINICAL SYNDROMES (BOX 59–11)

RSV can cause any respiratory tract illness, from a **common cold** to **pneumonia** (Table 59–4). Upper respiratory tract infection with prominent rhinorrhea (runny nose) is most common in older children and adults. A more severe lower respiratory tract illness, **bronchiolitis,** may occur in infants. Because of inflammation at the level of the bronchiole, there is air trapping and decreased ventilation. Clinically, the patient usually has low-grade fever, tachypnea, tachycardia, and expiratory wheezes over the lungs. Bronchiolitis is usually self-limited, but it can be a frightening disease to observe in an infant. It may be fatal in premature infants, persons with underlying lung disease, and immunocompromised people.

LABORATORY DIAGNOSIS

RSV is difficult to isolate in cell culture. The presence of the viral genome in infected cells and nasal washings can be detected by RT-PCR techniques, and commercially available immunofluorescence and enzyme immunoassay tests are available for detection of the viral antigen. The finding of seroconversion or a fourfold or greater increase in the antibody titer can confirm the diagnosis for epidemiologic purposes.

TREATMENT, PREVENTION, AND CONTROL

In otherwise healthy infants, treatment is supportive, consisting of the administration of oxygen, intravenous fluids, and nebulized cold steam. **Ribavirin,** a guanosine analogue, is approved for the treatment of patients predisposed to a more severe course (e.g., premature or immunocompromised infants). It is administered by inhalation (nebulization).

Passive immunization with anti-RSV immunoglobulin is available for premature infants. Infected children must be isolated. Control measures are required for hospital staff caring for infected children, to avoid transmitting the virus to uninfected patients. These measures include hand washing and wearing gowns, goggles, and masks.

No vaccine is currently available for RSV prophylaxis. A previously available vaccine containing inactivated RSV caused recipients to have more severe RSV disease when subsequently exposed to the live virus. This development is thought to be the result of a heightened immunologic response at the time of exposure to the wild virus.

Human Metapneumovirus

Human metapneumovirus is a recently recognized member of the pneumovirus family. Use of RT-PCR methods was and remains the means of detection and distinction of the pneumoviruses from other respiratory disease viruses. Its identity was unknown until recently because it is difficult to grow in cell culture. The virus is ubiquitous and almost all 5-year-old children have experienced a virus infection and are seropositive.

Infections by human metapneumovirus, like its close cousin, RSV, may be asymptomatic, cause common cold–like disease or serious bronchiolitis and pneumonia. Seronegative children, elderly persons and immunocompromised people are at risk to disease. Human metapneumovirus probably causes 15% of common colds in children, especially those of which are complicated by otitis media. Signs of disease usually include cough, sore throat, runny nose, and high fever. Approximately 10% of patients with metapneumovirus will experience wheezing, dyspnea, pneumonia, bronchitis, or bronchiolitis. As with other common cold agents, laboratory identification of the virus is not performed routinely but can be performed by RT-PCR. Supportive care is the only therapy available for these infections.

Nipah and Hendra Viruses

A new paramyxovirus, Nipah virus, was isolated from patients after an outbreak of severe encephalitis in Malaysia and Singapore in 1998. Nipah virus is more closely related to the Hendra virus, discovered in 1994 in Australia, than to other paramyxoviruses. Both viruses have broad host ranges, including pigs, man, dogs, horses, cats, and other mammals. For Nipah virus, the reservoir is a fruit bat (flying fox). The virus can be obtained from fruit contaminated by infected bats or amplified in pigs and then spread to humans. The human is an accidental host for these viruses, but the outcome of human infection is severe. Disease signs include flulike symptoms, seizures, and coma. Of the 269 cases occurring in 1999, 108 were fatal. Another epidemic in Bangladesh in 2004 had a higher mortality rate.

CASE STUDIES AND QUESTIONS

An 18-year-old college freshman complained of a cough, runny nose, and conjunctivitis. The physician in the campus health center noticed small white lesions inside the patient's mouth. The next day, a confluent red rash covered his face and neck.

1. What clinical characteristics of this case were diagnostic for measles?
2. Are any laboratory tests readily available to confirm the diagnosis? If so, what are they?
3. Is there a possible treatment for this patient?
4. When was this patient contagious?
5. Why is this disease not common in the United States?
6. Provide several possible reasons for this person's susceptibility to measles at 18 years of age.

A 13-month-old child had a runny nose, mild cough, and low-grade fever for several days. The cough got worse and sounded like "barking." The child made a wheezing sound when agitated. The child appeared well except for the cough. A lateral radiograph of the neck showed a subglottic narrowing.

1. What is the specific and common name for these symptoms?
2. What other agents would cause a similar clinical presentation (differential diagnosis)?
3. Are there readily available laboratory tests to confirm this diagnosis? If so, what are they?
4. Was there a possible treatment for this child?
5. When was this child contagious, and how was the virus transmitted?

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