Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The RA 27/3 strain of live-attenuated rubella virus is the rubella vaccine currently licensed for use in the United States. The vaccine is prepared in WI38 human embryonic lung tissue culture, and it produces a mild, noncommunicable infection. It is immunogenic in 98% of recipients and confers lifelong immunity to >90% of vaccinees.[78,79] It is available in a monovalent formulation as well as in combination with mumps and measles. A quadrivalent vaccine, including measles, mumps, rubella, and varicella, was licensed in the United States in 2005.

Adverse reactions to rubella vaccine include rash, fever, and lymphadenopathy in up to 15% of vaccine recipients. Joint pains occur in <1% of children, but arthritis and arthralgia occur in up to 25% of postpubertal women after vaccination[80,81]; arthropathy begins 1 to 3 weeks after vaccination and is transient. Persistent arthropathy has been reported but is uncommon. Rarely, transient peripheral neuropathy, thrombocytopenia, and central nervous system manifestations have been described.

Rubella vaccine should not be given to pregnant women or to women who are considering pregnancy within 3 months of vaccine administration.[82–86] The risk of congenital rubella infection after vaccination is based on accumulated data from 226 seronegative women who inadvertently received rubella vaccine during the first trimester of pregnancy and demonstrated seroconversion. Two percent of infants of these women had serologically confirmed rubella infection with no clinical manifestations; none had congenital defects.

Although administration of live-virus vaccine is contraindicated in immunosuppressed children, the one exception is administration of measles, mumps, rubella vaccine to children infected with the human immunodeficiency virus (HIV), because of the higher risk of morbidity and mortality associated with measles in this population. HIV-infected children should receive this vaccine at the generally recommended ages, although primary vaccine failure in this population may be substantial. Persons who have received immune globulin, blood or blood products, or immunosuppressive therapy should not be vaccinated for at least 3 months, and longer if a high dose of immune globulin was given intravenously (see Chapter 7, Active Immunization).

Passive Immunity

Immune globulin can modify or prevent clinical manifestations of acquired rubella infection among exposed susceptible individuals. However, absence of clinical infection may not indicate absence of viremia. Immune globulin is not therefore routinely recommended for postexposure prophylaxis of susceptible pregnant women and should only be considered if termination of the pregnancy cannot be considered. It can be given intramuscularly at a dose of 0.55 mL/kg; the maximum dose is 15 mL.

Public Health Measures

Children with acquired rubella should be excluded from school or group childcare until 7 days after the onset of rash. Infants with congenital rubella should be considered contagious until 1 year of age unless results of multiple urine and nasopharyngeal cultures for rubella virus performed after 3 months of age are negative.

Healthcare, childcare, and military personnel as well as college students should be screened for rubella immunity, and susceptible individuals should be vaccinated to prevent infection with and transmission of the virus.[87–90] Routine serologic screening of postpubertal women is not recommended.

Isolation Procedures

Contact isolation of persons with postnatal rubella is indicated for 7 days after onset of rash. Contact isolation is also required for neonates with suspected congenital rubella. Infants with confirmed congenital rubella should be considered infectious until they are 1 year of age unless results of multiple urine and nasopharyngeal cultures for rubella virus performed after 3 months of age are negative.

CHAPTER 222

Human Coronaviruses

Susan M. Poutanen

Coronaviridae are enveloped nonsegmented, single-stranded, positive-sense RNA viruses named after their corona- or crown-like surface projections seen on electron microscopy that correspond to large surface spike proteins (Figures 222-1 and 222-2). Coronaviruses are host-specific and can infect humans as well as a variety of different animals, causing diverse clinical syndromes.[1] Three serologically and genetically distinct groups of coronaviruses have been described. Human coronaviruses (HCoV) are part of groups 1 and 2 and primarily cause a variety of respiratory tract infections[1] (Table 222-1).

EPIDEMIOLOGY

In the 1930s, coronaviruses were recognized as disease agents in animals.[2] Thirty years later, coronaviruses were identified as agents of respiratory tract infections in humans. The first recognized HCoVs included the two familiar strains, 229E and OC43, but less well-recognized strains, such as B814, OC16, OC37, and OC48, were also

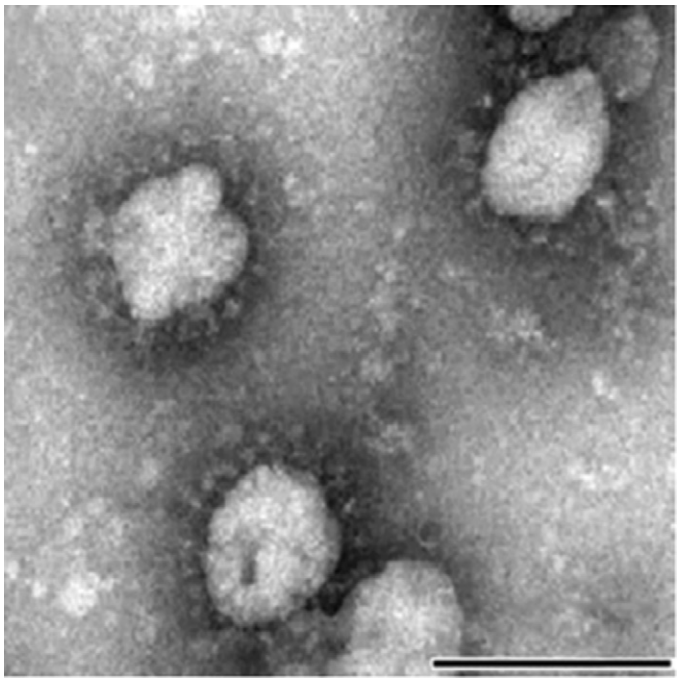

Figure 222-1. Electron micrograph of a typical coronavirus. Negative-contrast electron micrograph of severe acute respiratory syndrome coronaviruses (SARS-CoV). The typical crown-like spike proteins on the surface of the coronavirus particles are shown. Bar = 100 nm. (From Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–270.)

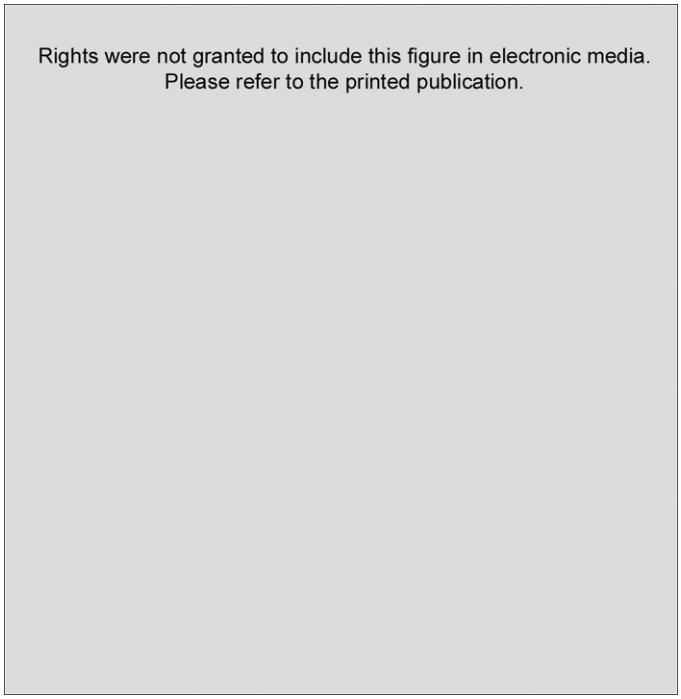

Figure 222-2. Pictorial illustration of a typical coronavirus. The organization of the spike (S), membrane (M), and envelope (E) glycoproteins is shown. The RNA is protected by the nucleocapsid proteins (N). (From Holmes KV, Enjuanes L. The SARS coronavirus: a postgenomic era. Science 2003;300:1377–1378.)

described.[3–5] Due to difficulties in isolating these latter viruses in culture, they were not investigated thoroughly and to date very little is known regarding their prevalence and associated clinical illnesses. In addition to respiratory HCoVs, coronavirus-like particles have been detected in stool, primarily in infants with gastroenteritis and necrotizing enterocolitis. However, further characterization of these possible human enteric coronaviruses has been hindered primarily because of the difficulty in isolating them in culture.[6–8]

The prevalence and associated illnesses due to HCoV 229E and OC43 have been well studied. Together, they are the second most common cause of the common cold after rhinoviruses.[9] They are typically isolated in 5% to 10% of adults and 2% to 5% of children with acute upper respiratory tract infections, and 7% of children with acute otitis media.[9–12] They are less frequent causes of lower respiratory tract infections in both adults and children.[13–17] In temperate climates most HCoV 229E and OC43 infections occur in the winter and spring months.[18–20] The seasonality of these infections in the tropies and subtropics has not been well defined. A rapid increase in the prevalence of antibodies to HCoV OC43 occurs after 23 months of age and almost all persons 6 years of age and older are seropositive, suggesting that exposure to HCoV OC43 occurs in early childhood.[21,22]

Most human disease caused by coronaviruses was thought to be secondary to 229E and OC43. However, in 2003, a novel HCoV was identified as the cause of the global outbreak of severe acute respiratory syndrome (SARS).[23–25] SARS was first recognized in Guangdong province, China, in November 2002. Over the subsequent 9 months, international travel facilitated global spread to 26 countries.[26,27] A total of 8098 infected people and 774 deaths were reported to the World Health Organization before the outbreak was declared over in July 2003.[26–28] Infants and children comprised the minority of those infected.[29] International cooperation and intense infection control and public health measures were critical to halting the outbreak. It is now recognized that SARS-CoV likely evolved from newly recognized animal SARS-like CoV, most frequently isolated from Himalayan civet cats and bats.[30–33] Since the SARS outbreak was declared over, 4 isolated cases of SARS with no associated transmission were identified in China in December 2003 and January 2004.[34] In addition, 2 isolated cases and one cluster of 11 cases, including 1 death, were identified in Southeast Asia related to breaches in biosafety practices in laboratories culturing SARS-CoV.[35–38] Whether or not a large-scale re-emergence of SARS will occur is speculative.

Since the recognition of SARS-CoV, there has been renewed interest in HCoVs and novel HCoVs have subsequently been discovered. HCoV NL63 (referred to in various publications as NL and NH) was first identified by two groups in the Netherlands in a 7-month-old child with bronchiolitis and conjunctivitis, and in an 8-month old child with pneumonia.[39,40] Since then HCoV NL63 has been identified in infants, children, and adults worldwide.[41–46] Analyses of its complete genome sequence revealed that it is a new group 1 coronavirus, closely related to 229E.[39,40] HCoV NL63 has been associated with upper and lower respiratory tract infections and has been found in 2% to 9% of respiratory specimens submitted to clinical laboratories that are test-negative for typical respiratory pathogens.[39–43,47] Coinfections with other respiratory viruses are common.[48] In temperate regions, HCoV NL63 appears to follow a similar seasonal pattern as 229E and OC43 with most infections occuring during winter months.[39–41,47] Reports from Hong Kong suggest high NL63 activity may peak during its summer months.[39–41,44,47,49] HKU1 was subsequently discovered as a novel coronavirus in Hong Kong in 2 adults with pneumonia. Analyses of its complete genome sequence revealed that it is a new group 2 coronavirus.[50] It has since been identified in 2.4% of patients with community-acquired pneumonia in Hong Kong, as well as infants and small children with upper and lower respiratory tract infections worldwide.[49,51–54] It appears to follow a similar seasonal distribution as HCoV 229E and OC43.[49,51] With novel molecular methods, it would not be surprising if additional HCoVs continue to be identified in the future.[55]

The modes of transmission for most HCoVs other than SARS-CoV have not been well studied. However, based on other human respiratory viruses, it is likely that transmission primarily occurs via a combination of droplet and direct and indirect contact spread.[56] Which of

TABLE 222-1. Human and Representative Animal Coronaviruses (CoV)

Group	Common Name of Virus	Acronym	Host	Associated Diseases
1	Human CoV-229E	HCoV-229E	Human	Respiratory tract infection
	Human CoV-NL63	HCoV-NL63	Human	Respiratory tract infection
	Feline infectious peritonitis virus	FIPV	Cat	Hepatitis, respiratory tract, enteric, and neurologic infection
2	Human CoV-OC43	HCoV-OC43	Human	Respiratory tract infection
	Human CoV-HKU1	HCoV-HKU1	Human	Respiratory tract infection and possibly gastroenteritis
	Severe acute respiratory syndrome-CoV[a]	SARS-CoV[a]	Human	Severe acute respiratory syndrome (SARS)
	Mouse hepatitis virus	MHV	Mouse	Hepatitis, encephalitis, and enteric infection
3	Infectious bronchitis virus	IBV	Chicken	Respiratory tract and enteric infection

[a]SARS-CoV appears to be an outlier of group 2 but some phylogenetic analyses suggest it is the first member of a fourth group of coronaviruses.[132]

these modes is most important remains to be determined, and the possible role of aerosol spread through talking, coughing, or sneezing needs further study. For SARS-CoV, studies suggest that droplet and direct contact spread are likely the most common modes of transmission, although evidence for indirect contact spread and aerosol spread also exists.[57–64] There is no evidence of vertical transmission of SARS-CoV.[65,66]

PATHOGENESIS AND IMMUNITY

The pathogenesis of HCoVs has been best described for HCoV 229E and SARS-CoV. For SARS-CoV, most of what is understood is based on adult infections given that few children were affected during the 2002 to 2003 outbreak.[29] Further studies are needed to understand further the pathogenesis of other HCoVs.

HCoV 229E and OC43 infections are initiated through inoculation of respiratory mucosal surfaces. HCoV 229E infection is associated with nasal mucosal plasma exudation and increased levels of interferon-γ in nasal lavage specimens that correlate with symptom severity.[67,68] Peak viral loads in respiratory tract specimens occur within 3 days of onset of infection. Within 1 week, a dramatic reduction in viral load corresponds with symptomatic improvement.[69,70] The development of antibodies, starting at 1 week, correlates with the drop in viral load.[71] Antibody titers peak at about 2 weeks after onset of infection and decline slowly thereafter. Immunity is not complete and reinfection is common.[71,72] Higher circulating antibody levels, and especially levels of specific IgA antibodies, correlate with reduced virus shedding and reduced symptoms upon re-exposure.[71,73]

SARS-CoV infection is most likely initiated through inoculation of the respiratory tract mucosa. It is then associated with viremia followed by predominant replication in the lung and gastrointestinal tract.[74,75] Replication at multiple other sites also likely occurs given the organ distribution of SARS-CoV found in tissues at autopsy.[76,77] Peak viral loads in nasopharyngeal specimens are noted during the second week of symptoms.[75,78] A rise in SARS-CoV-specific antibodies is typically seen starting at week 2 after infection. Increasing antibody titers during the second and third week are associated with a fall in SARS-CoV reverse transcriptase-polymerase chain reaction (RT-PCR) positivity and improvement in symptoms.[78,79] Paradoxically, despite a fall in SARS-CoV viral load and a rise in SARS-specific antibodies, clinical deterioration is observed in some patients. This suggests that the host immune response is responsible for this deterioration.[78] Indeed, SARS is associated with an elevation of interferon-γ, inflammatory cytokines interleukin-1, interleukin-6, and interleukin-12, as well as elevations in neutrophil chemokine interleukin-8, monocyte chemoattractant protein-1, and interferon-γ-inducible protein-10. Concentrations of interleukin-6 correlate directly with severity of disease.[80,81]

CLINICAL MANIFESTATIONS

HCoV 229E and OC43

HCoV 229E and OC43 are most commonly associated with upper respiratory tract infections, especially the common cold and acute otitis media.[49] Common colds due to HCoV 229E are typically mild with predominant rhinorrhea.[20] Colds due to HCoV OC43 are more severe and are indistinguishable from colds due to rhinoviruses; rhinorrhea, sore throat, and cough occur in approximately 50% of patients.[20] Symptoms typically peak 3 to 4 days after inoculation.[70] HCoV 229E and OC43 are associated with approximately 13% of asthma exacerbations.[82] Less frequently, HCoV 229E and OC43 are associated with lower respiratory tract infections, including bronchiolitis, bronchitis, croup, and pneumonia – primarily in infants and immunocompromised children and adults.[13–17]

HCoV NL63

HCoV NL63 is primarily associated with upper respiratory tract infections in infants, children, and adults. Symptoms include rhinorrhea, sore throat, and cough.[40,42,47,49] In addition, HCoV NL63 is frequently associated with acute otitis media, croup, and bronchiolitis in infants and young children.[47,48] Association with asthma exacerbations has been noted.[49] A possible association with Kawasaki disease is controversial.[83,84]

HCoV HKU1

Similar to HCoV 229E, OC43, and NL63, HKU1 is primarily associated with upper respiratory tract infections in children and adults.[49] An association with acute otitis media has been reported.[52] HCoV HKU1 appears to be more frequently associated with febrile seizures than other coronaviruses, and in one series, children with HKU1 upper respiratory tract infections also had vomiting and diarrhea.[49,52] HCoV HKU1 has been associated with bronchiolitis, asthma exacerbation, and pneumonia in children, and community-acquired pneumonia in adults.[49–51]

SARS-CoV

SARS-CoV disproportionately affects adults compared with children. It causes a spectrum of illness ranging from asymptomatic infection to the severe acute respiratory syndrome, after which the virus was named.[6–8,29,85] Patients with typical SARS become ill 2 to 10 days following exposure with fever, myalgia, headache, malaise, and chills. A nonproductive cough and dyspnea develop 3 to 5 days later, and approximately 25% of patients develop watery diarrhea. Twenty percent of patients develop worsening respiratory distress requiring intensive care support, the majority of whom require intubation and ventilation.[86–88] The overall mortality rate is approximately 10%; most deaths occur in the third week of illness.[27,89] The case-fatality rate in persons > 60 of age approaches 50%.[90] Typical laboratory abnormalities include lymphopenia, and increased lactate dehydrogenase and creatinine kinase levels.[91,92] The majority have progressive unilateral or bilateral ill-defined air-space infiltrates on chest imaging.[91,93–95] Cavitation, lymphadenopathy, and pleural effusions are not typical. Pneumothoraces and other signs of barotrauma are common in critically ill patients receiving mechanical ventilation.[87]

Infants and children appear to be protected against contracting the infection, and clinical manifestations in those affected are less severe. Notably, no infants or children died due to SARS-CoV infection during the 2002 to 2003 outbreak.[29,96–99] Infants and children < 12 years old who develop SARS typically have fever, cough, and rhinorrhea. Associated lymphopenia is less severe and radiographic changes are milder and generally resolve more quickly than in adolescents and adults. Adolescents who developed SARS had clinical courses more closely resembling that of adults, presenting with fever, myalgia, headache, and chills. They are more likely to develop dyspnea, hypoxemia, and worsening chest radiographic findings. Laboratory abnormalities are comparable to those in adults.

Women infected during pregnancy who survive have an increased risk of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction.[65,66,100] Two neonates born to women with SARS in the 2002 to 2003 outbreak developed gastrointestinal complications (jejunal perforation, necrotizing enterocolitis with ileal perforation) shortly after birth but neither had clinical evidence of SARS-CoV.[66] Whether these findings were related to complications of maternal SARS-CoV infection or treatments used during pregnancy, such as ribavirin and corticosteroids, is not clear.

DIAGNOSIS

The diagnosis of HCoV infections has not been attempted in clinical settings outside outbreak situations or epidemiologic surveys. However, given renewed interest in better understanding of the etiology of respiratory tract infections since the 2002 to 2003 SARS outbreak, increasing numbers of clinical laboratories are offering comprehensive respiratory diagnostic tests, including coronavirus diagnostics. Previously, diagnosis of HCoVs was based on culture, using cell lines

or organs, and serologic testing by various means.[20] However, more recently, direct detection of HCoVs using RT-PCR has become the standard diagnostic test, especially given the difficulty with culturing some coronaviruses and the increased sensitivity of RT-PCR.[49,101]

Upper and lower respiratory tract specimens are the most appropriate samples for testing.[42,49,69,102,103] Stool samples are also frequently positive in patients with SARS and have been positive in some children with HCoV HKU1 infection.[52,102,103] For HCoV 299E and OC43, specimens are most likely to be positive during the first few days of illness.[69] For SARS-CoV, respiratory tract and stool specimens may not be positive until the second week of illness when viral loads peak.[78,102] Serum samples may be positive for antibody in patients with SARS in the first week of illness.[104,105] Compared with adults, infants and children with SARS-CoV infections are less likely to have positive specimens for virus consistent with the milder symptoms and presumed corresponding lower viral loads seen in this age group.[96,106] The optimal time to collect specimens for HCoV NL63 and HKU1 infections needs further study.

TREATMENT

There have been few studies on treatment of HCoV infections because of the self-limited clinical syndromes typically associated with HCoV 229E and OC43. However, with increasing awareness of HCoVs and recent discovery of new strains infecting humans, interest in therapy is increasing. Fortunately, infections due to HCoV NL63 and HKU1, like those due to HCoV 229E and OC43, are generally self-limited and can be treated with supportive care. SARS-CoV infections are clearly different. Ribavirin, corticosteroids, type 1 interferons, convalescent plasma, and lopinavir/ritonavir have all been used to treat SARS.[91,107–110] Despite some anecdotal reports of clinical improvement associated with ribavirin, in vitro studies suggest minimum activity.[111–113] For most of the other treatments used, there are anecdotal reports of clinical improvement and favorable results in in vitro assays and animal models.[91,107–110,114–122] However, no definitive conclusions regarding the efficacy of any of these treatments can be made. This is especially important to note because controlled studies have not been completed for any of these agents, and there are reports of patients who were treated with just supportive care who recovered uneventfully.[123] Other agents have been tested since the SARS 2002 to 2003 outbreak and appear promising based on in vitro studies. These include inhibitors of viral entry, protease inhibitors, RNA interference, and glycyrrhizin.[124] In the event that SARS-CoV re-emerges, clarification of the effectiveness of all of these treatments through controlled clinical trials is needed.

PREVENTION

The best prevention for all HCoV infections is practicing healthy hand and respiratory hygiene.[125] Control of the 2002 to 2003 SARS outbreak is credited to aggressive surveillance, institution of infection control measures, including respiratory and contact precautions, and public health measures, including quarantine. If SARS-CoV re-emerges, all of these measures should be implemented quickly in an attempt to prevent a recurrent worldwide outbreak.

Other preventive measures have been assessed. Prophylactic intranasal interferon-α has been shown to reduce the duration and severity of HCoV 229E infection in research settings but has not been used clinically.[126,127] Whether this may be helpful in the prevention of other HCoVs has not been evaluated. A proprietary extract of the roots of North American ginseng (*Panax quinquefolium*) has been shown to reduce the number of colds as well as the severity and duration of cold symptoms in adults when taken daily, through presumed immune stimulation.[128–131] Whether this could result in a decrease in colds due to HCoVs has not been studied. The development of a SARS-CoV vaccine has been recognized as a priority and work completed to date has been encouraging.[124]

CHAPTER 223

Parainfluenza Viruses

Kelly J. Henrickson

Human parainfluenza viruses (HPIVs) cause a variety of respiratory tract infections in young children. Severe infections are especially common among infants and the immunocompromised. Among those with chronic underlying diseases and the elderly[1–3]; HPIV infections commonly trigger serious acute respiratory tract conditions that result in hospitalization. In one study of 1029 persons with chronic underlying conditions hospitalized for respiratory illnesses, 11.5% of the patients were infected with HPIVs compared with 17.3% infected with influenza and 10.4% infected with respiratory syncytial virus (RSV).[3]

MICROBIOLOGY

HPIVs are pleomorphic enveloped RNA viruses that belong to the family Paramyxoviridae, and they are closely related to RSV. Four serotypes of HPIV are recognized (types 1 to 4), two antigenic subtypes of HPIV-4 (4A and 4B), and subgroups/genotypes of HPIV-1 and -3 have been described.[4–6] These serotypes and subtypes display substantial serologic cross-reactivity. The single-stranded negative-sense nonsegmented genomes of HPIV are coated with the nucleocapsid protein. This nucleocapsid protein, in association with phosphoprotein and large (L) protein, is responsible for the polymerase activity of the virus. The viral envelope glycoproteins are the hemagglutinin–neuraminidase (HN) and fusion (F) proteins. HN is responsible for attachment to the cell, and the F protein mediates virion entry into the cell. The hydrophobic matrix protein mediates interactions between the glycoproteins and the nucleocapsid. Members of the parainfluenza family of viruses use different strategies to transcribe nonstructural proteins.

EPIDEMIOLOGY

The different serotypes of HPIV have distinct epidemiologic patterns that may vary depending on geographic location. Aprroximately 35 years ago, unexplained changes occurred in the epidemic and endemic nature of some types in the northern hemisphere.[7,8] Currently, HPIV-1 occurs primarily in biennial fall epidemics in odd-numbered years (Figure 223-1),[9] HPIV-2 occurs with substantial local variability in periodicity but generally also occurs in the fall (Centers for Disease Control and Prevention surveillance data).[10,11] HPIV-3 occurs in spring and summer epidemics in North America and Europe but demonstrates some endemicity in the immunocompromised and chronically ill.[9,12] A clear epidemic cycle for HPIV-4 has not been identified.[13]

Primary infection with HPIV is acquired early in life, but HPIV can be isolated from persons of all ages (Figure 223-2), particularly HPIV-3. The rate of HPIV-3 infection in infants is similar to that of RSV,[14,15] but the risk of hospitalization due to HPIV is lower than that attributable to RSV infection.[9] Nonetheless, approximately 50,000 hospitalizations in children occur each year in the United States due to HPIV-1, -2, and -3 infection. HPIV-3 infection is common early in life. After adjusting for decline in maternal antibody, estimated cumulative proportions of HPIV-3 infections in infants increased from 11% at 6 months of age to 47% at 12 to 15 months of age and 50% at 13 to 16 months of age.[14] In a prospective surveillance study conducted in Houston, Texas, rates of primary infection in the first and second year of life were 62 and 81 per 100 child-years, respectively.[8] The risk of lower respiratory tract infection (LRI) associated with primary infection was approximately 10% in the first and 20% in the second year of life.[8] Reinfections are common and are associated with a low