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Reducing the Impact of Viral Respiratory Infections in Children

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Recent years have witnessed a surge in understanding of viral upper and lower respiratory tract disease in children. Respiratory viruses include the following:

1. Respiratory syncytial virus (RSV)
2. Influenza viruses
3. Human metapneumovirus
4. Parainfluenza viruses
5. Coronaviruses (including SARS-CoV)
6. Adenoviruses
7. Rhinoviruses

The epidemiology of established viral pathogens (parainfluenza viruses, adenoviruses, rhinoviruses) continues to be clarified. New pathogens have been identified (human metapneumoviruses and the coronavirus that causes severe acute respiratory syndrome [SARS] [SARS-CoV]). The relentless emergence of antigenic variation among influenza viruses continues, but progress is being made in prevention and control of disease in children through active immunoprophylaxis (trivalent inactivated vaccine, live attenuated vaccine) and new antiviral agents (neuraminidase inhibitors). RSV causes two to three times more pediatric hospitalizations than influenza viruses, parainfluenza viruses, and human metapneumoviruses. Important advances in control of RSV infections among high-risk patients have been achieved using passive immunoprophylaxis despite slow progress in vaccine development. This article reviews current

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understanding of the major causes of viral respiratory tract disease with an emphasis on prevention and control.

Respiratory syncytial virus

In 1956, Morris et al [1] published a report of a virus that caused upper respiratory infections in chimpanzees. The pathogen was named *chimpanzee coryza agent* because it was initially isolated from chimps with coryza. A similar virus soon was isolated from a child with pneumonia, and the name was changed to *RSV,* reflecting the tendency of RSV-infected cells in vitro to fuse and form syncytia. RSV is a nonsegmented, negative strand RNA virus that encodes for 10 viral proteins. Two subgroups of RSV (A and B) each with multiple genotypes may circulate during annual outbreaks, although it has not been possible to associate more severe disease with one subgroup or another on a consistent basis [2,3].

RSV is the leading cause of hospitalization among infants and young children with respiratory tract disease. The outcome of RSV infection varies from mild upper respiratory tract infection, which occurs in approximately 75% of infected infants, to severe life-threatening disease in a small percentage of patients [4]. Each year in the United States, RSV accounts for 50% to 90% of the approximately 120,000 hospitalizations attributable to bronchiolitis and 20% to 50% of pediatric hospitalizations attributable to pneumonia [5]. During the 17-year period between 1980 and 1996, hospitalization rates for bronchiolitis in infants younger than 12 months old increased by more than twofold, whereas hospitalization rates for other respiratory diseases (pneumonia, asthma) showed little change [5]. Approximately 500 RSV-associated deaths occur each year in the United States, and most occur in non–high-risk patients [6]. Outbreaks of nosocomial RSV disease on pediatric wards continue to be a serious problem when effective infection control policies are not followed [7]. Serologic surveys show that by 2 years of age, more than 90% of children have been infected by RSV at least once. Reinfection throughout life is common, indicating that immunity to RSV after natural infection is inadequate. Whether RSV infection early in life predisposes to subsequent reactive airway disease is an important but unresolved question [8].

RSV lower respiratory tract disease (bronchiolitis, pneumonia) occurs primarily in infants younger than 1 year old. Premature infants and infants with chronic lung disease of prematurity constitute high-risk groups with rates of RSV hospitalization that are approximately five times the hospitalization rate in full-term, healthy infants [9]. Several factors place preterm infants at risk for severe RSV disease, including a relative lack of maternal antibodies, an immature immune response, and underdeveloped lungs with small bronchioles and reduced pulmonary reserve [10]. Transfer of maternal antibodies occurs mainly after the 28th week of pregnancy, so infants born before this time are likely to have lower antibody concentrations. In addition, maternal antibody concentrations to RSV

show seasonal variation, and infants born in the early fall or soon after the start of the respiratory virus season are more likely to be born to mothers with low serum antibody concentrations [11]. A low concentration of antibody to RSV correlates with susceptibility to severe RSV in infants [12].

Congenital heart disease in the United States occurs in 4 to 8 infants per 1000 live births. Morbidity and mortality resulting from RSV infection are increased in infants younger than 24 months old with hemodynamically significant congenital heart disease, including infants with large left-to-right shunts, pulmonary hypertension greater than half the systemic pressure, cyanotic heart disease, and complex heart disease such as single ventricular anatomy [13]. Other groups of patients, such as pre-engraftment bone marrow transplant recipients, solid organ transplant recipients, and lymphopenic children receiving chemotherapy, have high hospitalization rates secondary to RSV [14]. The average hospital stay and intensity of care for children in high-risk groups may be several times that of previously healthy infants.

In the Northern Hemisphere and particularly in the United States, RSV circulates predominantly between November and March [9]. In the United States, the inevitability of the RSV season is predictable, but the severity of the season, the time of onset, the peak of activity, and the end of the season cannot be predicted precisely. There can be substantial variation in timing of community outbreaks of RSV disease from year to year in the same community and between communities in the same year even in the same region. These variations occur, however, within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by the end of March or by April [15]. Communities in the southern states tend to experience the earliest onset of RSV activity, and midwestern states tend to experience the latest onset. The duration of the season for western and northeastern regions typically is between that noted in the South and the Midwest [15].

Despite the importance of RSV as a pathogen, options for prevention and treatment of disease are limited. Aerosolized ribavirin was licensed in 1986 for treatment of children hospitalized with severe RSV lower respiratory tract infection. Because of high cost and conflicting data regarding efficacy, however, this drug is not widely used. A vaccine remains the most practical means of reducing the burden of disease attributable to RSV, but it has proved difficult to develop an effective vaccine for young infants that produces protective immunity but does not enhance natural infection [16]. In contrast, remarkable progress has been achieved in showing the efficacy, ease of administration, and safety of passive immunoprophylaxis against RSV. In slightly more than 10 years, the field of passive immunoprophylaxis has evolved from clinical trials with standard intravenous immunoglobulin to the use of a RSV-hyperimmune, polyclonal intravenous globulin (RespiGam) to an intramuscular, humanized murine monoclonal antibody (palivizumab) directed against a conserved epitope on the fusion glycoprotein [4,17].

The US Food and Drug Administration licensed palivizumab in 1998 for monthly intramuscular administration for prevention of RSV lower respiratory

tract infections in high-risk infants and children. Results from two blinded, randomized, placebo-controlled trials with palivizumab involving 2789 infants and children with prematurity, chronic lung disease, or congenital heart disease showed a reduction in RSV hospitalization rates of 39% to 78% in different groups [13,18]. Results from postlicensure, observational studies suggest that monthly immunoprophylaxis with palivizumab may reduce rates of RSV-induced hospitalization to an even greater extent than rates reported in clinical trials [19].

Despite the fact that the highest rate of RSV hospitalization occurs in high-risk infants, most infants hospitalized with severe RSV disease are previously healthy infants who were born at term. Studies confirm that prematurity, chronic lung disease of prematurity, congenital heart disease, and young age at the beginning of the RSV season constitute the major risk factors for RSV hospitalization [20]. Household crowding seems to be another important risk factor for severe viral lower respiratory illness including that caused by RSV. As the number of household members increases, the risk of exposure to infectious respiratory secretions also increases. Numerous other risk factors have been associated with severe RSV disease, including gender (males > females), low socioeconomic status, daycare attendance, exposure to passive smoke, lack of breastfeeding, limited maternal education, and malnutrition. These factors have an inconsistent association with hospitalization across studies, however, and at most account for only a modest increase in risk [10,21]. The American Academy of Pediatrics has published guidelines for selection of high-risk infants who are most likely to benefit from monthly prophylaxis with palivizumab [22].

A crucial aspect of RSV prevention in high-risk infants is education of parents and other caregivers about the importance of decreasing infants' exposure to RSV. High-risk infants should be excluded from situations where exposure to infected individuals cannot be controlled, such as daycare centers. Emphasis on hand hygiene is important in all settings, including the home, and exposure to passive smoke should be avoided.

Influenza viruses

Influenza viruses are negative sense RNA viruses containing eight segments of RNA, which encode for 10 viral proteins. The segmented genome is one of the key features explaining the ability of influenza viruses to undergo antigenic change and cause annual outbreaks of disease. Influenza viruses are classified as one of three types (A, B, C) based on antigenic differences in the nucleocapsid protein. Type A strains infect humans and animals and are associated with the most severe disease, causing epidemics and pandemics on a worldwide basis. Influenza A viruses are categorized further into subtypes based on two surface glycoproteins, hemagglutinin and neuraminidase. Type B strains tend to cause less severe illness than type A, do not circulate in animals, and are not categorized into subtypes. Type C strains cause mild disease and have little public health impact.

The two major surface glycoproteins of the influenza virion are important in understanding epidemiology, pathogenesis, and treatment. The hemagglutinin glycoprotein enables viral attachment to respiratory epithelial cells that support influenza virus replication. The neuraminidase glycoprotein possesses enzymatic activity that cleaves sialic acid residues that is essential for efficient release of progeny virions as they escape from an infected cell. Antibodies directed against hemagglutinin and neuraminidase proteins confer immunity against a specific strain of influenza.

Annual outbreaks of influenza occur because types A and B undergo constant antigenic change classified as either antigenic shift or antigenic drift. *Antigenic drift* refers to mutations (nucleotide substitutions or deletions) in the hemagglutinin or neuraminidase genes. Selective pressure favors the emergence of antigenically altered strains as an increasing number of individuals in the community develop antibody against the circulating strain. New antigenic stains emerge, circulate, and are replaced by the next emerging strain against which the population has limited immunity. Depending on the extent of antigenic variation from strain to strain, the new circulating virus may cause more or less severe outbreaks of disease.

Antigenic shift refers to a different mechanism by which a new strain of influenza suddenly emerges. Type A viruses with genes encoding for different subtypes of hemagglutinin and neuraminidase reside in a diverse range of host species, including birds, horses, swine, and humans, although birds are considered to be the natural reservoir. To date, 15 immunologically distinct subtypes of hemagglutinin and 9 distinct subtypes of neuraminidase have been described. If a new gene encoding for either neuraminidase or hemagglutinin is acquired, a new strain may begin to circulate. Antigenic shift occurs less frequently than antigenic drift. Antigenic shift has not been described in influenza type B viruses.

In temperate climates, disease resulting from influenza activity peaks between late December and early March. Data from the Centers for Disease Control and Prevention (CDC) indicate that during 28 years, the month of peak activity due to influenza occurred in November in 4% of the years, December in 14%, January in 21%, February in 43%, March in 10%, April in 4%, and May in 4%. [23] On a yearly basis, influenza is responsible for approximately 36,000 deaths in the United States. Most deaths occur in the elderly, although there are few data on pediatric deaths. Approximately 200,000 excess hospitalizations occur each year because of complications of influenza.

Studies have determined that children age 6 to 23 months are at increased risk for influenza-related hospitalization [24,25]. This figure has been difficult to determine because of overlap of the RSV and influenza seasons. It now seems that in children 0 to 4 years old, hospitalization rates because of influenza in high-risk children are approximately 5 per 1000 and approximately 1 per 1000 for children without underlying disease. These rates are similar to hospitalization rates in adults 65 years old and older and for whom annual immunization is strongly recommended [23].

During an influenza outbreak, the highest attack rates occur in school-age children and may exceed 30%, whereas the attack rates among adults average 10% to 20% in interpandemic years [23]. Families with school-age children are twice as likely to experience influenza than families with older children, reflecting the importance of young children in transmission of influenza in a community. Influenza is highly contagious, and secondary spread to adults in the same household is common. Patients may be infectious for 24 hours before the onset of symptoms and continue to shed virus in nasal secretions for about 5 days after onset of symptoms. Young children may shed virus for longer periods. Annual outpatient visits because of complications of influenza vary from 6 to 29 per 100 children depending on the virulence of the circulating strain and the relatedness between the vaccine and the circulating strains. Complications from influenza infections are estimated to account for a 10% to 30% increase in antibiotic courses in infected children. In 2004, because of the high risk of influenza infection in young children, the Advisory Committee on Immunization Practices to the CDC and the American Academy of Pediatrics changed the recommendation for routine annual influenza vaccination to include infants 6 to 23 months old [23].

Transmission of influenza virus results from airborne spread of respiratory secretions generated by coughing, sneezing, or talking. Inhalation of small airborne particles accounts for most infections. Viral transmission also can occur by direct contact with contaminated secretions. Influenza has a short incubation period of 18 to 72 hours, with the shorter period occurring after exposure to a larger innoculum. Influenza infection typically begins with sudden onset of fever, followed by myalgia, malaise, headache, nonproductive cough, rhinitis, and sore throat (Table 1). Individuals with underlying medical conditions are at increased risk of pneumonia, which may be due to viral extension to the lungs or bacterial superinfection. Less severe complications of influenza include otitis media and sinusitis.

Primary influenza viral pneumonia is manifest by rapid onset of cough and dyspnea. It is associated with a high morbidity rate. In contrast, secondary bac-

Table 1
Influenza versus cold symptoms

Signs and symptoms	Influenza	Cold
Onset	Sudden	Gradual
Fever	>101 °F lasting >3 d	Rare
Cough	Can become severe	Less common
Headache	Prominent	Rare
Myalgia	Severe	Slight
Fatigue	Fatigue lasting >1 wk	Mild
Extreme exhaustion	Early and prominent	Rare
Chest discomfort	Common	Mild
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Common
Sore throat	Sometimes	Common

terial pneumonia caused by pneumococcus, group A beta-hemolytic streptococcus, or *Staphylococcus aureus* generally follows a period of improvement with recrudescence of fever associated with symptoms of pneumonia. Other pulmonary complications in children include croup and bronchiolitis. Children with a history of asthma may experience an acute exacerbation. Myositis, particularly in the gastrocnemius and soleus muscles, is a recognized complication of influenza. In severe cases, myoglobinuria with progression to renal failure may occur. Myocarditis and pericarditis also have been described. CNS complications include Guillain-Barré syndrome, transverse myelitis, postinfectious encephalitis, and encephalopathy [27].

The most important means of control of influenza is active immunization with either the killed inactivated trivalent influenza vaccine (TIV) or the live attenuated influenza vaccine (LAIV) [23,26]. When vaccine and epidemic strains are well matched, the vaccine confers protection in 70% to 90% of vaccinees. The optimal time for vaccination is between the beginning of October and the end of November. Vaccine should be offered throughout the influenza season as long as vaccine is available and until virus is no longer circulating (Box 1). Protective antibodies develop within 2 weeks after vaccination. The immunogenicity of a single dose of vaccine in young children is limited, especially if they have not been vaccinated previously or infected by influenza virus. Two doses of intramuscular vaccine should be administered at least 1 month apart to children younger than 9 years old (Table 2). The duration of immunity is likely to be less

Box 1. Target groups for influenza vaccination

1. Chronic pulmonary disorders, including asthma
2. Hemodynamically significant heart disease
3. Regular medical follow-up or hospitalization in the past year for any of the following:
   Metabolic disease, including diabetes mellitus
   Renal dysfunction
   Hemoglobinopathy
   Immunosuppression due to medical therapy or HIV infection
4. Persons 6 months old to 18 years old receiving long-term aspirin therapy
5. Women who will be pregnant during the influenza season
6. Infants 6 to 23 months old
7. Persons $\geq$65 years old
8. Persons $\geq$50 years old when vaccine supplies are adequate
9. Close contacts of high-risk persons, including household and other close contacts of infants <6 months old
10. Health care personnel
11. Anyone who wishes to reduce the risk of influenza infection

Table 2
Influenza vaccine schedule

Age group	Dose (mL)	No. doses
6–35 mo	0.25	1 or 2
3–8 y	0.50	1 or 2
≥9 y	0.50	1

than 12 months, so yearly vaccination is necessary to boost the immune response and to provide immunity to new antigenic strains. Hospitalization rates secondary to influenza in infants younger than 6 months old may be greater than 10 per 1000 [25]. Influenza vaccine is not recommended for this age group, however, because it has not been evaluated in such young children. It is important to vaccinate the contacts of these young, at-risk infants. The most frequent side effect of vaccination is soreness at the vaccination site, which occurs in 10% to 64% of vaccinees. Fever, malaise, and myalgia occur most often in young children who have had no previous exposure to influenza virus antigens.

A topical live attenuated, temperature-sensitive, cold-adapted, trivalent influenza vaccine administered by nasal spray was licensed by the Food and Drug Administration in 2003 (Table 3). Temperature-sensitive strains preferentially replicate at the lower temperature of the nasal cavity and less efficiently at core body temperature. Intranasal administration of vaccine results in a subclinical infection that induces immunity by simulating a natural infection of the upper airways. This vaccine was approved as an alternative to TIV for healthy persons 5 to 49 years old. It is likely that approval will be extended beyond these age limits. The advantages of LAIV are avoidance of intramuscular injection and possibly greater protection against mutated strains than that found with TIV [23,28]. LAIV should not be used to immunize persons who have close contact with severely immunocompromised patients who require isolation [23].

Antiviral drugs for treatment or prophylaxis are not a substitute for vaccination. Four influenza antiviral drugs are presently licensed in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Three drug are approved for treatment of influenza in children younger than 13 years old (Table 4). When therapy is initiated within the first 2 days of illness, all four medications are similarly effective in reducing the duration of symptoms by about 1 day [23,26]. Antiviral therapy with oseltamivir or zanamivir has been shown to decrease influenza-associated otitis media and antibiotic use in children. Amantadine,

Table 3
Comparison of live attenuated influenza vaccine versus killed inactivated trivalent influenza vaccine

Factor	LAIV	TIV
Route	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
Number of strains in vaccine	2 type A and 1 type B	2 type A and 1 type B
Vaccine strains updated	Annually	Annually
Approved age and risk groups	Healthy persons; age 5–49 y	Persons ≥6 mo old

Table 4
Antiviral drugs for influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Virus	A	A	A and B	A and B
Administration	Oral	Oral	Inhalation	Oral
Treatment indications	≥1 y	≥13 y	≥7 y	≥1 y
Prophylaxis indications	≥1 y	≥1 y	Not licensed	≥13 y
Adverse effects	CNS, GI	GI	Bronchospasm	Nausea, vomiting

rimantadine, and oseltamivir are the three antiviral medications approved for chemoprophylaxis of influenza in children [23,26,29].

Any person 1 year old or older experiencing a potentially life-threatening infection should be treated with antiviral medication. Any person 1 year old or older who is at risk of serious complications of influenza should be treated with antiviral medication, ideally within 48 hours of onset of symptoms. Treatment of persons who do not have conditions placing them at greater risk of serious complications also may benefit from antiviral therapy begun within 48 hours of onset of symptoms. For treatment of illness resulting from influenza A or if the type is unknown, oseltamivir or zanamivir is recommended to reduce the risk of development of amantadine-resistant isolates, which could be transmitted to contacts [26,30,31].

Persons who live or work in an institution caring for people at high risk of serious complications should receive prophylaxis during an institutional outbreak. Prophylaxis also may be considered for persons at high risk who cannot be vaccinated, vaccinated high-risk persons who are exposed within 2 weeks of immunization (before time for an adequate antibody response), immunosuppressed persons who may not respond to the vaccine, and health care workers who are not able to obtain vaccine [26,32,33]. For prophylaxis against influenza A, amantadine or rimantadine is encouraged because of greater availability and lower cost relative to the neuraminidase inhibitors.

Influenza pandemics refer to the sudden emergence and rapid spread throughout the world of a new strain of influenza virus that causes extensive social disruption and severe disease with increased mortality relative to typical annual epidemics. Three influenza pandemics occurred in the last century (Table 5). The occurrence of the next pandemic seems to be inevitable. Estimates from the CDC project that 200 million people may be infected during the next pandemic. Between 300,000 and 800,000 persons in the United States may re-

Table 5
Influenza pandemics in twentieth century

Years	Influenza	Virus
1918–19	Spanish	Type A (H1N1)
1957–58	Asian	Type A (H2N2)
1968–69	Hong Kong	Type A (H3N2)

quire hospitalization, resulting in 88,000 to 300,000 deaths. Because pandemic strains typically appear in the United States less than 6 months after detection elsewhere in the world, vaccine may be unavailable or in limited supply. Health care workers are at increased risk of early exposure and may become ill before much of the general population, compromising the delivery of health care.

Type A influenza virus is capable of infecting numerous different animal species, including birds, pigs, horses, whales, and humans. Birds are considered to be the natural host of influenza viruses because all known subtypes of influenza A have been isolated from birds. Wild birds generally do not develop symptoms when infected by influenza virus. In contrast, domesticated birds, such as chickens or turkeys, often become sick or die when infected. Influenza virus survives in the intestine and is spread in the saliva, nasal secretions, and feces of infected birds, although fecal-oral spread of virus among susceptible birds is the most common route of transmission. Transmission of avian influenza directly from birds to humans generally does not occur. The first reported instance of human infection by avian influenza A (H5N1) occurred in Hong Kong in 1997. During this outbreak, 18 people were infected, and 6 died. Killing 1.5 million chickens in Hong Kong removed the reservoir of virus and helped control the outbreak. In early 2004, widespread outbreaks of avian influenza H5N1 occurred in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam. More than 100 million birds died or were killed to control the outbreak. In summer 2004, a second wave of disease due to H5N1 was reported among poultry in China, Indonesia, Thailand, and Vietnam. If H5N1 strains acquire the ability for efficient human-to-human transmission, this strain could cause the next pandemic. The CDC recommends testing for H5N1 strains in patients with radiographically confirmed pneumonia or severe respiratory illness for whom a diagnosis has not been established and who have a history of travel within 10 days of onset of symptoms to a country with documented H5N1 avian influenza in poultry.

Human metapneumoviruses

Human metapneumoviruses were identified as a cause of respiratory tract disease in 2001 [34]. The spectrum of disease and the epidemiology of this RNA virus resemble that of RSV. Findings to date suggest this virus may cause hospitalization in young children at a rate that is second only to RSV [35–37].

Human metapneumoviruses cause upper and lower respiratory tract disease with symptoms including the common cold, bronchiolitis, pneumonia, croup, and exacerbation of reactive airway disease. Results from the New Vaccine Surveillance study found that approximately 4% of 668 hospitalizations of children were associated with human metapneumovirus, and that requirements for supplemental oxygen and mechanical ventilation were similar to the requirements in RSV-infected children [35]. Although the most serious lower respiratory tract

infections occur in children in the first year of life, symptomatic reinfection by human metapneumovirus seems to be common. Risk factors for severe human metapneumovirus disease are similar to the risk factors associated with severe RSV illness. Most cases of lower tract disease occur before 12 months of age, although the median age of human metapneumovirus–infected children in one study of hospitalized patients was greater than the age of RSV-infected children (3 months versus 11.5 months) [35]. Similar to RSV, the incidence of human metapneumovirus infection is greatest during the winter and early spring months, although human metapneumovirus activity seems to peak later in the season than the peak in RSV activity. No vaccine is available. Disease prevention in certain high-risk populations with passively administered antibody may be an option to vaccine development.

Parainfluenza viruses

Parainfluenza viruses that infect humans are divided into four categories, types 1 to 4, based on genetic and antigenic characteristics [38]. Parainfluenza viruses 1 through 3 are important causes of upper and lower respiratory infection in infants and young children, whereas parainfluenza virus 4 is isolated infrequently and seldom associated with severe disease. Although most parainfluenza virus infections in healthy children are restricted to the upper respiratory tract, parainfluenza viruses 1 through 3 are isolated from 9% to 30% of children hospitalized with viral lower respiratory disease. As with RSV, primary infection is more likely to be associated with severe disease in children, whereas recurrent infections typically result in mild illness, especially in adults. Among immunocompromised patients, such as bone marrow transplant patients or solid organ transplant patients, pneumonia is associated with high mortality rates.

Epidemiologic studies suggest that parainfluenza viruses 1 and 2 cause disease in the fall months of alternate years [39,40]. Parainfluenza virus 3 tends to be endemic through the year, with a peak in activity in the spring and early summer months. Most symptomatic infections resulting from parainfluenza viruses occur between 6 months and 3 years of age, although parainfluenza virus 3 is an important cause of bronchiolitis in the first 6 months of life. Upper respiratory tract symptoms secondary to parainfluenza viruses 1 through 3 tend to be similar and consist of coryza, cough, conjunctivitis, hoarseness, and fever. Manifestations of lower respiratory tract disease secondary to parainfluenza virus include croup, bronchiolitis, and pneumonia.

Efforts at disease control through vaccination are progressing slowly. Inactivated or subunit vaccines have met with limited success [16]. Experience with live attenuated vaccines is more promising [41]. A report describes the initial results from a clinical trial with a bivalent RSV/parainfluenza virus 3 intranasal vaccine and supports the feasibility of such a vaccine [42]. Subjects responded with an immune response to both components of the vaccine (no

significant interference), and the vaccine strains seemed to be genetically stable (no evidence of back mutation to a virulent phenotype). Questions to be resolved include shedding and transmissibility of the vaccine strain and development of symptoms in some subjects suggesting insufficient attenuation.

Coronaviruses

Coronaviruses have been classified into four groups based on antigenic and genetic characteristics. Coronaviruses have been recognized for several decades as a cause of respiratory and enteric disease in humans and animals. Human coronaviruses OC43 and 229E cause a common cold syndrome with symptoms similar to those of rhinovirus infection. Common symptoms include malaise, headache, nasal discharge, sore throat, and cough lasting 6 to 7 days. Fever is frequently absent. Asymptomatic infection is common, whereas lower tract disease in infants and children is uncommon. In temperate climates, coronavirus infection is more common in winter and spring than in summer and fall. Because there are multiple strains of coronaviruses, and because reinfection is common, a vaccine is unlikely to be developed.

In November 2002, the first reports of an atypical pneumonia were issued from Guangdong province, mainland China. In less than 1 year, more than 8000 patients (mostly adults) from 26 countries were diagnosed with SARS. Within months, the etiologic agent of SARS was determined to be a coronavirus (SARS-CoV). This virus is now known to circulate in animals, particularly Himalayan palm civets [43,44]. Seroepidemiologic data suggest that SARS-CoV did not infect humans previously. SARS provided a dramatic example of the sudden appearance of a new human respiratory virus arising from an animal source.

The incubation period of SARS is approximately 2 to 10 days. The use of appropriate infection control policies and public health measures showed that epidemics could be prevented. Most transmission of SARS-CoV occurred in health care settings, accounting for the high attack rate seen in medical personnel. SARS-CoV is spread when infectious respiratory droplets come in contact with mucous membranes of susceptible persons. SARS-CoV seems to be more stable than other respiratory pathogens, such as RSV. Profuse watery diarrhea that contains virus is a common feature of infection, and fecal-oral transmission may be another route of transmission [43].

Transmission of disease from adults to children seems to be rare. Infection in children younger than 12 years old is associated with milder disease and a lower fatality rate than infection in adults [45]. Disease in teenagers resembles disease in adults. SARS in patients older than 65, particularly in patients with chronic illnesses, such as diabetes mellitus or heart disease, may produce mortality rates that exceed 50%.

No specific treatment regimen has been shown to prevent disease progression. Supportive care includes supplemental oxygen and mechanical ventilation.

Adenoviruses

Adenoviruses are nonenveloped DNA viruses first observed in human adenoid tissue in 1953. Forty-nine serotypes have been identified. Adenoviruses cause a range of respiratory symptoms, including coryza, pharyngitis, tonsillitis, bronchitis, pneumonia, and conjunctivitis. Infection predisposes to otitis media and sinusitis. Although these viruses can produce sporadic outbreaks of disease, adenoviruses are not associated with the seasonality that characterizes other respiratory viruses. In contrast to some other respiratory viruses that show tropism for only the respiratory tract, adenovirus infection is not restricted to the respiratory tract and has the ability to cause multiorgan involvement, particularly including the gastrointestinal tract, heart, and CNS.

Most adenovirus respiratory infections are self-limited and resolve without long-term complications. There are no licensed antiviral agents for treatment of adenovirus infections. A live oral adenovirus vaccine consisting of serotypes 4 and 7 for use in military recruits was available for many years but was not studied in civilians. This vaccine is no longer available [46].

Rhinoviruses

Rhinoviruses are the principal cause of the common cold. Serotype immunity persists after infection, but there are more than 100 serotypes, and there is no cross-protection. Transmission of rhinovirus infection is common among school-age children, who transmit infection to family members. The peak incidence of colds secondary to rhinovirus in the United States occurs in the fall, when approximately 80% of colds are associated with positive cultures or reverse-transcriptase polymerase chain reaction assays for rhinoviruses. Symptoms in older children and adults consist of runny nose, nasal congestion, sore throat, and malaise, with a median duration of 11 days [47].

There are no licensed antiviral agents for treatment of rhinoviral infections, although pleconaril and interferon alfa have been studied. Because of the numerous serotypes, vaccination against rhinovirus infection is not practical.

Summary

Respiratory infections caused by RNA viruses continue to challenge clinicians' ability to prevent and control outbreaks of disease. In the years ahead, entirely new viral respiratory diseases will continue to emerge, previously unrecognized viruses will be identified using new techniques, and known viruses will continue to mutate. To address the growing public health threat posed by respiratory viruses, surveillance will be essential for establishing public health policy and for directing federal and industry-sponsored research efforts. Perhaps the greatest capacity for widespread disease and social disruption will come from

new strains of influenza viruses that acquire the capacity to move between species, from birds to humans, owing to natural evolution or to an act of bioterrorism with an intentionally altered strain. Determination of population-based incidence rates is a first step on the road to development of new vaccines and novel antiviral agents. The CDC has established the New Vaccine Surveillance Network to assess the disease burden attributable to certain viral illnesses against which new vaccines are likely to become available [48,49]. Data provided from ongoing surveillance of respiratory hospitalization in children younger than 5 years old will be useful in assessing the effectiveness of new vaccines and therapies.

References

[1] Morris JA, Blount RE, Savage RE. Recovery of cytopathic agent from chimpanzees with coryza. Proc Soc Exp Biol Med 1956;92:544–50.
[2] Hall CB, Walsh EE, Schanbel KC. Occurrence of groups A and B of RSV over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 1990;162:1283–90.
[3] Martinello RA, Chen MD, Weibel C, Kahn JS. Correlation between RSV genotype and severity of illness. J Infect Dis 2002;186:839–42.
[4] Meissner HC, Long SS. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infection. Pediatrics 2003;112:1447–52.
[5] Shay DK, Holman RC, Newman RD, Liu LL, Stoput JW, Anderson LJ. Bronchiolitis associated hospitalization among United States children 1980–1996. JAMA 1999;282:1440–6.
[6] Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis associated mortality and estimates of respiratory syncytial virus associated deaths among United States children 1979–97. J Infect Dis 2001;183:16–22.
[7] McCarney KK, Gorelick MH, Manning ML, Hodinka RI, Bell LM. Nosocomial respiratory syncytial virus infections: the cost effectiveness and cost benefit of infection control. Pediatrics 2000;106:520–6.
[8] Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J 2003;22:S76–82.
[9] Meissner HC, Anderson LJ, Pickering LK. Annual variation in respiratory syncytial virus season and decisions regarding immunoprophylaxis with palivizumab. Pediatrics 2004;114:1082–4.
[10] Meissner HC. The unresolved issue of risk factors for hospitalization of infants with respiratory syncytial virus infection born after 33–35 weeks gestation. Pediatr Infect Dis J 2004;23:821–3.
[11] LeSaux N, Gaboury I, MacDonald N. Maternal respiratory syncytial virus antibody titers: season and children matter. Pediatr Infect Dis J 2003;22:563–4.
[12] Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group and maternal antibody level. J Pediatr 1981;98:708–15.
[13] Feltes TF, Cabalka AK, Meissner HC, et al, and Cardiac Synagis study group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532–40.
[14] Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. Pediatr Infect Dis J 2003;22:S40–5.
[15] Mullins JA, Lamonte AC, Bresee JS, Anderson LJ. Substantial variability in community respiratory syncytial virus season timing. Pediatr Infect Dis J 2003;22:857–62.

[16] Durbin AP, Karron RA. Progress in the development of RSV and parainfluenza virus vaccines. Clin Infect Dis 2003;37:1668–77.
[17] Johnson S, Oliver C, Prince GA, et al. Development of humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997;176:1215–24.
[18] The IMpact-RSV study group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531–7.
[19] Romero JR. Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: results from four years of palivizumab usage. Pediatr Infect Dis J 2003;22:S46–54.
[20] Meissner HC, Welliver RC, Chartrand SA, et al. Immunoprophylaxis with palivizumab, a humanized RSV monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. Pediatr Infect Dis J 1999;18:223–31.
[21] Simoes EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003;143:S118–26.
[22] American Academy of Pediatrics. Revised indications of the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003;112:1442–6.
[23] Centers for Disease Control and Prevention. Prevention and control of influenza. MMWR Morb Mortal Wkly Rep 2003;52(RR-8):1–36.
[24] Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalizations for respiratory disease among infants and young children. N Engl J Med 2000;342:232–9.
[25] Neuzil KM, Mellen BG, Wright PE, Mitchel EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits and courses of antibiotic in children. N Engl J Med 2000;342: 225–31.
[26] Rennels MB, Meissner HC. Reduction of the influenza burden in children. Pediatrics 2002; 110:e80–98.
[27] Weitkamp J, Spring MD, Brogan T, et al. Influenza A virus-associated acute necrotizing encephalopathy in the United States. Pediatr Infect Dis J 2004;23:259–63.
[28] Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr 2000;136:168–75.
[29] Centers for Disease Control and Prevention. Neuraminidase inhibitors for treatment of influenza A and B infections. MMWR Morb Mortal Wkly Rep 1999;48(RR-14):1–9.
[30] Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J 2000;19:410–7.
[31] Whitely RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20:127–33.
[32] Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts. JAMA 2001;285:748–54.
[33] Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. N Engl J Med 2000;343:1282–9.
[34] van den Hoogen BG, deJong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24.
[35] Mullins JA, Erdman DD, Weinberg GA, et al. Human metapneumovirus infection among children hospitalized with acute respiratory illness. Emerg Infect Dis 2004;10:700–5.
[36] Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004;350:443–50.
[37] van den Hoogen BG, Osterhaus ME, Pouchier RAM. Clinical impact and diagnosis of human metapneumovirus infection. Pediatr Infect Dis J 2004;23:S25–32.
[38] Henrickson KJ. Parainfluenza viruses. Clin Microbiol Rev 2003;16:242–64.
[39] Knott AM, Long CE, Hall CB. Parainfluenza viral infections in pediatric outpatients: seasonal patterns and clinical characteristics. Pediatr Infect Dis J 1994;13:269–73.

[40] Reed G, Jewett PH, Thompson J, Tollefson S, Wright PF. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children < 5 years old. J Infect Dis 1997;175:807–13.
[41] Karron RA, Belshe RB, Wright PF, et al. A live human parainfluenza type 3 virus vaccine is attenuated and immunogenic in young infants. Pediatr Infect Dis J 2003;22:394–405.
[42] Belshe BB, Newman FK, Anderson EL, et al. Evaluation of combined live, attenuated respiratory syncytial virus and parainfluenza 3 virus vaccines in infants and young children. J Infect Dis 2004;190:2096–103.
[43] Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.
[44] Peris JSM, Yeun KY, Osterhaus ADME, Stohr K. The acute respiratory syndrome. N Engl J Med 2003;349:2431–41.
[45] Leung C, Kwan Y, Ko P, et al. Severe acute respiratory syndrome in children. Pediatrics 2004; 113:e535–43.
[46] Katz SL. A tale of two vaccines. Clin Infect Dis 2000;31:671–2.
[47] Arruda E, Pitkaranta A, Witek TJ, Doyle CA, Hayden FG. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35:2864–8.
[48] Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD, and the New Vaccine Surveillance Network Study Group. Epidemiology of respiratory infections in young children: insights from the New Vaccine Surveillance Network. Pediatr Infect Dis J 2004;23:S193–201.
[49] Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with RSV, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004;113:1758–64.