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Viral Pneumonia in Children

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Viral pneumonia causes a heavy burden on our society. In the United States, more than one million cases of pneumonias afflict children under the age of 5 years, costing hundreds of millions of dollars annually. The majority of these infections are caused by a handful of common viruses. Knowledge of the epidemiology of these viruses combined with new rapid diagnostic techniques will provide faster and more reliable diagnoses in the future. Although the basic clinical epidemiology of these viruses has been carefully investigated over the last 30 years, new molecular techniques are greatly expanding our understanding of these agents and the diseases they cause. Antigenic and genetic variations are being discovered in many viruses previously thought to be homogeneous. The exact roles and the biological significance of these variations are just beginning to be explored, but already evidence of differences in pathogenicity and immunogenicity has been found in many of these substrains. All of this information clearly will impact the development of future vaccines and antiviral drugs. Effective drugs exist for prophylaxis against influenza A and respiratory syncytial virus, and specific therapy exists for influenza A. Ribavirin is approved for use in respiratory synctial virus infections, and it alone or in combination with other agents (eg, IGIV) may be effective in immunocompromised patients, either in preventing the development of pneumonia or in decreasing morbidity and mortality. Many new antiviral agents are being tested and developed, and several are in clinical trials.

Viral respiratory infections are the most common diseases plaguing humankind. The majority of morbidity and mortality accompanying these infections occurs in children under the age of 5. However, increasingly these "childhood" viruses are causing disease and even death in a significant number of normal adults, the elderly, and especially immunocompromised individuals.[1,2] With the advent of new and improved techniques in molecular biology, many new diagnostic, therapeutic, and preventive strategies are now or soon will become available. Even our understanding of basic viral epidemiology is rapidly changing with these tools. This article will concentrate on the viruses that most frequently infect children and cause pneumonia.

Epidemiology of Pneumonia

Acute respiratory infections (ARI) cause or contribute to the death of an estimated 4 to 5 million children each year in developing nations.[3-5] The majority of these deaths are in children with pneumonia. Approximately 30 to 48 percent of these children have had respiratory viruses other than measles isolated during their illnesses, which are frequently complicated by bacterial infections of the lower respiratory tract.[3,6-7]

In the United States each year, the number of children younger than 5 years of age who have lower respiratory infections (LRI) is estimated at greater than 5 million.[8] The frequency of LRI in children by age and sex from a private practice in Chapel Hill, North Carolina is shown in Figure 1. Boys have a higher incidence of LRI for the first 10 years of life and one approximately equal to that of girls through adolescence.[9] The incidence of LRI is highest in the first year of life, peaking at between 30 and 35 cases of LRI per 100 children per year, then gradually decreasing to about 5 per 100 children per year in those 9 to 10 years of age, and staying in this range until later in life.[10]

Pneumonia represents only one of many clinical presentations for LRI. It represents on average 29 to 38 percent of pediatric inpatient admissions for LRI and is found in 23 percent of children with LRI treated as outpatients.[9,11-14] However, the age-related incidence of pneumonia does not follow exactly the incidence of LRI (Fig 1). In the first year of life, pneumonia accounts for only approximately 10 percent of the LRI in children observed in an ambulatory care setting.[9] The incidence increases until it reaches a peak in the second and third years of life (approximately 4 to 5 cases/100 child years), then gradually decreases to 2 cases per 100 child years in the 5 to 9 age group and to about 1 case per 100 child years thereafter.[9,15-16] In children hospitalized for LRI, pneumonia accounts for approximately 33 to 50 percent of the causes in the first year of life, then declines somewhat until school age, when it increases to become

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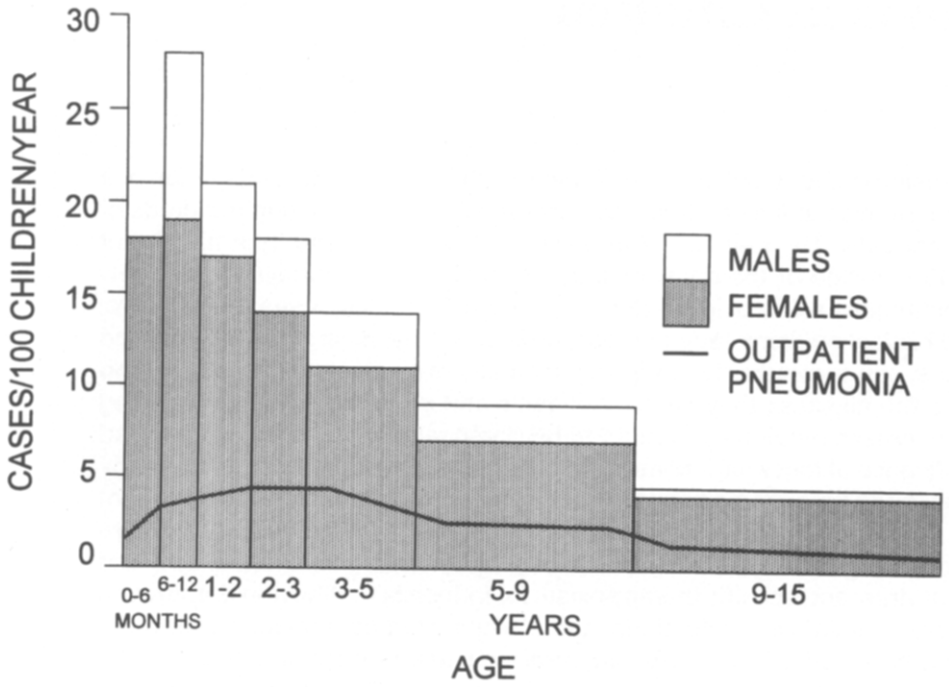

Figure 1. The frequency of lower respiratory infection and pneumonia in children. (Adapted and reprinted with permission from Denny FW, et al: Acute respiratory tract infections: An overview. Pediatr Res 17:1023-1076, 1983 and Murphy TF, Am J Epidemiol 113:14, 1981.)

the major cause for hospitalizations.[15,17-18] However, because the majority of LRI in children occurs in their first 5 years of life, as previously stated, pneumonia comprises about one-third of the total LRI observed in the pediatric age range.

Boys develop pneumonia at a slightly higher rate than do girls, but this rate usually is not significant.[9,15,16] In one study, African-American children had significantly more cases of pneumonia than did Caucasians (relative risk = 1.85).[16]

Between 3 and 18 percent of admissions to pediatric hospitals in developed nations can be for LRI, depending on the time of year.[12,16,19] Approximately 4 percent of all admissions during the fall of 1991 at Children's Hospital of Wisconsin were for pneumonia in children under the age of 6. The actual cost of these respiratory infections has not been calculated, but it is staggering in terms of both dollars and time lost from work for the parents. In the United States, hospitalization costs for infection caused by respiratory syncytial virus (RSV) has been calculated at approximately $300,000,000,[20] and for emergency room and hospitalization for human parainfluenza viruses 1 and 2 (HPIVs-1 and -2), the costs are approximately $190,000,000.[16]

Signs and Symptoms

The World Health Organization has developed guidelines for defining and managing pneumonia in infants in developing nations. A recent evaluation of these guidelines showed that using cough and/or rapid (difficult) breathing as an initial screen, coupled with a respiratory rate of at least 60 per minute, severe chest wall in-drawing, and nonspecific signs (eg, poor feeding, fever, etc), identified 83 percent of the cases of pneumonia confirmed by chest radiograph.[21]

In older infants and children (the majority of pediatric pneumonia cases), the documentation of fever and rales and evidence of pulmonary consolidation on physical examination is the traditional method of diagnosing pneumonia. Most observers also require evidence of radiograph changes sometime during the course of the illness to corroborate the physical examination findings.

Viruses

Depending on the age of the child and the particular respiratory symptoms,[9,11-13] between 50 and 90 percent of LRI are caused by viruses. Viruses have been shown to cause up to 90 percent of pneumonias, especially in the first year of life,[9,15,22-24] and this percentage decreases to approximately 50 percent by school age.[9,11] Viruses cause a decreasing but still significant number of pneumonia cases in immunocompetent individuals 9 to 10 years of age and older. The percentage of pneumonias with a viral cause eventually declines to approximately 12 percent by adulthood.[1,25] This figure does not include excess bacterial pneumonias that occur during specific viral epidemics (eg, yearly influenza or RSV epidemics) or increased pneumonias in the elderly.[26]

The viruses that frequently cause LRI in children are listed in Table 1. Also shown is the relative frequency of each respiratory virus as a cause of total viral LRI. The most frequent causes of viral pneumonia in children are listed in Table 2. The same viruses that cause LRI also are the causes of pneumonia. Several different LRI "syndromes" (eg, bronchiolitis, croup, bronchitis), including pneumonia, can occur at the same time or progressively in the same child. Usually they are caused by a single agent.

Two or more respiratory viruses can be isolated in 5 to 20

Table 1. Causes of Lower Respiratory Infections in Young Children

	Outpatient		*Inpatient*	
	% *Detected*	% *Positives*	% *Detected*	% *Positives*
RSV	6-19	14-44	12-30	32-63
HPIV				
type 1	2-3	7-8	2-6	5-12
type 2	1	4	<1-3	2-12
type 3	1-8	6-19	<1-12	1-23
Total types 1-3	8-16	16-35	4-21	9-41
Influenza				
type A	<1-5	<1-10	<1-7	1-13
type B	1-2	3-9	0-3	0-8
type C or not typed	<1	<1-2		
Adenovirus (many types)	2-10	7-35	3-9	5-25
Rhinovirus (many types)	1-3	3-6	0-12	0-25
Herpes simplex type 1	0-3	0-5	<1-2	1-4
Enterovirus (many types)	1	2-6	<1-2	1-6
Coronavirus	12*	24*	8*	33*
Other viruses†	<1	2		
Total (average)	33	75‡	41	98‡

NOTE: This includes virus isolation, antigen detection, and polymerase-chain reaction.
Abbreviations: RSV, respiratory syncytial virus; HPIV, human parainfluenza virus.
*Children with chronic asthma.
†Human parainfluenza virus type 4, cytomegalovirus, influenza virus type C, nontypeable hemadsorbing viruses.
‡These rates are syndrome and age dependent.
Data from references 9, 11-16, 77, 134, 156, 257-259 and K.J. Henrickson, unpublished data.

percent of acute LRI and may increase the severity of disease.[27] In addition, these viruses routinely cause otitis media, pharyngitis, conjunctivitis, and coryza (common cold) in combination with pneumonia.

One of the difficulties in trying to summarize incidence data on these viruses is that great differences exist in study designs.

Table 2. Viruses Associated with Pneumonia in Children

	Developed Countries (%)	*Developing Countries (%)*
RSV	29 (24-63)	36 (26-78)
Parainfluenza		
type 1	9 (3-11)	
type 2	2	
type 3	9 (3-26)	
Total types 1-3	20	5 (3-13)
Influenza		
type A	4 (3-9)	5 (4-13)
type B	4	2 (1-6)
Total types A-B	8	8
Adenovirus	7 (6-7)	9 (3-48)
HSV	3	4
Rhinovirus	5 (2-25)	
Enteroviruses	5	

Abbreviations: RSV, respiratory syncytial virus; HSV, herpes simplex virus.
Data from references 3, 6, 7, 10, 11, 23, 24, 259.

Also, these numbers are limited by each institution's ability and interest in recovering certain viruses, whether an outpatient or inpatient population was studied, the number of years or time of year studied, the ages of the children, and whether they reported or looked for other pathogens or causes for each child's lower respiratory symptoms. As an example, in the United States, the sum of the reported incidences of LRI caused by RSV and HPIV-3 during the first year of life is 33 per 100 children per year.[28,29] Because this percentage is almost exactly the reported incidence for LRI in general, not much room is left for the other common pathogens. However, a clear pattern among all of the reported data indicates which viruses consistently cause the most infections and illnesses in young children. This pattern has not changed substantially in over 30 years of observation, and it seems to hold true throughout the world.

Clearly, in developed nations, RSV is the largest single pathogen resulting in hospitalization. It also seems to be a major cause of pneumonia in developing countries (Table 2). RSV is the most common cause of pneumonia in infants and preschool age children. In young hospitalized infants, it routinely causes about 60 percent of pneumonias.[11,13,30] Parainfluenza viruses as a group cause at least as many LRI, but they result in lower hospitalization rates and less pneumonia than does RSV. HPIVs-1 and -3 each cause approximately 10 percent of outpatient pneumonias. However, HPIV-3 results in a higher rate of hospitalization for pneumonia in infants and children and is second only to RSV in young infants. HPIVs-2 and -4 both have been reported to cause pneumonia, but the exact proportion of disease caused by these viruses is unclear. Influenza viruses A and B are the next most frequent causes of pneumonia and vary significantly from year to year. Adenoviruses and rhinoviruses are recovered consistently from children with pneumonia. In young infants, enteroviruses play an important role, whereas influenza becomes more important during the school years. RSV; parainfluenza 1, 2, and 3; influenza A and B; and adenovirus together cause the vast majority of all pneumonia in preschool children and are the major causes of viral pneumonia throughout life.[31]

A seasonality to the viruses that cause LRI in children has been well-documented and presented (Fig 2).[9,12,32] Although one virus predominates within a community, overlap always occurs (Fig 3). Also, considerable variation takes place in the severity and exact timing of epidemics between years.

Immunocompromised Hosts

RSV, HPIV, influenza, and adenovirus all have been reported to cause serious and fatal LRI in immunocompromised children and adults. Adenoviruses have been associated with pneumonia in an agammaglobulinemic patient[33] and with bronchial necrosis in a patient with thymic disfunction.[34] Giant-cell pneumonia with HPIV-2 has been reported in severe combined immunodeficiency syndrome (SCIDS)[35] and with HPIV-3 in SCIDS,[36,37] acute myelomonocytic leukemia,[38] and after bone marrow transplantation.[39] Many of these patients had dual infections with other pathogens. Persistent respiratory tract infection and viral excretion by HPIVs-1, -2, and -3 have been described in SCIDS, with HPIV-3 in a child with DiGeorge syndrome after thymic transplant,[40] and with RSV and HPIV-3 in children infected with HIV.[41,42] The HIV group of children did not seem

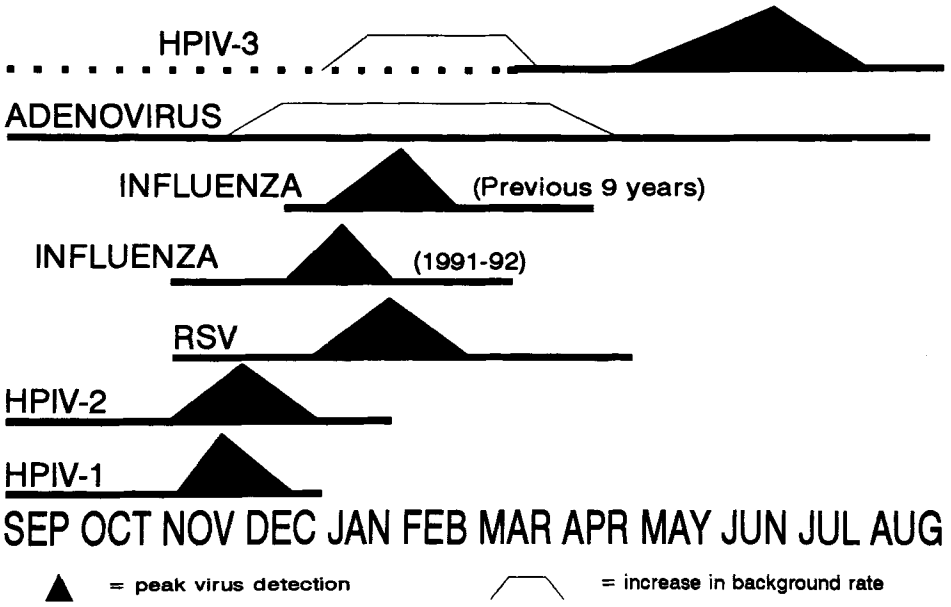

Figure 2. Major "seasons" of viruses causing lower respiratory infections in children in North America. Schedule of major respiratory viruses causing seasonal epidemics.

to have more severe disease with these viruses until they were significantly deficient in T-cells, but the epidemiology of respiratory viruses in this population still needs to be studied.[43] HPIV-3 and influenza have been associated with acute rejection episodes in renal and liver transplant recipients.[44] Influenza has been associated with encephalitis or meningitis in recipients of organ transplant.[44]

RSV; HPIVs-1, -2, and -3; and influenzae A and B upper and lower respiratory tract infections, including pneumonia, and death have been reported in organ and bone marrow transplant (BMT) patients.[2,44] Pneumonia occurred in 50 to 78 percent of infected adult immunocompromised patients, and 16 to 44 percent died. The early preengraftment period seems to be a particularly dangerous time to become infected with one of these viruses. In children, the epidemiology and natural history is not well-described. However, 56 percent of 45 children who were recipients of solid organ transplants and were infected with these respiratory viruses developed pneumonia, and 19 percent died.[45] Also, these common respiratory viruses have been shown to cause 20 percent of the episodes of fever in children with cancer.[46] Adenoviruses have been associated with pneumonia in 3 of 83 pediatric BMT patients; two of the three patients died of respiratory failure and one of hepatic failure.[47]

Viruses as Pathogens

The basic structural and biological characteristics for each of the major pediatric respiratory viruses have been well-described in great detail in several recent textbooks.[48,49]

RSV

RSV is a small pleomorphic enveloped virus with a single strand of ribonucleic acid (RNA) (negative polarity). It belongs to the large paramyxoviridae family of viruses, and thus it can be differentiated morphologically from HPIV, mumps, and measles only by its narrower nucleocapsid.[48] This virus is the number one cause of pediatric hospital admissions for LRI in most areas of the world,[50] causing almost 100,000 hospitalizations per year in the United States alone.[51] RSV causes yearly epidemics lasting 3 to 5 months, usually beginning in the early winter or the equivalent rainy season in tropical climates. Most severe disease

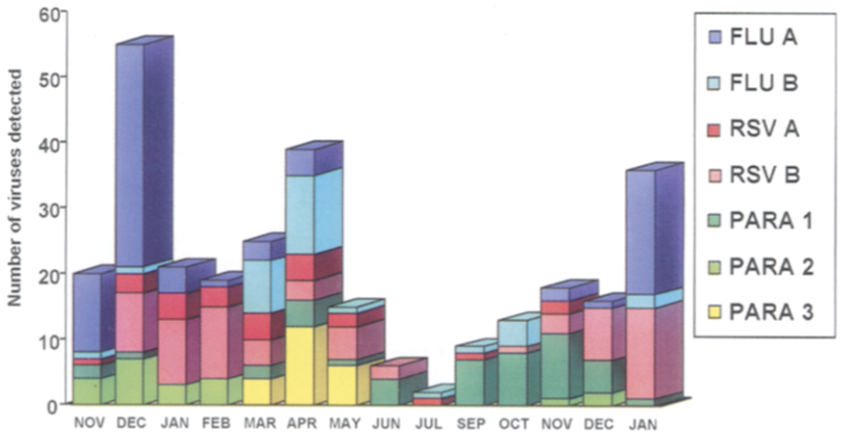

Figure 3. Respiratory viruses detected by RT-PCR-EHA at Children's Hospital of Wisconsin during 1996-1997.

occurs in children under 1 year of age, with a peak occurring between 2 and 5 months of age, and, as indicated previously, manifests itself as bronchiolitis or pneumonia. Two RSV subtypes (A and B) have been determined mostly by antigenic and genetic differences found in their surface glycoproteins (G and F).[52] Further subgroups of A and B have been described on the basis of antigenic changes on the G protein.[52] Both subtypes circulate in any one year, although often one type predominates. Subtype A strains may be more virulent than are B strains, and they may cause more hospitalization,[53,54] but some investigators have found no difference between subtype strains in type or severity of LRI in children.[55]

HPIV

Human parainfluenza viruses are separated functionally from RSV by their ability to hemagglutinate red blood cells, a property they share with influenza viruses. Four major virus groups within HPIV (Types 1-4) exist. Further subtypes of HPIV-4[56] and subgroups of HPIV-1[57-60] and HPIV-3[61] have been described.

HPIV-1 usually occurs in biennial epidemics during the fall in both hemispheres.[9,12] At least 50 percent of croup cases (approximately 250,000 per epidemic) in the United States can be linked to this virus.[9] HPIV-1 causes LRI predominantly in children 7 to 36 months of age, with a peak incidence in the second and third years of life. HPIV-1 can cause LRI in young infants, but it is rare in children younger than 1 month. In the United States, an estimated 35,000 children younger than 5 years of age are hospitalized each biennium because of HPIV-1.[8,9,14,16,61] Infection with HPIV-2 has been reported to occur biennially with HPIV-1, alternate years with HPIV-1, and more recently in yearly outbreaks.[12,19,62] The majority of respiratory tract infections caused by this virus appear in the fall to early winter. Croup is the most frequent LRI caused by HPIV-2, but all of the respiratory syndromes have been described. LRI caused by this virus have been reported much less frequently than with HPIV-1 and -3, perhaps because of difficulties in isolation and detection. The peak incidence of HPIV-2 occurs in the second year of life, but significant numbers of infections occur in infants under 1 year of age, and approximately 60 percent occur in a child's first 5 years. Although frequently overshadowed by HPIVs-1 and -3, HPIV-2 can, in any one year, be the predominant parainfluenza virus causing LRI in young children.

HPIV-3 is unique among the HPIVs in its propensity to infect young infants less than 6 months of age. This virus causes the majority of its infections in the first 12 months of life (approximately 40%), with bronchiolitis and pneumonia being the most common clinical syndromes. It is second only to RSV as a cause of LRI in neonates and young infants. Approximately 20,000 infants and children are hospitalized each year in the United States because of LRI caused by HPIV-3. Although endemic throughout the world, this virus also occurs in spring epidemics in North America. Epidemics may be dependent on ambient climate conditions.[63]

HPIV-4 has been isolated from a very small number of children and adults, and few reports have been published on the epidemiology of this virus.[64-67] Approximately one-third of cases have been in infants less than 1 year of age, one-third in preschool children, and one-third in school-age children and adults. Seroprevalence studies have shown that 60 to 84 percent of infants have significant antibody levels after birth (presumably maternal in origin). These levels drop to 7 to 9 percent by 7 to 12 months of age and stay low before increasing to about 50 percent by 3 to 5 years of age. Antibody levels to HPIV-4 continue to rise throughout childhood until approximately 75 to 95 percent of adults have antibody.[66] All of the different respiratory tract syndromes can be caused by HPIV-4. Severe LRI and pneumonia have been associated with hospitalization of infants and young children.[68] However, based on the seroprevalence data, because infection with HPIV-4 is almost universal, serious disease either is rare or difficult to diagnose.

Influenza

This important group of orthomyxoviruses can be separated morphologically from its cousins, the paramyxoviruses, by its segmented genome. This characteristic also allows for the genetic reassortment, which leads to rapid shifts in the antigenic characteristics of the influenza viruses and results in pandemic disease. The three major types of influenza (A, B, and C) are differentiated by stable type-specific ribonucleic acid-associated nucleoprotein. Major subtypes infecting humans are determined by variation in the two surface glycoproteins hemagglutinin (H1, H2, and H3) and neuraminidase (N1 and N2). These viruses have many minor antigenic subtypes, with antigenic variations occurring fastest in type A and slowest in type C. Although all three types cause LRI in children, types A and B cause the majority of cases. Influenza epidemics occur each year during the winter, but they vary greatly in their intensity. Also, one type often predominates in any one year (eg, in 1990-1991, B predominated, and in 1991-1992, A predominated). In years in which influenza type B predominates, increased morbidity in school-age children occurs.[69]

Typically, in the early part of the epidemic, influenza infects young school-age children, who then spread it to preschool children and the elderly later in the season. These latter two groups have the highest rates of hospitalization annually (0.5% for infants less than 1 year of age and approximately 0.3% for both children 1 to 4 years and adults over 65 years).[70] The contribution of influenza to the total cases of viral pneumonia varies year to year and by age, but averages 8 percent.[9,11,12] In preschool age children (1 to 4 years of age), influenza causes all of the typical respiratory syndromes. Very young infants often present with fever only and no specific lower respiratory symptoms. School-age children and adolescents most often present with symptoms of classic influenza with cough, which usually is the only evidence of possible lower respiratory tract involvement.[70] Influenza may cause a large percentage of the cases of tracheobronchitis in older children.[9]

Adenovirus

This small nonenveloped virus is the only deoxyribonucleic acid (DNA) virus to cause frequent LRI in children (Tables 1 and 2). Its nomenclature has been confusing in the past, with subgrouping by hemagglutination patterns (subgroups 1-4) and by the newer system of determining each strain's guanine plus cytosine content and oncogenic potential in rodents (subgroups A-F).[71-73]

Distributed throughout these latter 6 subgroups are 47 distinct serotypes, approximately one-third of which cause most of the disease in humans.[74] In fact, most of the adenoviral LRI in children are caused by subgroups B and C, specifically serotypes 1, 2, 3, 5, and 7.[74]

Adenoviral infection does not seem to have as much seasonal variation as do those caused by the ortho- and paramyxoviruses. Disease can occur year round and throughout the world, but outbreaks and epidemics occur less often in the fall.[75] The majority of LRI and pneumonia occur in preschool-age children, the most severe disease developing in children younger than 2 years of age.[72] The most common lower respiratory syndrome caused by adenoviruses is pneumonia, but all syndromes can occur. Unique to LRI caused by adenovirus is a pertussis-like syndrome that can mimic clinical pertussis in every way.[76] Asymptomatic rectal excretion (persistence) of this pathogen (as high as 6%) with less then 0.6 percent oral excretion suggests that rectal cultures have no place in the diagnosis of pneumonia caused by this virus.[77,78]

Rhinovirus

These very small (pico) ribonucleic acid (RNA) viruses are probably the most ubiquitous respiratory pathogens on earth (Tables 1, 2, and 3).[79,80] Until recently, rhinoviruses were not thought to cause significant numbers of LRI in children,[9] but several investigators now have shown that these agents can cause up to 12 percent of LRI in young children,[30,81,82] with tracheobronchitis and pneumonia being the most common clinical syndromes. Why previously reported investigations failed to document such high rates of isolation for rhinovirus as a cause of LRI is unclear. However, these viruses are difficult to culture and antigen detection has not been available widely in the past. Many more studies are needed to clarify the roles rhinoviruses play in pediatric LRI and pneumonia. Neutralization assays currently can differentiate approximately 100 rhinovirus serotypes capable of infecting children.[79] These serotypes do not seem to circulate widely between different geographic locations or recur in any predictable pattern.[79] Multiple rhinovirus serotypes may circulate within one community while different serotypes are causing disease nearby. Similarly, the following year, different serotypes may be in both locations. Rhinoviruses can be recovered year round, but they are recovered more often during the spring, summer, and fall.

Table 3. Direct and Indirect Immunofluorescent Assays Detection of Common Respiratory Viruses

	Sensitivity (%)	*Specificity (%)*
RSV	61-93	88-94
Influenza A	43-86	100
Influenza B	83	
HPIV-3	31-93	72
HPIV-1, 2	50-83	88
Adenovirus	40	

Abbreviations: RSV, respiratory syncytial virus; HPIV, human parainfluenza virus.
Data from references 27, 137, 142, 144, 145, 152-157.

Coronavirus

This group of viruses is the largest of the RNA viruses found to date, with genomes almost twice as large as those of the paramyxoviridae.[79] Coronaviruses also are extremely difficult to culture, and most studies of LRI or pneumonia in children have not attempted to isolate this agent. The two known human serotypes (HCV-229E and HCV-OC43)[83] do not cross-react with each other. This agent is a frequent cause of URI in children and adults, causing as many as 18 percent in one study,[84] but its role in LRI is still being investigated. Coronoaviruses cause significant numbers of LRI in the large group of children with chronic respiratory disease (asthma, etc),[83,85] but they may play minor roles in other hosts with LRI.[27,86]

Transmission/Nosocomial Infections

Person-to-person transmissions of the two most common respiratory virus families (RSV and HPIV) are very similar, but they differ from the other common respiratory viruses in the method. Studies of RSV and HPIV-1 have shown that transmission by small particle aerosols is unlikely.[87,88] Furthermore, studies of RSV have shown that aerosolization of large droplets may be important for transmission to close contacts and surfaces. The secretions on these surfaces allow for contamination of hands, which in turn leads to direct self-inoculation.[89] HPIVs-1, -2, and -3 all have been shown to survive up to 10 hours on nonporous surfaces and for 4 hours on porous surfaces.[90] However, HPIV-3 experimentally placed on fingers has been shown to lose greater than 90 percent of its infectivity in the first 10 minutes and could not be transferred to other fingers.[91] Therefore, person-to-person spread by direct hand contact seems to be an unlikely means of transmission. Most common disinfectants or antiseptic agents effectively remove RSV or HPIV from surfaces. Alcohol and water were least effective.[90] Influenza,[92] adenovirus,[93] rhinovirus,[94] and coronavirus[95] all are transmitted by small particle aerosols. These viruses seem to be spread most efficiently without any physical person-to-person contact. Although hands, fomites, and secretions may be able to spread these pathogens, they are not considered the predominant transmission pathway. Influenza and adenovirus show very fast and efficient intrafamily spread,[96,97] whereas rhinovirus and coronavirus have much lower levels of transmission within families.[98,99]

Respiratory viruses frequently are transmitted inside medical institutions, including physician offices, hospitals, and chronic care facilities. Nosocomial transmission of RSV and HPIV is most significant in young preschool-age children and the elderly. Transmission to infants varies in direct proportion to the length of hospitalization and has been reported as greater than 45 percent during RSV epidemics. In addition, 50 percent of the staff have become infected.[88] Approximately 20 percent of previously uninfected control children on the same ward with HPIV-3 infected children will excrete virus during their hospital stay.[100] In RSV infections, up to one-third of infants will develop serious LRI.[88,101] The majority of nosocomial HPIV infections will be asymptomatic, but mild respiratory symptoms will develop in about one-third of patients, and some will experience serious LRI or even death.[19,100] Serious sequelae are most

common in patients with underlying medical problems. Even in those with only mild symptoms, the mean length of hospitalization usually is increased by many days because of unnecessary tests and therapies that are ordered because of their new signs and symptoms. Less is known about nosocomial transmission of the other common respiratory viruses. Influenza and adenovirus also have caused outbreaks within hospitals and wards during their peak activity within a community.[63,102-104]

Isolation of all children admitted to hospitals with respiratory signs and symptoms clearly is not practical. However, enforcing strict hand-washing among patients, cohorting high-risk patients away from those with respiratory infections, and limiting potentially-infected visitors (children and adults) or staff may help decrease nosocomial respiratory infections.

Pathogenesis

Malnutrition, overcrowding, vitamin A deficiency, lack of breast-feeding, and environmental smoke or toxins, which occur in both developing and developed countries throughout the world, may contribute to morbidity and mortality in pneumonia.[3,23,105]

All of the respiratory viruses described above gain access to children via the respiratory epithelia of the eyes, nose, and mouth. The eyes and nose usually are the easiest to infect. Most viral pneumonia in children is thought to develop by direct spread from the upper respiratory tract, with viremia playing no or a very minor role. Adenoviruses may be an exception in this regard.[106]

Local secretory antibody, serum antibody, and cell-mediated immunity all play a role in defending the child from LRI. Nasal secretory IgA may play roles in preventing or ameliorating reinfection with homotypic virus (eg, if challenged with an identical strain) during the same respiratory season, but it does not seem to play a significant role in preventing heterotypic infection or in protecting against spread to the lower respiratory tract once infection takes place.[107-111] More work in this area is needed to fully understand the interaction of nasal antibodies with the other parts of the immune system. Serum neutralizing antibody directed at the surface glycoproteins or attachment proteins is very important in protecting the lower respiratory tract.[110,112,113] Also, cytotoxic T-cells seem to play a critical role in lower respiratory tract protection.[114-116] Besides the more common alpha-beta T-cells, gamma-delta T-cells and natural killer cells also may be involved.[117,118] Targets for the cytotoxic T-cells have included the surface glycoproteins and internal proteins (eg, nucleoprotein), but which viral epitopes are most important for stimulating this line of defense in children is not known. Antibody-mediated cytotoxic T-cell or complement activity may have some role in viral clearance from the lower respiratory tract, but this remains to be fully elucidated.[119,120]

One of the most important aspects of these respiratory pathogens is their ability to escape the immune defenses that were just described. RSV and HPIV can reinfect people multiple times throughout their lives. However, usually only the first encounter with these viruses during infancy and childhood leads to LRI or pneumonia. Most often, repeat infections are manifest as upper respiratory infections until the immune system declines with age or becomes deficient.[2,121] RSV and HPIV-3 have higher rates of recurrent pneumonia than do other pathogens. The exact mechanism by which these viruses continue to infect us remains unclear. Maternal antibody, age at exposure, virus, heterologous antibodies, and a child's genetic milieu all influence the development of protection against pneumonia. Pneumonia does not occur after sufficient humoral and cell-mediated immunities are established.

Influenza A has overcome immune mechanisms by rapidly developing antigenic change. Immunity to different serotypes of rhinovirus will develop, but several upper respiratory infections may be needed before immunity is complete. Also, repeat infections with coronaviruses are common and are usually upper respiratory.[122] Very little is known about immune protection against LRI and pneumonia caused by these latter two virus groups, but presumably it is similar to that just discussed for RSV, HPIV, and influenza. Adenovirus is the only DNA virus that is a common respiratory pathogen, and it also is the only pathogen that appears to give long lasting protection. Reinfection with the same serotype of adenovirus is unusual.[123]

Persistent RSV and HPIV infections have been shown in chronically ill or immunosuppressed patients.[124-126] Adenovirus rarely may remain latent (no viral replication) for many years[127,128] and perhaps contribute to the development of chronic lung disease later in life.[129]

Diagnosis

The causative agent in pneumonia cannot be diagnosed reliably by using clinical, radiologic, or nonmicrobiological laboratory tests (eg, C-reactive protein).[130,131] Radiograph changes can lag behind the clinical diagnosis, both in showing initial pathology and resolution. In one recent study, only 19 of 39 patients diagnosed clinically with pneumonia had radiographic changes compatible with pneumonia. In the same study, 21 children with acute respiratory disease and radiographic evidence of pneumonia had not received a clinical diagnosis of pneumonia.[131] In addition, significant variability (24%) in the radiographic diagnosis of pneumonia has been reported between radiologists and, over time, with the same radiologist.[132] Indeed, "false" histories have been shown to influence the interpretation of "normal" chest films in children.[133]

In the United States, use of serological data for the diagnosis of LRI caused by viruses is not common. However, serological data have been used extensively in other countries as an adjunct to diagnosis by culture and antigen detection.[134] Young infants often do not develop a significant serological response to many of these pathogens (eg, RSV). Also, HPIV serotypes, especially HPIVs-1 and 3, often cannot be distinguished.[49] Antibodies to these pathogens can be detected by enzyme immunoassay (EIA), indirect immunofluorescent assay, complement-fixation, hemagglutinin-inhibition, radioimmunoassays, Western blot, and neutralization assays.[49] Complement-fixation once was the most widely used assay and probably is the most specific for most of these viruses, but EIA has proven to be superior in sensitivity and is becoming more widely used.

A detailed understanding of these agents and their seasonal-

ity (Figs 2 and 3) helps suggest the most likely pathogen(s), but as can be seen, most of these viruses are recovered in most months of the respiratory virus "season." Rapid diagnosis of the specific pathogen(s) may be very important for initiating antiviral therapy, cohorting patients, stopping unnecessary antimicrobial therapy (helping to decrease antibiotic resistance), eliminating unnecessary diagnostic tests and procedures, decreasing hospital stay, and reducing costs.[135]

One of the most important aspects of diagnosing respiratory viruses in children is the proper collection and transport of samples of respiratory secretions. Throat swabs, nasopharyngeal swabs, nasal wash, and nasal aspiration all have been used successfully to recover these pathogens. The latter two methods have been the most successful.[136-140] Swabs, brushes, or scrapers have been effective in providing epithelial cells (or antigen) for IFA or EIA.[139,141,142] Nasal-wash specimens should be transported on ice and processed within 8 hours for best virus isolation.

RSV, HPIV, influenza, and adenovirus all can be detected or isolated by many methods. Tissue culture isolation is the standard against which everything else is compared, although rapid antigen detection for RSV without culture confirmation is widely practiced. The first three viral groups can be isolated in 1 to 14 (average, 4 to 5) days in approximately 50 percent of viral pneumonias.[49] Adenovirus usually takes longer to isolate. Tissue culture isolation is affected dramatically by the different methods of obtaining and transporting clinical samples and by cell culture conditions.[143] Many clinical isolates cannot be grown rapidly, even under the best conditions. Furthermore, even after initial identification, additional immunologic assays may need to be performed for specific typing (eg, HPIV-1, influenza A, etc). Accordingly, standard tissue culture rarely is useful in making clinically-relevant decisions.

Enzyme-linked, radio-, and fluroimmunoassays (ie, EIA, RIA, FIA) all have been developed to detect viral antigens from each of these four common pathogens,[144-149] although the majority of data are on RSV and influenza. In general, these assays have good specificity compared with tissue culture (87 to 100%), but they have decreased sensitivities (74 to 85% range). The largest clinical experience is with RSV EIAs, which have been reported to have a sensitivity range of 60 to 90 percent, with the lowest sensitivities being reported from laboratories with the highest yield from tissue culture,[140,141] which implies that the sensitivity may actually be only about 60 percent. Antigen detection for adenovirus has yielded the poorest results, with sensitivity as low as 22 percent.[145,148,150] Assays for HPIV are not available commercially at this time in the United States. Direct and indirect immunofluorescent assays (DFA/IFA) using monoclonal and polyclonal antibodies have been developed for all of these virus groups (Table 3).[27,142,144,145,151-157] In general, the sensitivity of DFA/IFA is lower than that of EIA (~80%),[157] but the specificity usually is slightly higher (average, 91%). Once again, the largest clinical experience is with assays to detect RSV directly from clinical specimens. These studies have shown IFA to be as sensitive if not more sensitive than is EIA.[140,141,144,153-155,158,159]

IFA for direct detection of HPIVs-1, -2, and -3 has shown highly variable sensitivities, averaging between 60 and 80 percent and often even much lower.[49] However, with currently-available monoclonal antibodies, improved sensitivities as high as 80 percent are being reported.[157] Specificities usually have been excellent. RSV, HPIV, influenza, and adenovirus all have shown 5 to 20 percent false-positive rates for EIA and IFA.[49,144,153,155,157,159] However, some of these "false" positives may be true positives because the tissue culture was "falsely" negative. In addition, the majority of these studies have suggested that DFA/IFA is subjective and needs significant experience to obtain the best results. Also, in the majority of these studies, 6 to 11 percent of the samples were "uninterpretable" and were removed before statistical analyses were performed.

Centrifugation in tissue culture shell vials coupled with DFA/IFA for rapid identification has been shown to speed recovery of most of these viruses, especially adenovirus.[160] The majority of the data concern RSV and influenza. The published sensitivities compared with tissue culture when read at 48 hours vary between 48 and 100 percent, depending on the virus. Averaging the data indicates that accuracy of adenovirus detection is approximately 70 percent, HPIV (mostly type 3) approximately 80 percent, RSV approximately 90 percent, and influenza approximately 95 percent, compared with detection by standard tissue culture.

The development of rapid molecular techniques such as polymerase chain reaction (PCR) has allowed for the sensitive and specific detection of the majority of these respiratory viruses from clinical specimens.[161-169] A commercial laboratory has offered multiplex PCR assays for these viruses for several years.[165] A multiplex PCR for HPIVs-1, 2, and 3 was first available in 1995, followed in 1996 by a multiplex PCR to RSV A, B; influenza A, B, and HPIVs-1, -2, and -3. Figure 3 shows the results of this multiplex PCR assay used to diagnose the seven most common respiratory viruses from symptomatic hospitalized children. In 318 children, comparison with standard tissue culture showed a sensitivity of 97 percent (confidence interval 0.89 to 1.0) and a specificity of 98 percent (confidence interval 0.97 to 0.98). This assay takes only about 10 hours to complete, is semiquantitative or quantitative, and is less sensitive to factors that interfere with other methods (eg, viral viability and handling of samples). In addition, PCR technology seems to be more sensitive than is tissue culture or antigen detection,[170,171] suggesting that PCR assays for the common respiratory viruses may become the new gold standard in diagnosis. This new method should provide exciting new diagnostic and epidemiological information over the next 5 years.

Rhinoviruses and coronaviruses are difficult to grow in tissue culture, even with experience.[84] Coronavirus isolation may not even be available commercially at this time.[79] Investigators have used standard strains (HCV-229E and OC43) in EIA to detect either virus or antibody to these and closely-related viruses with good success.[27,83,85,172] Also, IFA has been used to detect coronaviruses in children.[86] A tissue culture cell line with a cloned human receptor to coronavirus has been developed that may allow increased recovery of these viruses from clinical samples.[173] In addition, PCR-based assays are beginning to be used more frequently in research studies. Application of this technology may provide answers to many important epidemiological and clinical questions.

Sequelae

Many of the viruses that cause pneumonia in children cause other syndromes or have sequelae not related to the respiratory tract (eg, influenza or adenovirus). However, this section will deal only with physical and physiological sequelae of pneumonia in children (and only from developed nations). Certainly, these sequelae are only worse in countries with lower socioeconomic development. The greatest portion of morbidity and mortality caused by these viruses is in young infants and the immunocompromised and medically-compromised populations. The majority of deaths caused by RSV each year occur in infants and children who have congenital heart disease[174] or chronic lung disease[175-177] or who are immunocompromised.[178-180] Likewise, HPIV causes death usually only in young infants, the elderly, and the immunocompromised, but it can cause serious morbidity in infants with chronic pulmonary disease.[49,181]

Apnea is a major complication of viral LRI and pneumonia in young infants (younger than 6 months of age). RSV causes the majority of pneumonia in this age group and, therefore, has been implicated most frequently.[182] RSV has not been shown to have a specific pathological role in apnea different from other respiratory viruses that cause similar diseases (eg, HPIV-3, etc). Apnea in infants with RSV infection occurs usually at the beginning of the illness, is nonobstructive, brief in duration, and, for most infants, does not cause sequelae.[50,183]

Secondary bacterial infections of the lung can occur with any of these pathogens, especially influenza.[184] Bacterial involvement has been implicated in 31 percent of LRI caused by HPIV.[185] Also, as many as 53 percent of children with bacterial pneumonia have had a concomitant viral infection.[95] Viruses isolated included RSV, HPIV, enterovirus, rhinovirus, and adenovirus. However, the RSV isolation rate has been reported to be the same as the controls without bacterial pneumonia, whereas a statistical association between bacterial pneumonia and viral infection has been noted for HPIV.[95] The exact roles of viral LRI as causative agents in bacterial pneumonia still are being determined.

Long-term pulmonary abnormalities found in children after having RSV pneumonia include decreased gas exchange,[186] restrictive lung disease,[187] obstructive lung disease, and hyperreactivity.[186,188] Even adults have been reported to develop chronic lung disease after HPIV LRI.[189] Viral-specific IgE or cytokine production (eg, IL-11, TGF-beta-1, etc) in the lung may play a role in both acute and recurrent wheezing caused by RSV and HPIV.[190,191] However, the exact roles of IgE, allergy, cell-mediated immunity, and tissue cytokines and the possible biased selection of genetic susceptibilities or "at risk" individuals in long-term follow-up studies remain unclear. Parainfluenza LRI in animal models have shown persistent changes in lung mechanics and hyperresponsiveness,[192] suggesting that viral LRI may lead to real pulmonary damage in some people.

Bronchiolitis obliterans, bronchiectasis, unilateral hyperlucent lung, and chronic atelectasis all have been described after infection by many different viruses.[49] However, adenoviruses have been reported more frequently than have the other common viruses. The exact roles of viruses in general, or adenovirus in particular, in the pathogenesis of these rare sequelae are unknown.

Prophylaxis, Therapy, and Prevention

Prophylaxis

Antiviral prophylaxis against pneumonia or other LRI needs to be extremely safe, inexpensive, and widely available for long-term use in children. So far, these criteria have been successfully fulfilled only in preventing influenza A infections. The recently approved prophylaxis for severe RSV disease still does not meet these criteria because it is very expensive and in limited supply.

Immunoglobulin (IGIV). Human plasma with high-micro-neutralization titers to RSV has protected mice from challenge infections with RSV.[193] Also, human immunoglobulin with high-neutralization titers to RSV has decreased viral shedding from challenged primates[194] and has been shown to be protective against other paramyxoviruses.[195] Initial studies using standard IGIV to prevent RSV disease in high-risk infants showed only minimal benefit; however, after increasing the specific RSV-neutralizing antibody titer further, trials were successful in showing protection.[196-197] The most recent trial showed a 40 to 60 percent reduction in RSV illness, severity, and hospitalization.[197] In addition, disease caused by other respiratory viruses also was reduced. The American Academy of Pediatrics has recommended the use of RSV-IGIV in children younger than 2 years of age with bronchopulmonary dysplasia currently or recently (last 6 months) on oxygen therapy or who were prematurely born (<32 weeks gestation), but not in children with congenital heart disease, especially cyanotic disease.[198]

Amantadine/Rimatidine. These two agents have shown usefulness in chemoprophylaxis against influenza A, showing between 71 and 100 percent protection against illness. Amantadine should be considered during influenza season for any child who is (1) unimmunized and at high risk (Table 4), (2) any unimmunized adult/child with regular prolonged contact with high-risk children, (3) immunized high-risk children who were immunized late or with vaccine strains that do not match the current epidemic strains, and (4) as an adjunct in certain

Table 4. Children at High Risk for Serious Complications From Viral Pneumonia

Definite Risk
Primary or secondary immunodeficiencies (including human immunodeficiency virus)
Congenital heart disease (hemodynamically significant)
Chronic lung disease (including moderate to severe asthma, cystic fibrosis, bronchopulmonary dysplasia)
Residents of chronic-care facilities
Hemoglobunopathies
Possible Risk
Diabetes mellitus
Chronic renal disease
Chronic metabolic disease
Children on long-term aspirin therapy

high-risk children not expected to respond well to immunization.

Vitamin C. Controversy continues about the usefulness of vitamin C for prophylaxis against URI, especially with recent studies showing protection against rhinovirus infection.[199a] In addition, previous trials have suggested that vitamin C may protect against LRI or pneumonia in children.[199b] Further study of this issue is warranted.

Vitamin A. Recent evidence has shown a significant role for vitamin A in reducing morbidity and mortality in acute measles infections,[200,201] including pneumonia and croup.[202-203] Acute infection seems to lower the level of vitamin A in well-nourished children with previously normal levels.[204] Measles, RSV, and HPIV are closely related paramyxoviruses, but the role of vitamin A in preventing or treating LRI caused by these other viruses is unknown. However, evidence that paramyxovirus specific B and T cell function may be improved with vitamin A supplementation exists, and such could hold true for RSV and HPIV as well.[205]

Nonspecific immunostimulators have been shown to protect against challenge infections with HPIV in animal experiments.[206-208] They have included interferon-gamma, human granulocyte colony-stimulating factor, and human interleukin-1 beta. Many other agents have shown antiviral activity toward these viruses, but none are near clinical application at this time.

Therapy

Immunoglobulin (IGIV). Recent studies have shown some benefit when high-titer anti-RSV antibody is administered to animals infected with RSV.[209] Infants treated with IGIV showed decreased viral shedding and improved clinical response without differences in mortality.[210] Also, aerosolization of the immunoglobulin recently has been shown effective in dramatically reducing virus titers in infected cotton rats.[211] Anecdotal use of immunoglobulin to treat adenovirus disease in immunocompromised children has been reported with both positive[212] and negative results.[213] Similarly, IGIV has been coupled with ribavirin anecdotally for the treatment of RSV, HPIV, and influenza B pneumonia in immunocompromised patients.[2] Liposome encapsulation as a means of delivery is being investigated for many drugs, including IGIV and antiviral agents. Liposome encapsulated antibody has shown effectiveness both in prophylaxis and in treatment of influenza virus A in mice.[214] Evidence suggests that specific high-titer antiviral IGIV in some form may find a place in the treatment of severe pneumonia in children. However, RSV-IGIV recently has been shown not to be effective in the treatment of high-risk children hospitalized with LRI caused by RSV.[215]

Interferon. Parenteral interferon causes many systemic side effects and, as such, has not been thoroughly investigated as a therapeutic agent in children with pneumonia.[216] Furthermore, adenovirus antagonizes interferon's antiviral activity; accordingly, the use of this drug in the treatment of pneumonia does not seem promising.[217]

Ribavirin. Ribavirin, delivered by small particle aerosol, has been shown to be effective in treating influenza in college students.[218-220] Treated students had decreased symptoms and virus excretion. The only published cases of influenza virus LRI treated with ribavirin recovered.[22] Ribavirin should be considered as an adjunct to amantadine for the treatment of serious LRI with influenza virus. Several clinical trials have shown that the use of ribavirin results in clinical improvement in children with LRI caused by RSV.[222-224] However, more recent efficacy trials have failed to show benefit. At this time, ribavirin should be considered in specific clinical situations when RSV is a likely pathogen. They include young infants (less than 6 weeks of age) and those with severe LRI or at high risk for serious complications, which have been well-described in the Red Book.[225] High-dose, short-duration therapy with ribavirin has been shown to be safe in intubated and nonintubated infants.[226] This therapy consists of 6 g/100 mL administered over 2 hours three times each day. Ribavirin has both in vitro and in vivo activity against HPIV. Furthermore, anecdotal reports show decreased HPIV shedding and clinical improvement when infected immunocompromised patients have been treated with ribavirin.

A recent report suggested that ribavirin may be useful in treating RSV, influenza B, and HPIV pneumonia in adult BMT patients.[227] Ribavirin should be considered in these types of situations until better drugs become available or controlled trials are completed. Ribavirin has some activity against adenoviruses, rhinoviruses, and coronaviruses in vitro, but it has not been tested clinically.[228]

Ganciclovir. Ganciclovir seems to have some inhibitory effect on adenovirus, both in vitro and in vivo, but it has not been studied systematically.[229]

Amantadine/Rimantadine. Amantadine has been approved in the United States for over 30 years for the treatment of influenza A. A recent review describes amantadine and rimantadine in great detail.[230] Both of these drugs cause a significant improvement in clinical signs and symptoms and decreased viral shedding. Treatment with amantadine currently is recommended for children with severe LRI or those at risk to develop serious LRI when infected with influenza A. This latter group includes immunocompromised children and those with serious medical conditions (Table 4). Therapy should be started as soon as possible, preferably within 24 hours.

Although numerous exciting new antiviral agents are being developed, most of them are still years away from being available clinically. However, two agents may be close to being marketed in the United States. The first is zanamivir (GG167), which is a potent and highly specific neuraminidase inhibitor for both influenza A and influenza B. This drug is currently in phase II and III clinical trials and has shown a decrease of one to two days in the length of time symptoms persist, with no significant toxicity.[231,232] Another agent, MEDI-493 (RSV monoclonal antibody), has just been shown in a phase III clinical trial to reduce RSV hospitalizations by 55 percent.[233] This agent has the advantage that it can be administered intramuscularly and can be used for outpatients.

The only vaccines currently available in the United States are for influenza A, influenza B, and adenovirus. Live oral enteric-coated adenovirus vaccine against types 4 and 7 has been used extensively in the military (greater than 10,000,000 doses). This vaccine is effective in preventing epidemics of acute respiratory disease. Live oral vaccines for strains of adenovirus causing LRI in children (types 1, 2, and 5) were tested 20 years ago and found to be effective in stimulating good immunologic responses in seronegative adults,[234] but they have not been

studied in clinical trials. Problems facing the development of any live adenovirus vaccine for use in children include formulation problems (to maintain protection from the acid environment of the stomach) and the inclusion of the majority of serotypes infecting children. No vaccine is nearing clinical application at this time, but effort is warranted to protect children from LRI caused by this agent, especially among the growing population of immunocompromised children.

Influenzae A and B vaccines are widely available, safe, and effective. The current vaccines usually contain two type A strains and one type B, with inactivated whole virus preparations administered to children older than 12 years and "split" vaccine (where the membrane antigens are separated from the core) being administered to younger children. All of the children listed in Table 4 *should* receive the current vaccine starting at about 6 months of age; the vaccine includes two doses during the first year that vaccine is administered if the child is younger than 9 years of age (see Redbook). Any child over 6 months of age *may* receive the current influenza vaccine (those with allergies to chickens or eggs should be skin tested first). However, the intramuscular route of vaccination has been an impediment to universal vaccination of young children. Live cold-adapted intranasal influenza vaccines have proven to be safe and immunogenic in infants less than 6 months old and also protective in children and adults.[235] These vaccines currently are being tested for efficacy and could lead to universal infant immunization with the additional benefit of decreased disease in adolescents and adults.

Future Vaccines

RSV. Currently, the major immunization strategies for RSV involve live cold-adapted (CA) or chemically mutated strains, subunit vaccines, and recombinant vectors. The major protective immunogens on the surface glycoproteins of RSV have been incorporated into vaccinia and adenovirus expression vectors.[236] Studies in cotton rats and some species of primates have shown good immunologic responses and protection from LRI (viral shedding),[237,238] whereas results in other species of primates have been less promising.[239] Further evaluation of this approach will have to include the use of suitable vectors for children and efforts to increase immunogenicity. Subunit vaccines containing purified RSV surface proteins have progressed to clinical trials in children.[240] Vaccines tested in humans and/or animals have contained mostly G, mostly F, and a recombinant chimeric protein F/G.[240-244] So far, studies have shown poor immunogenicity in seronegative humans or chimpanzees, low-neutralization antibody titers, suppression of immune response in the presence of maternal antibody, and concern over disease potentiation as seen with formalin-inactivated vaccine. These problems render this approach unlikely to produce a safe and efficacious vaccine in the near future.

Live CA strains of RSV A and B currently are being studied and seem to be promising as vaccine candidates. These new vaccine strains differ from previous vaccine strains by containing multiple mutations (3 or more); they have been shown to retain stability against reversion to wild type after replication in rodents and primates.[236,245,246] Human trials are in progress.

HPIV. CA strains of HPIVs-1, -2, and -3 have been developed and are at different levels of testing. Most work has been on HPIV-3, for which clinical trials are in progress. CA HPIV-3 vaccines have shown immunogenicity and attenuation in younger infants, but symptoms still developed.[247] Additional clinical and molecular studies are in progress on CA HPIV-3 strains with greater attenuation.[248] A Jennerian approach using bovine PIV-3 failed to produce significant immune responses in adult volunteers or seropositive children.[249] However, initial results in a small number of seronegative infants and children indicate that BPIV-3 is safe, immunogenic, and phenotypically stable.[250] Further studies are planned using this vaccine. Subunit vaccines containing envelope glycoproteins and virus vectors expressing these same proteins have been immunogenic in animals,[251-256] but clinical trials have not been reported.

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