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## CHAPTER 10

### RESPIRATORY VIRUSES

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#### Introduction

Acute respiratory disease, including the common cold, influenza-like illness, croup, bronchiolitis, and viral pneumonia, can be caused by a wide variety of viral and non-viral agents. Among the viruses, those with RNA genomes tend to play a more prominent role, particularly among immunologically intact individuals. DNA viruses are also associated with respiratory disease, these agents are described elsewhere in this text. The characteristics of the viruses most often associated with respiratory disease are described briefly below.

## Descriptions of Viruses

### *Influenza Virus*

Three distinct types of influenza viruses are recognized, influenza A virus, influenza B virus, and influenza C virus, based on antigenic differences in the nucleoprotein and matrix proteins. All three viruses share certain characteristics including the presence of a viral envelope containing glycoproteins important for viral entry and egress from cells, and a segmented genome. The standard nomenclature for influenza viruses includes the influenza type, place of initial isolation, strain designation, and year of isolation.

The hemagglutinin (HA) of influenza virus mediates attachment of virus to susceptible cells and fusion of the viral envelope with the cell membrane. Antibody to the HA neutralizes viral infectivity and is the main protective mechanism induced by infection or immunization. The neuraminidase (NA) is also an envelope glycoprotein and plays an important role in release of virus from cells. Antibody to the NA also inhibits viral replication, and the NA is an important target for antiviral therapy. A third membrane protein, the M2, is present in small quantities on virions, and is inhibited by amantadine and rimantadine. Finally, viral structural proteins such as the matrix (M) and nucleoprotein (NP) are important targets for cytotoxic T lymphocytes (CTL).

### *Parainfluenza Virus*

Parainfluenza viruses are also enveloped viruses, but with a linear single-stranded RNA genome. Four distinct human serotypes are recognized, termed types 1, 2, 3, and 4. Viral envelope glycoproteins include HN, which serves as both the viral hemagglutinin and neuraminidase, and F, which mediates fusion of the viral envelope with the cell membrane. Antibody to either HN or F neutralize infectivity, but only antibody to F prevents cell to cell fusion. Antibody to both the HN and F proteins play a role in resistance to infection. Passive transfer of monospecific antisera to either F or HN can protect animals, and vaccinia viruses expressing either F or HN induce protective immunity in experimental animals.

### *Respiratory Syncytial Virus*

Another enveloped, single-stranded RNA virus of importance to the respiratory tract is respiratory syncytial (RS) virus. The RS genome encodes 10 distinct proteins, including the envelope glycoproteins F and G. The G or attachment protein mediates binding of the virus to the host cell, while the F or fusion protein allows entry of the virus into the cell and promotes cell to cell spread. Only the F and G viral surface glycoproteins appear to play a role in the induction of neutralizing antibody. Monoclonal antibodies to both the F and G protein neutralize infectivity *in vitro*, but while the majority of monoclonal antibodies to F neutralize virus, only a small proportion of G monoclonal antibodies do so. Two antigenic subgroups of RS virus, denoted A and B, have been recognized primarily due to differences in the G glycoprotein between subgroup A and B. Both subgroups circulate in the population, with some indication of a general

predominance of one or the other in alternate years. It has been suggested that infections with subgroup A viruses may be somewhat more severe, with a greater frequency of hospitalizations with RS virus in years in which subgroup A viruses predominate compared to subgroup B.

### *Rhinovirus*

Rhinoviruses are members of the picornavirus family of viruses, non-enveloped viruses with a linear, single stranded genome of positive polarity. Rhinoviruses are differentiated from the related enteroviruses by their relative acid lability and thermal stability. In addition, rhinoviruses replicate most efficiently in cell culture at lower than body temperature. Humans are the only known natural host. To date, over 100 distinct neutralization serotypes of rhinovirus have been identified. This antigenic diversity is the result of amino acid sequence variation in four recognized antigenic sites, which surround the receptor binding site. The majority of human rhinoviruses utilize intracellular adhesion molecule-1 (ICAM-1) as the receptor. This "major binding group" accounts for 91 of 102 known rhinovirus serotypes. Rhinovirus serotypes which do not bind to ICAM-1 are referred to as the minor receptor group viruses.

### Illnesses

Acute respiratory infections are one of the commonest problems prompting medical consultation. Data from the United States, collected in the 1992 National Health Interview Survey, suggest that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year, and account for 54% of all acute conditions exclusive of injuries. In the national morbidity survey in England and Wales conducted in general practice in 1991/92, acute respiratory infections accounted for 14% of all consultations and approximately 25% of the entire population consulted at least once in the survey year because of acute respiratory infection: in pre-school children these figures were 28% and 60% respectively. From a clinical perspective, the distinction between upper and lower respiratory illness is particularly important because the potential for complications is higher and more serious in lower respiratory disease. Nevertheless, some complications of upper respiratory illness can be serious, for example, acute sinusitis. Damage to the cells lining the lower respiratory tract results in impairment of the oxygenation of the blood and thus persons with pre-existing respiratory or cardiac disease are at particular risk from such infections.

In the assessment of patients presenting to doctors with respiratory infections, cough is a critical symptom. While a minimal cough associated with post nasal drip can be accepted as part of an upper respiratory illness, any significant degree of coughing is indicative of illness at the level of the larynx or major airways. Fever, respiratory rate and pulse are useful markers of the severity of illness, although an absence of fever in an older person does not exclude serious respiratory illness. In older persons, lower respiratory infection can prompt disturbances in cardiac rhythm (particularly atrial fibrillation) and drive patients into heart failure.

The diagnostic terminology applied to respiratory viral infections is largely syndrome driven, reflecting the pattern of symptoms and signs observed. These terms are then often used to determine treatment. However, it is important first to consider the likely causes. There is a poor match between the diagnostic terms in common use and the etiological agent, although for some syndromes there is a stronger link (for example, between croup and parainfluenza virus). For most, the link is more tenuous and disease management must take into account the likely specific etiology. The association between clinical syndromes and viruses is described in the following paragraphs.

### *Common Cold*

There is really no single definition of the syndrome of the common cold, but generally this term is taken to mean an acute illness with rhinitis and variable degrees of pharyngitis. Predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but true fever is unusual. The presence of lower respiratory tract signs and symptoms indicate the possibility of some complication. Headache and mild malaise may be reported. Although a multitude of viruses may be associated with this syndrome, the pattern of symptoms associated with colds does not appear to vary significantly between agents. Physical findings are non-specific and most commonly include nasal discharge and pharyngeal inflammation. More severe disease, with higher fever, may be seen in children. Colds are generally self-limited, with a total duration of illness of approximately 7-14 days in adults. Recognized complications of colds include secondary bacterial infections of the paranasal sinuses and middle ear, and exacerbations of asthma, chronic bronchitis, and emphysema.

The differential diagnosis of individuals presenting with typical signs and symptoms is not extensive. However, in the presence of additional signs or symptoms which are not part of this clinical description, such as high, persistent fever, signs of respiratory distress, or lower respiratory tract disease, alternative diagnoses should be sought. Allergic causes should be considered in individuals who present with recurrent symptoms restricted to the upper respiratory tract.

The evaluation of patients who present predominantly with pharyngitis centers upon the differentiation of bacterial from viral or other non-bacterial etiologies. The presence of nasal symptoms or of conjunctivitis favors a viral etiology, as does pharyngitis in children less than 3 years of age. The presence of exudate is suggestive of bacterial etiology, but exudates may also be seen with adenovirus or infectious mononucleosis. The presence of tender, palpable cervical lymph nodes is also indicative of a bacterial cause. A rapid test for group A streptococci may be indicated in cases of significant illness where the etiology is uncertain, but routine studies for other bacterial and non bacterial pathogens are usually not obtained.

### *Otitis Media*

Otitis media is commonly thought of as a complication of upper respiratory tract infections, though many children present with a combination of upper respiratory symptoms with concurrent earache at the outset. Infection of the upper respiratory tract

is associated with mucosal edema which interferes with the normal function of the Eustachian tube. Pressure in the middle ear increases and gives rise to pain. This can be relieved by tympanic paracentesis though this procedure is rarely adopted since most such illnesses resolve spontaneously with or without rupture of the tympanic membrane. There has been much debate about the usefulness of antibiotics in the treatment of acute otitis media. The critical factor is whether any secondary bacterial infection is established or not. Any virus causing acute respiratory infection predisposes to otitis media, and many viruses can be recovered from middle ear fluid.

### *Croup*

Croup is a clinically distinct illness affecting children under the age of three. The illness typically begins with upper respiratory tract symptoms of rhinorrhea and sore throat, often with a mild cough. After two or three days, the cough deepens and develops a characteristic brassy, barking quality, which is similar to a seal's bark. Fever is usually present, generally between 38° and 40°C. The child may appear apprehensive, and most comfortable sitting forward in bed. The respiratory rate is elevated, but in contrast to bronchiolitis is usually not over 50 breaths per minute.

The characteristic physical finding of croup is inspiratory stridor. Inspiration is prolonged and chest wall retractions may be observed. Children with this finding on presentation have a higher risk of hospitalization or of requiring ventilatory support. Rales, rhonchi, and wheezing may be heard on physical examination. These signs, including the barking cough and inspiratory stridor, arise mostly from inflammation occurring in the larynx and trachea, which is greatest at the subglottic level, the least distensible part of the airway. It is important to recognize inflammatory changes are noted throughout the respiratory tract in croup and hypoxemia is detected in about 80% of children hospitalized with this illness. A fluctuating course is typical for viral croup, and the child may appear to worsen or improve within an hour.

Overall, viruses can be recovered from croup cases more frequently than from other types of respiratory illnesses. The parainfluenza viruses, particularly types 1 and 2, are the most common viruses responsible for croup, accounting for about 75% of cases. Other viral causes of croup include respiratory syncytial virus, influenza A or B viruses, rhinoviruses, and adenoviruses. Although no longer endemic in the United States, measles has long been recognized as a cause of severe croup. Parainfluenza virus type 2, and influenza A viruses are associated with more severe disease, but generally the clinical presentation of the croup syndrome due to individual agents is similar.

It is important when evaluating children with stridor to distinguish the croup syndrome from other, potentially more serious causes of airway obstruction such as bacterial epiglottitis and tracheitis. Epiglottitis is an acute cellulitis of the epiglottis and surrounding structures. Patients present with acute respiratory distress and drooling, but the barking cough of croup is absent. Bacterial tracheitis is a relatively rare syndrome that mimics croup, but abundant purulent sputum is often present. Other infectious causes of stridor include peritonsillar or retropharyngeal abscess and diphtheria. Non-infectious causes of stridor such as trauma or aspiration of a foreign body, should also be considered.

### *Acute Bronchitis*

Acute bronchitis is characterized by cough often with expectoration of sputum and accompanied by wheeze and rales on auscultation. The distinction from asthma can be difficult, though the link with a recent cold or other respiratory symptoms in a person not subject to recurring asthma provides the basis for diagnosis. Persons with chronic obstructive pulmonary disease experience exacerbations of their illness which may be precipitated by virus infections, but may often be complicated by secondary bacterial infection.

Acute bronchitis affects persons of all ages though its effects are greater in young children and elderly persons. It is predominantly a winter illness and incidence increase when respiratory viruses such as RSV and influenza are circulating in the community. The early stages of the illness may primarily relate to the upper respiratory tract but the development and persistence of cough three or four days later is often the reason that prompts consultation. It is not particularly linked to any specific virus but there has only been limited research into the causes of such respiratory exacerbations.

### *Bronchiolitis*

Bronchiolitis is a form of acute bronchitis particularly experienced by young children in which the main focus of the infection is in the small peripheral airways. The syndrome is characterized by wheezing and other symptoms due to obstruction to expiratory air flow. The onset of lower respiratory symptoms is usually preceded by rhinitis, often with nasal congestion and discharge, with more severe symptoms characteristically occurring 2-3 days later. Cough may not be prominent initially but when present may be paroxysmal in nature. The presence or absence of cyanosis is not a reliable indicator of the degree of oxygenation. Physical findings are generally confined to musical or moist rales. Fever is frequently present at the beginning of the illness, but one-third or more of hospitalized infants are afebrile. The hospital course is variable, but most infants will show improvement in 3 to 4 days.

The peak age incidence of bronchiolitis is between two and 6 months of age, with over 80% of cases occurring in the first year of life. The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition, infants born prematurely, and those who are less than 6 weeks of age at the time of presentation are also at risk.

Respiratory syncytial virus causes the majority of cases of bronchiolitis, and during the RS virus epidemic season, generally between November to February in the Northern hemisphere, essentially all cases are due to this virus. Overall, RS virus is recovered from about three-fourths of all infants admitted to the hospital with bronchiolitis. Several other respiratory viruses are associated with bronchiolitis, including rhinoviruses, parainfluenza viruses, influenza virus and mumps. Adenoviruses types 3, 7, and 21 are relatively uncommon causes, but may be associated with more severe disease, including the development of a more chronic form of bronchiolitis referred to as bronchiolitis obliterans. The differential diagnosis of diseases characterized by expiratory airflow obstruction in infants is relatively small. Pertussis can occasionally be confused with

bronchiolitis, however, more frequent vomiting and more paroxysmal cough would be clues to the diagnosis. Differentiation of acute infectious bronchiolitis from the initial presentation of allergic asthma is difficult, and contributes to the difficulty in assessing therapeutic interventions in this disease. Anatomic defects such as vascular rings can cause obstruction of the airway. Foreign bodies should be considered strongly especially in young infants. Gastroesophageal reflux is an additional consideration.

### *Influenza-like Illness*

The onset of influenza is typically abrupt, and the illness is characterized by the predominance of systemic symptoms, including fever, prostration, myalgias, and malaise. Non-productive cough tends to predominate late in the illness. Other respiratory symptoms may be relatively minimal, particularly early in the course, and include nasal complaints, sore throat, and hoarseness. The presence of fever and cough on presentation are significantly associated with a higher likelihood of isolation of influenza virus from nasopharyngeal secretions. Because of the involvement of tracheal epithelium in infection, complaints of burning throat and substernal pain may be seen. Other than fever, there are usually few findings on physical exam. Individuals with influenza may exhibit rhinitis, pharyngitis, conjunctival injection, and tracheal tenderness. The chest is usually clear in uncomplicated cases. Most acute symptoms resolve in 3-5 days, but complete recovery may take weeks, with malaise and easy fatigability being among the most prolonged symptoms. The clinical features of influenza A and B virus infection are similar. It has been estimated that in the course of an intense influenza epidemic, 70% to 80% of healthy adults who present with the above symptoms will have laboratory evidence of influenza virus infection.

Influenza is also an important cause of acute febrile illness in children during epidemics. Generally symptoms of influenza are similar to those in adults, although children may have higher fever with febrile seizures. In addition, some complaints, such as myalgias, may be less common in children because of their inability to communicate such symptoms. However, parents may note lack of activity or lethargy. Influenza is associated with otitis media, and influenza virus can be isolated from middle ear fluid in affected children.

The impact of influenza on elderly populations is well recognized, and this age group contributes disproportionately to hospitalizations and deaths during influenza epidemics. However, the clinical presentation of influenza in the elderly may be somewhat blunted, with relatively lower fever and a more subtle onset of symptoms. Particularly in elderly individuals who are not very verbal, the only signs of influenza may be low grade fever and lethargy.

Other acute respiratory viral illnesses may present initially with an influenza-like picture, including infections of adults with parainfluenza and respiratory syncytial viruses. In addition to influenza virus, acute infection with respiratory syncytial virus may completely mimic the clinical picture of influenza in this age group. The initial stages of many bacterial infections may resemble influenza, so that the clinician must be aware that individuals initially diagnosed as having acute influenza may have bacterial illnesses such as meningitis.



### *Viral Pneumonia*

Overall, pneumonia represents one end of a spectrum of viral infections of the lower respiratory tract which includes croup, bronchiolitis, tracheobronchitis, and reactive airways changes. The development of pneumonia is defined by the development of abnormalities of alveolar gas exchange accompanied by inflammation of the lung parenchyma, often associated with visible changes on chest xray or abnormalities of other radiologic studies such as gallium scanning. Although there can be considerable variety to the presentation of this syndrome depending on the age and immunologic competence of the host and the specific viral pathogen, there are certain general features.

The clinical features of primary viral pneumonia in adults include cough which is generally non-productive, although production of frothy, pink-tinged sputum is seen in some severely ill individuals. Cyanosis and hypoxemia are typical of severe primary viral pneumonia. Physical findings are often non-specific, and variety of chest xray patterns have been described, including lobar infiltrates, but most typically primary viral pneumonia presents with diffuse, bilateral interstitial infiltrates. The clinical course of primary influenza virus pneumonia is often progressively downhill, and most patients died in the era prior to the availability of mechanical ventilation, but mortality in healthy adults in the non-pandemic era is low.

The basic presentation of viral pneumonia in children is similar, if somewhat milder. The clinical presentation varies considerably with the specific causative agent, but typically includes fever and lower respiratory tract signs and symptoms, such as difficulty breathing, non-productive cough, and physical findings of wheezing or increased breath sounds. Young infants may present with apneic episodes with minimal fever. The clinical presentation may be dominated by the associated croup or bronchiolitis, which are frequently present.

The majority of cases of viral pneumonia in healthy adults are due to or associated with influenza viruses. In addition, adenoviruses have been described as causes of significant outbreaks of atypical pneumonia in military recruits. Other viral cause of pneumonia in otherwise healthy adults include varicella, RSV, and parainfluenza virus. In certain geographic regions clinicians may encounter the hantavirus pulmonary syndrome (HPS) characterized by severe pulmonary dysfunction after a 2 to 3 day prodrome of non-specific influenza-like symptoms, accompanied by increased hematocrit due to hemoconcentration, and thrombocytopenia with coagulopathy.

In children, respiratory syncytial virus has been associated with the largest proportion of viral pneumonia in young children, particularly if accompanied by bronchiolitis. Parainfluenza viruses, particularly type 3, are the second most common viral cause followed by influenza A and B viruses, especially during periods of epidemic prevalence. Other viral etiologies in children include adenoviruses, measles, and more rarely, rhinoviruses, enteroviruses, rubella virus, and herpes simplex virus.

Bacterial superinfection is a common complication of viral lower respiratory tract infection, particularly in adults. The classic history is that of a typical episode of viral illness with more or less complete recovery, followed 2 to 14 days later by a recurrence of fever and development of cough and dyspnea. CXR reveals lobar infiltrates, and the clinical course is typical of bacterial pneumonia. In addition, combined bacterial

and viral pneumonia, with clinical features of each, are common in adults and with certain viruses in children. Bacterial superinfection of viral pneumonia can occur with many bacteria, but the most common bacteria responsible for bacterial pneumonia complicating influenza is *Streptococcus pneumoniae*. There are also increases in the relative frequency of Staphylococci and *Hemophilus influenzae*. Differentiation between viral and bacterial forms of pneumonia in children on clinical grounds can be difficult, and radiologic criteria do not always distinguish these entities well. However, in normal infants and children with RS or parainfluenza virus pneumonia, bacteria do not appear to play an important role, and routine addition of antibacterial agents is not useful. The exception to this observation is in developing countries, where mixed viral and bacterial pneumonias in children are frequent and severe.

Individuals with diminished host immunity may develop severe, life-threatening pulmonary infections with the entire spectrum of RNA and DNA viruses, including both viruses that are typical causes of lower respiratory tract disease in normal hosts, and other, more opportunistic viral pathogens. DNA viruses, including cytomegalovirus (CMV), herpes simplex viruses (HSV), varicella zoster virus (VZV) and adenoviruses have received the most recognition in this regard. Antiviral agents for these pathogens are described elsewhere in this book.

RNA viruses have also received increasing recognition as potential causes of significant morbidity and mortality in the immune compromised. RS virus has been well recognized as a cause of pneumonia in recipients of bone marrow and solid organ transplantation. In the typical presentation, an initial upper respiratory infection becomes relentlessly progressive, with involvement of the lower respiratory tract, significant hypoxia, and oftentimes death. Clinical features have been non-specific, but mortality of over 50% has been reported despite treatment with aerosolized ribavirin. Parainfluenza viruses (PIV) have also been reported as an infrequent lower respiratory tract pathogen in both solid organ and bone marrow transplantation. PIV-3 has been most frequently seen, but all four serotypes have been implicated. Influenza may also cause severe disease in transplant recipients, but most subjects have survived.

### Laboratory Diagnosis

Generally, the gold standard for specific etiologic identification has been isolation in cell culture. Most of the viruses responsible for respiratory disease can be readily detected in such cell culture systems, provided appropriate care is exercised in the collection and transportation of the specimens. The specific types of cells used depends on the spectrum of viruses being sought, and will vary both with the specific clinical situation and the season during which the cultures are obtained. For example, a laboratory might routinely inoculate respiratory cultures into Hep-2, RhMK, and MRC-5 cells year round, and add LLC-MK2 cells for isolation of parainfluenza viruses for cultures obtained during the spring and fall, while adding MDCK cells to facilitate isolation of influenza viruses during the winter months.

Viral culture is highly sensitive and specific, and also has the advantage that after isolation the virus is available for further characterization. However, under the best of circum-

stances, the results of such tests are not available during the time when decisions regarding management and therapy of an individual case must be made. Thus, there has been considerable interest in the development of rapid tests for respiratory viral diagnosis.

The most widely used tests are based on immunologic detection of viral antigen in respiratory secretions. For influenza, such tests include the Directigen Flu A (Becton-Dickenson), Flu OIA (Biostar), and QuickVue Influenza A/B test (Quidel Corporation). In addition, the Zstat Flu (ZymeTx) test detects the presence of the viral neuraminidase enzymatically. With the exception of the Directigen test, all of the tests are designed to detect both influenza A and B, and a modification of the Directigen test to allow detection of both types is in clinical development.

The reported sensitivities of each test in relationship to cell culture has varied between 70% and 100% and is somewhat dependent on the nature of the samples tested and the patients from whom they were derived. There is no published comparative data currently available that conclusively demonstrates superiority of one of the tests over another, thus decisions regarding a specific test are generally made on the basis of convenience, cost, and the familiarity of the operator with the specific technique.

Direct antigen detection in respiratory secretions has also been used extensively for rapid diagnosis of respiratory syncytial virus. Direct or indirect immunofluorescent techniques have been used for many years. This technique has an advantage in that microscopic examination of the sample for exfoliated nasopharyngeal cells allows a rapid judgment as to the quality of the sample. However, the techniques are labor intensive and require specialized equipment and highly experienced staff to be performed accurately. For this reason, many laboratories now use ELISA based technologies for rapid detection. Several test kits are currently available with reported sensitivities of 80% to 95% compared to culture. Antigen detection tests for parainfluenza virus or rhinoviruses are not currently commercially available.

A variety of approaches to direct detection of viral nucleic acids in clinical specimens have also been explored for rapid diagnosis, including nucleic acid hybridization and polymerase chain reaction amplification (PCR). PCR in particular has the advantage of potentially being more sensitive than cell culture, and possibly detecting virus in samples in which the virions have lost viability. In addition, it is possible to devise multiplex techniques such that a single test can detect a number of different agents. However, PCR techniques are more labor intensive and technically demanding, and also require the availability of specialized laboratory equipment. Thus, they have generally not supplanted antigen detection for rapid diagnosis.

## **Treatment Algorithms**

### **Influenza**

#### *Amantadine and Rimantadine*

The antiviral drugs amantadine and rimantadine belong to the class of M2 inhibitors, and their antiviral effect is primarily manifested in cell culture as inhibition of virus

uncoating. Although influenza B viruses use a similar replication strategy, a different protein, the NB protein, appears to serve the role of ion channel for this virus. Therefore, M2 inhibitors are active only against influenza A viruses.

The antiviral activities of the two members of the class, amantadine and rimantadine, are similar. Both drugs are active against all strains of influenza A virus in a variety of cell culture systems and animal models [1]. In cell culture, inhibitory levels for influenza A virus range from 0.2-0.4 ug/mL for amantadine, and from 0.1-0.4 ug/mL for rimantadine [2], most strains are inhibited at concentrations of 0.1 ug/mL or less.

Several studies to evaluate the effectiveness of amantadine in the treatment of H3N2 influenza A viruses were initiated during the 1968 pandemic. In these studies, therapy within the first 48 hours of illness was associated with decreases in the duration of fever by about 24 hours, and a greater proportion of subjects considered to be "rapid resolvers" [3, 4]. In addition, treated individuals had more rapid decreases in individual symptoms of cough, sore throat, and nasal obstruction [5]. The effect of treatment on recovery of virus from the nasopharynx was minimal in these studies. In an additional study conducted in non-institutionalized adults and children infected with the A/Hong Kong/68 virus, treated subjects had an approximately 24 hour reduction in the duration of fever, but no change in other symptoms [6]. Treatment with amantadine has resulted in significantly more rapid improvement in small airways dysfunction in healthy adults with uncomplicated H3N2 influenza [7, 8].

Additional trials of amantadine therapy were performed when H1N1 viruses reappeared in the late 1970's, with similar results. Early therapy of influenza A/USSR/77 in otherwise healthy adults with amantadine was shown to result a more rapid decrease in fever, and in a higher frequency of subjects reporting improved symptoms at 48 hours compared to placebo [9]. In addition, treated subjects were less likely to shed virus at 48 hours. In a second study conducted in young adults infected with A/Brazil/78, amantadine therapy was associated with a more rapid decrease in symptoms compared to aspirin therapy [10]. Amantadine treated subjects also had decreased virus shedding in this study.

Studies of the therapy of acute influenza in adults with rimantadine have shown levels of benefit essentially identical to those seen with amantadine. Treatment of adults with H1N1 [9] and H3N2 [11] influenza A resulted in improved symptoms, decreased fever, and reduced virus shedding compared to placebo. When rimantadine and amantadine were directly compared in a randomized trial of early therapy [9], the efficacy of the two drugs was essentially identical.

Rimantadine has also been evaluated in the treatment of influenza A in children, and shown to reduce the level of virus shedding early in infection when compared to acetaminophen [12, 13]. More variable effects on clinical symptom scores have been seen, with one study showing a slight decrease in scores and fever compared to acetaminophen [12], and the other, in which illness was relatively mild, showing no significant difference [13]. In both studies, virus shedding was relatively prolonged in those receiving rimantadine, and resistant virus was shed late in the course of illness.

Neither amantadine or rimantadine has been subjected to extensive efficacy evaluation in high-risk subjects. One placebo-controlled study carried out in nursing home residents showed more rapid reduction in fever and in symptoms in rimantadine recipients.

Furthermore, physicians who were caring for these patients, but who were blinded to study drug status, prescribed significantly fewer antipyretics, antitussives, and antibiotics and obtained fewer chest x-rays for the rimantadine recipients [14].

Antiviral drug resistance has been one factor which has limited the more widespread use of these agents. Amantadine and rimantadine resistant viruses emerge fairly frequently in treated individuals [15, 16], although resistance is infrequent in unexposed individuals [17]. Resistant virus retain full pathogenic potential in experimental animals and can cause disease in susceptible contacts [15, 16, 18].

### *Neuraminidase Inhibitors*

The influenza virus neuraminidase is a membrane protein whose major function is to remove terminal sialic acid residues from viral receptors on the host cell, thereby releasing virus to spread to other cells. Two neuraminidase inhibitors, zanamivir and oseltamivir, have been licensed for therapy of acute influenza. Both agents are broadly active against all 9 of the known neuraminidase subtypes of influenza A virus as well as against influenza B viruses. Inhibitory levels against most clinical isolates range from 2 to 20 nmol/L in cell culture [19]. The two agents are similar in many respects, but differ in that zanamivir is administered by inhalation (see below), while oseltamivir is administered orally.

Inhaled zanamivir was initially demonstrated to be effective for the treatment of uncomplicated influenza in otherwise healthy adults [20]. In an initial study conducted in Europe and North America, treatment of individuals with laboratory evidence of influenza virus infection within 48 hours of symptom onset was associated with a 0.9-day reduction in the duration of illness, from 6.3 days in the placebo group to 5.4 days in the inhaled zanamivir group. More striking differences were seen when the analysis was restricted to individuals with fever ( $T \geq 37.8^{\circ}\text{F}$ ) on enrollment, or those enrolled within 30 hours of onset of symptoms, in whom the difference between treated and placebo groups was approximately 2 days. Treatment within 30 hours of symptom onset was also associated with a significantly more rapid return to normal activities, by approximately 1.5 days. In this study, there was no difference in the level of clinical efficacy between subjects infected with influenza A and influenza B viruses [20].

In a second study conducted in the Southern Hemisphere, treatment of individuals aged 12 and older within 36 hours of symptom onset was associated with a 1.5-day difference in the duration of illness among these infected subjects, from 6 days in the placebo group to 4.5 days in the treated group [21]. Similar to the earlier study, there was no significant difference in the effect on influenza A and B virus, and treatment was associated with an earlier return to work or normal activities. Zanamivir was also of benefit in the small number of subjects enrolled in the study who were considered to be at relatively higher risk for influenza-related complications, and the rate of respiratory complications among such subjects was reduced from 46% in the placebo group to 14% in the treated group. Recently, a third study of zanamivir therapy conducted in Europe showed a 2.5-day reduction in duration, from 7.5 days in placebo recipients to 5 days in zanamivir recipients [22].

To date, results from two trials of oral oseltamivir therapy of acute influenza have been published. In the first trial, treatment of adults 18 and older within 36 hours of symptom onset resulted in a 30% decrease in the duration of illness (from 4.7 days to 2.5 days) and a 40% decrease in the severity of illness [23]. In addition, early therapy was associated with a significantly earlier return to work or other normal activities, and with reductions in the rate of complications, primarily sinusitis and bronchitis. The overall rate of any complication in the placebo group was 17%, this was reduced to 8% in those receiving oseltamivir [23]. The majority of cases of influenza in this study were due to influenza A (H3N2) viruses. Similar results were reported from a treatment study performed concurrently in Canada and Northern Europe [24]. In that study, early therapy was associated with a 25% reduction in the duration of illness among infected subjects, and a 37% reduction in duration among those treated within 24 hours.

Studies of neuraminidase inhibitor therapy in other populations have been reported in abstract form. Early treatment with inhaled zanamivir is associated with reductions in the duration of illness in elderly and high-risk subjects [25], slight reductions in the frequency with which patients require additional prescriptions or health care contacts [26], and an approximately 28% reduction in the rate of complications [27]. Use of oseltamivir in this same type of patient was also reported to result in reductions in the duration of illness and fever, and reductions in the rate of complications [28]. When used for treatment of otherwise healthy children aged 5-12 years, zanamivir reduced the duration of illness by 1.25 days, and showed benefits in the severity of illness and use of ancillary medications [19]. More recently, administration of a liquid formulation of oseltamivir at a dose of 2 mg/kg b.i.d. resulted in a 38% reduction in the median duration of illness in children aged 1 to 10. Oseltamivir also resulted in a 40% reduction in the frequency of complications, primarily otitis media, for which antibiotics were prescribed [29].

Because the neuraminidase inhibitors interact with highly conserved residues within the influenza virus neuraminidase, it has been hypothesized that antiviral resistance will be a relatively limited problem. Viruses resistant to the *in vitro* antiviral activity of these agents have been isolated after passage in cell culture [19]. Analysis of these viruses has revealed two basic mechanisms of resistance, and illustrate the interactive roles of the viral HA and NA in binding to and release from infected cells. Mutations within the catalytic framework of the NA which abolish binding of the drugs have been described. Resistance mutations in the NA may be associated with altered characteristics of the enzyme with significantly reduced activity. A second type of mutation associated with cell culture resistant viruses involve mutations in the receptor binding region of the hemagglutinin. HA mutations associated with resistance to neuraminidase inhibitors reduce the affinity of the HA for its receptor, allowing cell to cell spread of virus in the absence of NA activity. Resistant viruses with HA mutations exhibit cross resistance to these drugs in cell culture, but may retain susceptibility in animal models. Many of these viruses also exhibit reduced virulence in animals. However, resistant viruses have been rarely isolated from humans treated with neuraminidase inhibitors in clinical trials to date [30]. The most well characterized resistant virus reported so far was recovered from an immunosuppressed child receiving Zanamivir [31]. Preliminary results from clinical trials in immunologically intact individuals suggest that resistant viruses arise very infrequently during treatment.

*Strategies For Treatment*

Antiviral therapy of influenza can be considered in any adult who seeks treatment within the first 48 hours of onset of illness. There is clinical experience with the use of M2 inhibitors, and very extensive data from randomized, controlled trials of neuraminidase inhibitors, that leave little doubt that both classes of drugs are effective for this indication, with the exception that only the neuraminidase inhibitors have activity against influenza B virus. To summarize the data presented earlier, the benefits that can be expected include an approximately 1 to 2 day reduction in the duration of symptoms, a return to work or usual activities about 1 day sooner, and possibly, a reduction in rates of complications. The decision about whether to treat any individual patient involves balancing the impact of these benefits on the individual against the cost of therapy, since for the most part, the drugs are without significant risk.

The effectiveness of treatment initiated beyond the 48 hours window after onset of symptoms has not been determined, but is likely to be very low in healthy adults, in whom influenza is generally self-limited. This poses a significant hurdle to the effective use of antiviral therapy for influenza, in that patients must correctly identify their illness, seek medical attention, interact with the medical system and achieve some form of diagnosis, and be prescribed and obtain drug within a very short time frame. For physicians, the issue may balance on the level of comfort in making a clinical diagnosis of influenza, since it may not be practical to confirm each case microbiologically, at the current state of technology. Certainly the evidence from randomized trials of neuraminidase inhibitors suggest that with appropriate epidemiologic support, a clinical diagnosis of influenza can be made with some confidence, since in these trials subjects who met a clinical case definition had a 60-70% rate of microbiologically documented influenza. Individual physician practices therefore will need to adapt the strategies that best suit their patient populations.

Less published information is available regarding therapy of high-risk individuals. There are essentially no studies supporting the utility of amantadine or rimantadine in the elderly or in individuals with cardiac or pulmonary conditions, although with appropriate dosage reductions the drugs can be used safely. Studies of therapy with neuraminidase inhibitors have been conducted in much larger populations, and have included high-risk subjects. Preliminary analysis of studies with both zanamivir and oseltamivir suggest that these drugs also provide benefit to high risk adults, resulting in more rapid recovery of illness, again by about 1 to 2 days. However, these studies have not been able to demonstrate convincingly that early treatment of influenza in such individuals would lead to reductions in subsequent hospitalizations or deaths. It may never be possible to organize prospective randomized controlled trials to demonstrate such an effect, since even in high-risk subjects such events occur rarely.

There is also little information on use of any antiviral therapy for influenza in immunosuppressed individuals or in individuals with severe influenza who are seen beyond 48 hours after the onset of symptoms. Because immunosuppressed patients may exhibit prolonged replication of influenza virus, it is reasonable to imagine that there may be a greater window of opportunity to intervene with antiviral drugs in this situation, but there is no data on which to base this speculation. Similarly, it is

reasonable to imagine that severely ill patients who are virus positive at the time that therapy is initiated might benefit even if they more than 48 hours into their illness. Since most adults who are hospitalized with influenza are outside the 48 hour window, this is an extremely relevant issue, and in fact many such individuals currently do receive antiviral therapy. However, it has never been possible to successfully complete a study to evaluate this question in a definitive way.

Therapy of acute influenza in children has also received relatively little attention. Only amantadine is licensed for this indication in the U.S., although there is data, summarized earlier, supporting the efficacy of rimantadine as well. However, use of M2 inhibitors is associated with particularly high rates of development of resistance in children. Zanamivir is currently licensed for use in individuals 7 or older, while oseltamivir is licensed for use in individuals 13 years of age and older, although as described earlier, preliminary evidence of efficacy in younger subjects has been reported.

Studies that directly compared amantadine and rimantadine have shown that there is no significant difference in the therapeutic efficacy of these two drugs. However, there are no studies that have directly compared the efficacy of zanamivir with oseltamivir, or of M2 inhibitors with neuraminidase inhibitors. The published results of individual clinical trials suggest that for influenza A virus infections, all of the available drugs have similar efficacy. In addition, the two drugs with activity against influenza B virus, zanamivir and oseltamivir, appear to have similar levels of benefit against influenza B generally, although neither drug has been evaluated extensively against influenza B in humans. Therefore, decisions regarding the choice of an individual agent should be individualized and consider the side effects, ease of use, concern regarding development of resistance, and cost. There is currently no information regarding the potential use of drugs from the two classes in combination, although theoretically this strategy might be synergistic, since they involve two distinct antiviral targets.

## RSV

### *Ribavirin*

Ribavirin (1- $\beta$ -D-ribofuranosyl-1,2,3-triazole-3-carboxamide) is a broad spectrum antiviral agent with structural similarity to guanosine. In cell culture, this agent has antiviral activity against both DNA and RNA viruses, including RSV. The mechanism of action of the drug is unclear and may be multifactorial, including alterations in cellular nucleotide pools [32] and inhibition of viral mRNA formation. Perhaps for this reason, antiviral resistance is rare and has been reported only for Sindbis virus. Ribavirin is inhibitory to RSV in cell culture at levels of 3-10  $\mu$ g/mL, and in aerosolized form has been demonstrated to be effective for treatment of experimental infection in a variety of animal models, including in cotton rats and primates.

Several randomized placebo-controlled trials of ribavirin small particle aerosol in naturally occurring RS virus lower respiratory tract disease of normal infants [33-37], or infants with high-risk underlying disease [38] have been conducted. While there have been differences in the measures by which outcome was assessed in these studies, each has indicated some beneficial effect of the drug on both virus shedding and clinical illness.



Ribavirin has also been shown to be of benefit when administered to infants requiring mechanical ventilation, with a markedly decreased total duration of ventilation and hospitalization compared to infants receiving placebo [39]. However, other studies, using both randomized prospective as well as retrospective case-control designs, have not shown beneficial effects of the drug [40-43]. The reasons for these disparate results are not clear, but may involve such factors as the choice of placebo, the endpoints used in the studies, and the specific patient populations involved. However, doubts about the efficacy of ribavirin have led to reduced enthusiasm for its use among practitioners.

### *Strategies For Treatment*

The variable results of treatment trials and the expense of the drug has recently prompted a reconsideration of recommendations for use of this drug [44]. Current recommendations regarding the treatment of RSV limit such treatment to selected infants and young children who are at high risk for serious RSV disease [45]. Specifically, these indications include infants with congenital heart disease, bronchopulmonary dysplasia, cystic fibrosis, and other chronic lung condition, premature infants, children with immunodeficiency, recent transplant recipients, patients undergoing chemotherapy for malignancy, and severely ill infants such as those receiving mechanical ventilation, and those at high risk of progression.

The optimal treatment of RSV infection in immunocompromised individuals is unclear. Ribavirin therapy of RSV pneumonia in these patients is usually not successful. Use of RSV-IGIV (see below) has been reported to be useful in uncontrolled trials [46, 47], but the doses required are generally not practicable in adults. Because severe RSV lower respiratory tract infections in transplant recipients are usually preceded by several days of upper respiratory tract symptoms, one option would be preemptive therapy before the development of severe disease. Preliminary results with the use of preemptive ribavirin aerosol or ribavirin plus RSV-IGIV have been encouraging [48, 49], but need to be confirmed in controlled trials.

## **Dosing Schemes, Drug Interactions, Side Effects**

### *Amantadine*

The usual dose of amantadine for treatment in healthy adults is 100 mg orally twice a day for 5 days. Amantadine is absorbed readily from the gastrointestinal tract and is excreted unchanged in the urine, with an average plasma elimination half-life of approximately 16 hours in young adults and over 25 hours in the elderly. Consequently, lower doses (100 mg per day) are indicated for older adults in order to minimize the risk of toxicity, although this dose has also been associated with excess side effects in nursing home residents [50].

The major side effects of amantadine are minor, reversible, CNS side effects such as insomnia, dizziness, or difficulty in concentrating. These side effects may be more troublesome in the elderly. In addition, amantadine use has been associated with seizures

in individuals with prior seizure disorder [51]. Minor gastrointestinal complaints have also been reported.

Because the elimination of amantadine is almost exclusively renal, significant dosage reductions must be made in the presence of renal impairment. In individuals with complete renal failure, the serum half life can be as long as 30 days [52]. Only small amounts of amantadine are removed during hemodialysis.

The CNS side effects of amantadine are increased when these drugs are co-administered with anticholinergics or antihistamines [52]. In addition, trimethoprim-sulphamethoxazole may inhibit tubular secretion of amantadine and increase the potential for CNS toxicity. There are no other known significant drug interactions with amantadine. However coadministration of amantadine with other drugs having CNS side effects could conceivably exacerbate these effects.

### Rimantadine

The usual therapeutic dose of rimantadine is also 100 mg orally twice a day for 5 days. Rimantadine undergoes extensive metabolism in the liver prior to excretion of the inactive metabolites via the kidney. There is relatively little effect of moderate renal or hepatic insufficiency of serum levels of rimantadine. However, reductions to about one-half of the normal daily dose is recommended in the presence of severe dysfunction. There are no known drug interactions that significantly affect the levels or metabolism of rimantadine.

Rimantadine is associated with a considerably reduced rate of CNS side effects compared to amantadine, and in comparative studies of long term administration, the rate of CNS side effects was not significantly different than placebo [53]. However, it is recommended that the dose of rimantadine should be reduced to 100 mg per day in the elderly, similar to the recommendations for amantadine in this population.

### Oseltamivir

Based data showing no difference in clinical trials between the 75 mg and 150 mg bid doses, the recommended dose of oseltamivir for treatment is 75 mg of oseltamivir phosphate twice a day for 5 days. Administration of the drug with food may improve tolerability without impacting drug levels. Oseltamivir is rapidly absorbed from the gastrointestinal tract and is converted in the liver by hepatic esterases to the active metabolite, oseltamivir carboxylate (GS4107). The metabolite is excreted unchanged in the urine by tubular secretion, with a serum half live of 6-10 hours [19].

The dose of oseltamivir should be reduced to 75 mg once daily in individuals with renal impairment, ie., with creatinine clearance of less than 30 mL/min. No data are available regarding the use of the drug in individuals with more significant levels of renal impairment. Likewise, no information is available regarding the use of oseltamivir in individuals with hepatic impairment. Preliminary results of an ongoing study in elderly but otherwise healthy subjects suggests that no dosage adjustment is necessary in this group.

Clinically significant drug interactions are felt to be unlikely with oseltamivir. Competition for hepatic esterases has not been extensively reported in the literature. In addition both oseltamivir phosphate and its carboxylate metabolite exhibit low protein binding. Oseltamivir is a poor substrate for the CYP isoenzymes and hepatic glucuronyl transferases. Because the drug is eliminated by tubular secretion, probenecid increases serum levels of the active metabolite approximately two-fold. However, dosage adjustments are not necessary in individuals taking probenecid. Co-administration of cimetidine, amoxicillin, or acetaminophen has no effect on serum levels of oseltamivir or its metabolite.

### Zanamivir

Zanamivir is not bioavailable by the oral route, and must be administered topically in order to be effective. Studies evaluating various modes of administration have determined that the optimal dose for therapeutic use is 10 mg bid x 5 days. The drug as supplied is supplied in blister packs in which each blister contains 5 mg of zanamivir and 20 mg of lactose carrier. The standard dose is therefore two inhalations twice a day. Using the Diskhaler it is estimated that approximately 4 mg of drug are actually delivered with each inhalation.

Studies with radiolabeled carrier suggests that when the Diskhaler device is used by healthy adults, the drug would be distributed throughout the respiratory tract, with relatively little initial distribution into the oropharynx. Approximately 4% to 17% of the inhaled dose is adsorbed systemically, where it is eliminated by the kidneys with a serum half life of from 2.5 to 5.1 hours. The fate of drug that remains in the respiratory tract is unclear. Presumably it remains in the respiratory tract until it is expectorated or swallowed, and excreted in the feces. Although significant increases in serum half life are seen in the presence of renal failure, the small amounts of the drug that are absorbed systemically suggest that dosage adjustments would not be necessary. Studies of the pharmacokinetics of the drug in the presence of impaired hepatic function have not been reported.

Zanamivir has exhibited an excellent safety profile in the majority of studies performed to date. The most commonly reported symptoms in individuals treated with the drug have included diarrhea, nausea, and nasal signs and symptoms which have occurred at essentially the same rate in zanamivir as in placebo recipients. In one study in which zanamivir was used in influenza-infected subjects with asthma or COPD, the frequency of significant changes in FEV<sub>1</sub> or peak flow rates was higher in zanamivir than in placebo recipients. For this reason, individuals with these pulmonary conditions should have ready access to a rapidly acting bronchodilator when using zanamivir, in the event that the drug precipitates bronchospasm.

Because of the low systemic exposure to drug, significant drug-drug interactions would not be expected. In addition, zanamivir does not interact with the CYP series of hepatic microsomal enzymes.

## Ribavirin

Ribavirin is significantly more effective for treatment of RSV when delivered topically than when administered systemically. Therefore, the drug is typically administered as a small particle aerosol, designed to generate particles of 1-2  $\mu\text{m}$  in diameter. The normal dose is 20 mg/mL in 300 mL of water, administered over 12-20 hours. Treatment duration is usually for 3 to 5 days depending on the patient's clinical course, with a longer duration of therapy sometimes needed in immunodeficient individuals [54]. A higher dose, shorter duration mode of therapy in which the drug is concentrated to 60 mg/mL and administered for a 2-hour period three times daily, appears to be of equal efficacy [55]. At the standard dose, plasma levels vary with the duration of exposure, varying from 0.5 to 3.3  $\mu\text{g/mL}$  in pediatric patients. In contrast, levels in respiratory secretions are much higher, as high as 1,000  $\mu\text{g/mL}$  [52].

Generally, the drug is extremely well tolerated. Reversible bronchospasm has been reported very rarely. In addition, the drug can precipitate in ventilator tubing, which may create mechanical difficulties depending on the ventilator system. When administered systemically, ribavirin can result in anemia, and in preclinical studies, has been shown to be teratogenic and mutagenic. In addition, possibly because of alteration of intracellular metabolic pools, ribavirin has immunosuppressive effects in experimental animals [52]. Under most circumstances of use, it is possible to detect ribavirin in the environment of the hospital room. Although evaluation of exposed health care workers have generally not detected significant levels of ribavirin in blood, the drug has been detected in the urine of exposed nurses [54]. Therefore, it is recommended that pregnant women should be advised not to care directly for patients who are receiving ribavirin, and the drug should be administered in well-ventilated rooms.

## Prophylaxis and Vaccination strategies

### Influenza

#### *Vaccination*

Currently, inactivated influenza vaccines, consisting of either whole virus, detergent treated "split-product", or subunit HA/NA vaccines are licensed for the prevention of influenza. Because disease due to influenza A (H1N1), A (H3N2) and influenza B viruses may all occur in a single season, a trivalent vaccine is currently used. Inactivated vaccine is generated by growth of influenza viruses in embryonated hen's eggs. The virions are harvested from the egg allantoic fluid and inactivated by treatment with a chemical agent such as beta-propiolactone, and partially purified. Three preparations are licensed for use: whole virion vaccines; split-product or subvirion vaccines generated by treatment of the virions with detergent, or purified subunit vaccines that predominantly contain HA and NA protein. The safety and immunogenicity of each of these types of vaccines appears to be comparable in adults.

Randomized, placebo-controlled trials of modern influenza vaccines have demonstrated these vaccines to be well tolerated in all age groups. One-quarter to one-half of vaccine recipients feel some discomfort at the vaccine site 8 to 24 hours after vaccination, but only about 5 percent have moderately severe transient local pain and swelling. Systemic symptoms, such as malaise, headache, or myalgias, occur at a low rate similar to placebo. Systemic complaints may be more common in individuals with low levels of prevaccination antibody. Guillain-Barre syndrome has been reported after receipt of influenza vaccine in some years. During the 1976 National Immunization Program against swine influenza the estimated risk of acquiring GBS was 1 in 100,000 vaccinations [56]. National surveillance conducted since 1976 has generally not identified increased rates of this syndrome following vaccination. However, very slight increases in the risk of GBS were seen following the 1992-93 and 1993-94 vaccines, representing an excess of approximately 1 case per million persons vaccinated [57].

Inactivated influenza vaccine has been shown to be effective in the prevention of influenza A in both randomized cohort studies conducted in young adults, with levels of protection of 70 to 90% when there is a good antigenic match between vaccine and epidemic viruses [58]. However, when the antigenic relatedness of the vaccine strain and epidemic strain is low the effectiveness of inactivated vaccine effectiveness is considerably lower. Studies suggest that vaccines reduce the frequency of severe illness to a greater degree than the frequency of infection, in both young adults and in the elderly [59, 60]. Vaccination of healthy adults in the US was associated with decreased absenteeism from work or school and is significantly cost saving [61].

Relatively few prospective trials of protective efficacy have been conducted in high risk populations. In one recent randomized placebo controlled trial in an elderly population, inactivated vaccine was approximately 58% effective in preventing laboratory documented influenza [62]. In addition, numerous retrospective case-control studies are available which have documented the effectiveness of inactivated influenza vaccines in these individuals. A recent meta-analysis of published cohort observational trials derived a very similar estimate of 56% for the level of vaccine efficacy against influenza respiratory illness in the elderly [63]. Vaccine is protective against influenza and pneumonia related hospitalization in the elderly, and is even accompanied by a decrease in all-cause mortality [64]. A recently conducted Medicare demonstration project indicated that vaccine usage had a beneficial effect on reduction of hospital admissions associated with laboratory-documented influenza A or B infection [65]. It has been estimated that among elderly persons in the US, influenza vaccination is associated with a direct savings of \$117 per year per person vaccinated [66]. It has also been suggested that vaccination of staff in chronic care facilities can have a major impact on mortality in elderly residents of these institutions [67].

### *Antiviral Prophylaxis*

Prophylactic administration of amantadine has also been shown to prevent influenza due to H1N1, H2N2 and H3N2 influenza A viruses. The majority of studies have utilized a seasonal prophylaxis study design, in which subjects begin the drug at the beginning of influenza epidemic activity and continue prophylaxis for the duration of the epidemic,

generally for from 4 to 8 weeks. The levels of protection against illness in adults associated with microbiologically documented influenza A virus infection have been reported as 70% [68] to 90% [53] against H1N1 viruses, and 68% against H3N2 viruses [69]. Seasonal prophylaxis has also been effective in children, in whom an approximately 90% reduction in laboratory confirmed illness due to influenza A H2N2 was reported [70, 71].

Amantadine has also been evaluated for the prevention of influenza in individuals exposed to an index case. These studies have been carried out in the family setting, in which members of a family receive prophylaxis for 10 days after exposure to an index case within the family. In studies where the index case was not treated with amantadine, protection of family contacts was noted [72]. However, if the index case was treated with amantadine at the same time as contacts received prophylaxis, no protection was seen [73], presumably because of the generation and transmission of amantadine-resistant virus in this setting.

Prophylaxis of contacts with amantadine has also been recommended in institutional settings such as nursing homes. There have never been controlled clinical trials documenting the efficacy of this approach, but anecdotal reports of significant decreases in the rate of influenza A cases after initiation of prophylaxis support the concept of outbreak-initiated prophylaxis [51, 74, 75]. Key features that contribute to the success of this strategy include rapid recognition and response to outbreaks, and isolation of individuals who are receiving treatment with amantadine from those who are receiving prophylaxis. Similar to the findings in the family setting, failure to adhere to this practice is associated with the development and transmission of resistant viruses within the institution [18, 76].

Significantly fewer studies of prophylaxis with rimantadine have been performed. However, when rimantadine and amantadine were directly compared in seasonal prophylaxis in healthy adults, the level of protection was approximately equal [53]. Rimantadine has also been evaluated in contact prophylaxis in the family setting, with results similar to those described for amantadine. When only contacts received prophylaxis, rimantadine resulted in significant protection [77, 78], but when the index case also received therapy with rimantadine, no protection was seen, and rimantadine-resistant viruses were recovered from prophylaxis failures [15]. Controlled studies of the prophylactic use of rimantadine in elderly or high-risk subjects have not been reported.

Neuraminidase inhibitors have also been shown to be effective in the prevention of influenza infection and illness. The first studies evaluated the use of zanamivir for seasonal prophylaxis [79], similar to the strategy used in evaluation of M2 inhibitors. In this study, adults were randomized to receive either zanamivir 10 mg once daily by inhalation, or placebo, beginning when an increase in influenza activity was documented at the study sites, and continuing for the next 4 weeks. The frequency of respiratory illness associated with microbiological documentation of influenza infection was reduced from 6% in the placebo group to 2% in the zanamivir group, resulting in 67% protective efficacy against this endpoint. The overall rates of all febrile respiratory illness, irrespective of the results of laboratory tests, were reduced by 43%, from 10% in the placebo group, to 6% in the zanamivir group. Oseltamivir has also been assessed in the seasonal prophylaxis model, where administration of oseltamivir at 75 mg once

daily to healthy adults during the duration of the influenza season (6 weeks) was associated with a 74% reduction in the overall rate of respiratory illness associated with laboratory confirmed influenza infection, from 4.8% in the placebo group to 1.2% in those receiving oseltamivir [80]. In a recent study, oseltamivir was also reported to result in a 91% reduction in laboratory confirmed influenza in a vaccinated elderly population living in nursing homes or chronic care facilities [81].

These drugs have also been evaluated for prophylaxis of influenza in individuals after exposure to an index case have also been reported. In one study, [82] families in which one individual had acute influenza-like illness of 36 hours duration or less were randomized to either receive zanamivir (treatment of the index case with 10 mg bid x 5 days and prophylaxis of other family members with 10 mg qd. x 10 days) or placebo. Zanamivir prophylaxis was associated with a 79% reduction in the frequency with which one or more contacts developed influenza in the family, from 19% in families receiving placebo to 4% in families receiving zanamivir. Oseltamivir has also been tested for family prophylaxis with similar results. In this study, the index case did not receive treatment. However, prophylaxis of family members resulted in an 89% reduction in families experiencing illness [83].

The most frequent use of contact prophylaxis currently is for the termination of outbreaks within chronic care facilities. There have been several anecdotal reports of success when using zanamivir in this fashion [84]. In addition, zanamivir and rimantadine were recently compared in a prospective randomized trial of outbreak initiated prophylaxis [85]. In this study, use of zanamivir resulted in 61% fewer cases than seen in individuals randomized to receive either rimantadine (influenza A outbreaks) or no therapy (influenza B outbreaks). Of note, the majority of instances of failure of rimantadine prophylaxis were associated with infection with rimantadine resistant viruses.

### *Strategies For Prevention*

The most efficient approach to prevention of influenza is the yearly administration of inactivated influenza vaccine. Influenza vaccine should be administered as a dose of 0.5 mL by intramuscular injection, to those 3 years of age and older, while younger children should receive 0.25 mL. Adults and older children should receive vaccine in the deltoid, while younger children are generally vaccinated in the anterolateral aspect of the thigh. Only a single dose of vaccine is required in individuals who have been previously vaccinated or who have experienced prior infection with a related subtype, but a two dose schedule is required in children less than 9 who are receiving influenza vaccine for the first time and in other unprimed individuals [86, 87]. Use of a second dose of vaccine otherwise does not provide any additional benefit [88]. Whole virus vaccines should be avoided in children under 12 years of age as they are associated with relatively higher rates of fever in this age group.

It is possible to identify certain individuals who are at particularly high risk of influenza related hospitalizations and deaths, and towards whom programs of vaccination should be particularly directed. The currently recommended target groups for influenza vaccination are summarized in Table 5. Specific recommendations regarding target groups are reviewed each year and updated [89]. Additional individuals in whom

vaccination is recommended include individuals such as health care workers, who can transmit virus to others at high risk, individuals infected with HIV, and high-risk individuals who will be traveling to an area where influenza epidemics are occurring. While it is relatively easy to identify such individuals, it is not always easy to deliver vaccine to them. Rates of influenza immunization in individuals 65 and older in the U.S. have risen dramatically, and now exceed the 60% “healthy people 2000” goal in all 50 states. However, the vaccine coverage rate in high-risk individuals under 65 is considerably lower, estimated to be approximately 30% to 35%.

Antiviral drugs could also be considered for prevention in certain limited circumstances. At the moment, only amantadine and rimantadine are licensed for the prevention of influenza, so that currently licensed antiviral strategies currently would be effective only for prevention of influenza A. In, individuals are administered the antiviral drug for the duration of potential exposure. As reviewed earlier, the seasonal prophylaxis strategy has been the basis for multiple clinical trials demonstrating the prophylactic activity of the M2 and neuraminidase inhibitors. In this is fairly obviously not a practical solution for the general use, but seasonal prophylaxis should be considered in particularly high-risk individuals who cannot be vaccinated or would not be expected to respond to vaccination at all. In addition, seasonal prophylaxis would be one method of dealing with a situation in which the vaccine did not include the prevalent epidemic strain, such as during a pandemic. However, there might be expected to be significant logistic and supply difficulties with the use of antiviral prophylaxis on such a large scale.

Antiviral drugs can also be used for short-term prevention. One scenario is the individual who is not vaccinated until influenza epidemic activity has already begun. Under these circumstances, it is reasonable to use antivirals until vaccine immunity has been established. Because immunity develops quite rapidly following inactivated vaccine in adults, generally 2 weeks of prophylaxis after vaccination is recommended. The other form of short-term prophylaxis that is commonly employed is after exposure, either in the family or institutional setting. As described above, there is good evidence to support the effectiveness of a 7-10 day administration of antivirals to contacts after a family member develops acute influenza. For the most part, this strategy would be appropriate in the setting of a high-risk individual within the family, but under unusual circumstances (e.g., a vacation or other important life event) such a strategy could be considered in healthy persons. Because of the possibility of generation and transmission of resistant influenza viruses, the success of this strategy when M2 inhibitors are utilized depends on not also using M2 inhibitors to treat the index case. It is not clear whether such a proscription would be important for neuraminidase inhibitors as well.

The more common use of short term prophylaxis is after potential exposure in the institutional setting. In this situation, the recipients have generally already been vaccinated, but constitute a group in whom vaccine efficacy may not be ideal, and in whom the potential consequences of influenza demand that every additional effort be taken to prevent infection. There is surprisingly little placebo-controlled data to support the use of outbreak-initiated prophylaxis with any antiviral, but the experience with family studies and various anecdotal reports suggest that there may be some benefit to this approach. If outbreak initiated prophylaxis is to be used, it is essential that it be instituted promptly



to be most effective, since influenza can spread rapidly in the institutional setting, and the peak of the outbreak may occur only a few days after recognition of the index case. Therefore, programs that utilize standing orders are generally more successful. Rapid diagnostic tests for detection of influenza may also be quite useful in this regard, since the clinical presentation of influenza in this population can be muted and difficult to differentiate from other respiratory viruses such as RSV and rhinovirus. Although these tests may have lower sensitivity than culture, the aggregate sensitivity in detecting at least one positive out of several samples should be adequate to allow early recognition and response to influenza outbreaks. For any individual outbreak, the recommended duration of prophylaxis is from 2 to 3 weeks, or for one week beyond the last documented case. For the same reasons as described for family prophylaxis, isolation of individuals receiving treatment with M2 inhibitors from individuals receiving prophylaxis with M2 inhibitors is important to reduce the generation and spread of resistant viruses. Alternatively, one could consider treatment with one class of agent (e.g., neuraminidase inhibitors) and prophylaxis with the other class (e.g. M2 inhibitors).

## Respiratory Syncytial Virus

### *Passive Antibody*

Passive immunization has received considerable attention for both the treatment and prevention of respiratory syncytial virus infection. This strategy is based on early observations that passively transferred antibody to either the F or G protein prevented infection in experimental animals and was also effective therapeutically. Although therapeutic administration of antibody has not resulted in clinical benefit in humans [90], prophylaxis with passive antibody has been successful in selected infants. Initial studies utilized selected pools of immunoglobulin screened for high titers of RS virus neutralizing antibody, referred to as RSV-IGIV (RespiGam) [91]. When administered intravenously at monthly intervals during RSV seasonal activity, RSV-IGIV was shown to reduce the incidence of RSV-related respiratory hospitalizations in infants with prematurity or bronchopulmonary dysplasia [92, 93]. The currently recommended dose of RSV-IVIG is 750 mg/kg IV monthly during the RSV season. However, administration of this agent involves administration of large volumes of fluid, and children with cyanotic congenital heart disease who received RSV-IGIV had a higher incidence of severe adverse events, and those that went on to have cardiac surgery had enhanced mortality [94]. Thus, this product is considered to be contraindicated in infants with cyanotic congenital heart disease [45].

One approach to circumventing the problem of the large volumes of RSV-IVIG that must be administered is the use of humanized monoclonal antibodies with very high RS virus neutralizing titers [95]. Paluvizumab (Synagis) is a humanized monoclonal antibody directed against a conserved region of the F protein with high-titered neutralizing activity against RSV. When administered intramuscularly at monthly intervals to premature infants or infants with chronic lung disease, paluvizumab was shown to result in a 55% reduction in RSV hospitalizations, as well as in reductions in total days of RSV hospitalization, O<sub>2</sub> requirements, and ICU admissions [96].

The recommended dose of this agent is 15 mg/kg intramuscularly once monthly during the RSV season [97]. Of note, although this product is a humanized, rather than human, monoclonal, development of antibody to paluvizumab has not been reported in infant recipients, and its use has not been associated with significant adverse events.

### *Vaccines*

The success of passive antibody approaches suggests that under the right circumstances, prevention of severe disease due to RS virus by active immunization is a reasonable goal. The traumatic experience of enhanced disease with inactivated RS virus vaccine remains a major obstacle to further vaccine development. Initial attempts to develop a vaccine for RS virus involved use of formalin inactivated virus. However, this vaccine failed to provide protection in field trials carried out in the 1960s, despite inducing high levels of RS virus antibodies. Instead, subjects who received vaccine experienced enhanced disease with subsequent RS virus infection, compared to others who received control vaccines. The mechanism of this enhancement remains unknown. At the moment there is no commercially available vaccine for the prevention of RSV, although several are in clinical development.

### *Strategies For Prevention*

The cornerstone of prevention of RSV remains the institution of appropriate infection control practices, as vaccination is not currently available, and immunoglobulin prophylaxis is currently only recommended for limited categories of patients. Immunoglobulin prophylaxis should be considered for infants and children less than 2 years of age with chronic lung disease who are receiving medical management on a long-term basis (e.g., have required medical therapy within the previous 6 months) [97]. The benefit for this group has mostly been shown for the first RSV season, and there are limited data on the effectiveness of prophylaxis during a second season of exposure. Another group to consider for prophylaxis are infants born at 32 weeks of gestation or earlier. Because such children generally have low levels of maternal antibody, they are at higher risk for severe disease. Children with congenital cyanotic heart disease or with immunodeficiencies could also theoretically benefit from prophylaxis, but data supporting the efficacy of either preparation in these conditions are not available.

There are several potential advantages of paluvizumab over RSV-IVIG for the prevention of RSV infection, including the relative ease and convenience of IM compared to IV administration, the considerably smaller volumes of fluid administered, and the fact that paluvizumab is not a human blood-derived product. For this reason, paluvizumab is generally favored for most clinical circumstances. In addition, RSV-IVIG is contraindicated in children with cyanotic congenital heart disease. However, RSV-IVIG, likely because it contains polyclonal antibodies to a variety of pathogens, is associated with decreased rates of non-RSV respiratory hospitalizations. Thus, this product might be a consideration for infants in whom fluid considerations are not paramount and who already have IV access, for example infants with severe combined immunodeficiency disease or other recipients of chronic immunoglobulin therapy.

**Table 1.** Viral respiratory syndromes

Disease Syndrome	Age group	Modifying circumstances	Predominant etiologies
Common cold	Any	Any	Rhinovirus, coronavirus, RSV, parainfluenza viruses
Otitis media	Children	Any	Respiratory syncytial virus, influenza, others
Croup	Children	Any	Parainfluenza, influenza, measles
Acute bronchitis	Any	Any	None established
Bronchiolitis	Infants and children	Any	Respiratory syncytial virus, influenza, measles
Influenza-like illness	Any	Any	Influenza virus, RSV, parainfluenza
Viral pneumonia	Children	Healthy	RSV, parainfluenza, measles, influenza
	Adults	Healthy	Influenza, adenovirus
		Immunocompromised	CMV, HSV, RSV

**Table 2.** Diagnostic tests for viral respiratory diseases

Test	Application	Examples	Advantages	Disadvantages
Cell culture	All viruses	MDCK (influenza), Hep2 (RSV)	Gold standard for diagnosis High sensitivity Virus available for study	Requires cell culture Time consuming
Antigen detection	Influenza RSV	Directigen Flu OIA Directigen	Very rapid Least amount of operator skill	Somewhat insensitive compared to cell culture
Genome detection	All viruses	Nucleic acid hybridization PCR	Highly sensitive Adaptable for all viruses	Technically complex Expensive Takes longer than antigen detection

**Table 3.** Treatment strategies

Virus	Modifying circumstances	Primary therapy	Alternate therapy
Influenza A	Healthy adults < 48 hours	Amantadine/Rimantadine <sup>1</sup>	Zanamivir/Oseltamivir
	Immunocompromised	Zanamivir/Oseltamivir <sup>2</sup>	
	Children <sup>3</sup>	Amantadine	Rimantadine, Oseltamivir, Zanamivir
	Elderly	Rimantadine <sup>4</sup>	Oseltamivir, zanamivir
	Institutional outbreak <sup>5</sup>	Oseltamivir, zanamivir	Rimantadine, amantadine
Influenza B	Any	Oseltamivir, zanamivir	
RSV	Severely ill <sup>6</sup>	Ribavirin	
	Immunocompromised	Ribavirin (?+IG) <sup>7</sup>	
	All others	Supportive care	
Parainfluenza	All <sup>8</sup>	Supportive care	
Rhinovirus	All <sup>8</sup>	Supportive care	

1 – All licensed drugs appear to have equivalent efficacy, so choice is often made on basis of cost.  
 2 – Use of M2 inhibitors in immunocompromised individuals is associated with high rates of development of resistant virus and treatment failure  
 3 – Only amantadine currently licensed for treatment of children, zanamivir licensed to age 7, oseltamivir application for use in children 1 year of age and older is pending review  
 4 – Amantadine is associated with frequent CNS toxicity in this age group  
 5 – Consider use of NI for treatment if other individuals in institution are receiving prophylaxis with M2 inhibitor  
 6 – See American Academy of Pediatrics guidelines [44]  
 7 – IG = immunoglobulin. No data from randomized controlled trials support use, but success rate with ribavirin alone is poor  
 8 – There is no approved therapy available at this time

**Table 4.** Doses and side effects

Agent	Modifying circumstances	Dose	Adverse effects
Amantadine	Children 1-9 years	5 mg/kg/day up to 150 mg/day in two divided doses	CNS, GI
	Ages 10 to 64	100 mg bid	
	≥65 yrs	100 mg qd	
	Cr Cl ≤ 50 mL/min	See package insert	
Rimantadine	Children	Not licensed for this application	GI, CNS (rare)
	Aged 14-64	100 mg bid	
	≥65	100 mg or qd or bid	
	Cr Cl ≤ 10 mL/min	100 mg qd	
Zanamivir	Severe hepatic dysfunction	100 mg qd	Bronchospasm (rare)
	Ages 7 and above	2 inhalations (10 mg) bid	
	Renal and hepatic impairment	Limited data, dose reduction does not appear to be needed	
Oseltamivir	Ages 18 and above	75 mg bid	Nausea and vomiting
	Cr Cl < 30 mL/min	75 mg qd	
	Hepatic dysfunction	Not studied	
Ribavirin	Infants with severe RSV	20 mg/mL continuous small particle aerosol for 12-20 hours per day	Reversible bronchospasm (rare)

Derived from [89]

**Table 5.** Groups at increased risk of influenza complications, for whom annual vaccination is recommended [89].

- Persons aged 50 years or greater
- Residents of nursing homes or other chronic care facilities
- Adults and children with chronic disorders of the pulmonary or cardiovascular systems, including asthma
- Adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including HIV).
- Children and teenagers receiving long-term aspirin therapy.
- Women who will be in the second or third trimester of pregnancy

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