112 Influenza

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Definition/Classification

Influenza is an acute, respiratory infection caused by members of the Orthomyxovirus family. Influenza viruses are enveloped, irregular, spherical particles containing a segmented, negative-sense RNA genome (*Fig. 112.1*). Three distinct types exist, termed influenza A, B, and C. Influenza A viruses are zoonoses derived from the wild bird population, while influenza B and C viruses are human pathogens. Influenza virus strains are named according to a standard nomenclature defining the type, the host species if not human, the geographic source, the isolate number from that geographic region, and the year, for example, B/Memphis/13/03. For influenza A viruses, the subtype is based on antigenic variation in the two major surface glycoproteins, the hemagglutinin (HA or H) and neuraminidase (NA or N), and this is indicated in parentheses during designation of strains (*Fig. 112.2*). There are 16 distinct HA subtypes and 9 NA subtypes in birds, although only 3 HA and 2 NA subtypes have to our knowledge established long-term lineages in human populations.

Etiology

Disease from influenza manifests from a complex mixture of direct viral damage, host responses, and the effects of co-pathogens. Primary influenza is considered a viral infection of the upper and lower respiratory tract. However, much of the disease that occurs during influenza epidemics and pandemics is mediated by secondary pathogens or host responses. The most common agents complicating influenza are the gram-positive bacteria *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pyogenes* (Group A streptococcus). Bacterial otitis media, sinusitis, pneumonia, and meningitis can all be mediated by co-pathogens in the setting of influenza. In addition, influenza interacts with host factors in vulnerable populations to cause disease through exacerbation of preexisting conditions. Acute worsening of cardiac disease, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) are common accompanying morbidities during influenza. Deaths during influenza epidemics are often described as "excess" mortality since the underlying chronic diseases are classified in vital statistics as the official causes of death, even though influenza was the inciting factor.

Epidemiology

Seasonal influenza is primarily a disease of children, with clinical attack rates of 20–30% annually, concentrated in naive hosts. Children are also the primary vectors of disease due to this high clinical attack rate, their high social contact rate, and a relative lack of cross-reactive immunity allowing unrestricted replication and shedding of large quantities of the virus. However, most deaths are in persons with chronic comorbidities, so mortality is mostly in the elderly. Annual death rates are approximately 1 in 10,000 in developed countries and are presumed to be higher in the developing world, although data are lacking. The excess mortality rate for influenza A viruses varies significantly by strain and season, based on both the degree of preexisting immunity in the population, the potency of viral virulence factors, and how well the circulating viruses support secondary bacterial infections from regionally endemic bacterial strains. Since influenza B viruses do not have an animal reservoir and are well adapted to humans, their epidemiology resembles that of well-adapted seasonal strains with a high clinical attack rate in children, and little mortality outside of those with underlying chronic illnesses. The epidemiology of influenza C viruses is poorly understood, but it is not thought that significant disease results from typical infections.

Pandemics of influenza occur several times a century when a novel influenza A virus enters humans and achieves worldwide spread. A virus must meet three criteria to be considered pandemic: (1) a novel HA protein to which most of the population is immunologically naive, which allows a high clinical attack rate; (2) ease of transmission enabling worldwide spread; and (3) ability to cause severe disease. Four pandemics have taken place in the last 100 years. In 1918, an H1N1 subtype virus entered humans from the animal reservoir, causing severe disease and killing more than 40 million people worldwide.

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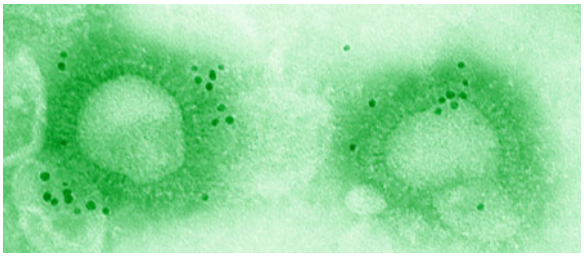

Figure 112.1
Influenza virions. Influenza virions as seen by electron microscopy. The dark beads are gold particles labeling neuraminidase spikes on the surface of the virions

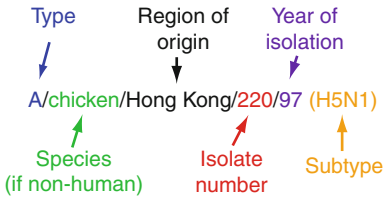

Figure 112.2
Nomenclature of influenza viruses

This virus adapted to humans and circulated until 1957, when it was replaced by an H2N2 subtype virus that took part of its gene constellation from the circulating H1N1 strain (since influenza viruses have a segmented genome, they can swap genes through a process called reassortment in intermediate hosts such as pigs), and the remainder from an avian source. The 1957 pandemic was severe, but not on the same scale as that of 1918, killing several million persons. In 1968, another novel strain emerged, again by reassortment. This H3N2 virus had a novel HA, but retained the NA and several other genes from the 1957 strain. Disease and mortality were milder than in previous pandemics, perhaps because of the retention of the NA antigen from the previously circulating strain. Adapted versions of this virus continue to circulate today. This virus was joined in circulation in humans in 1977 when a 1950 version of the previously circulating H1N1 strain was released from a frozen source. Although this virus achieved worldwide circulation and continues to be endemic in humans today, co-circulating with H3N2 strains, this event was not considered to be a pandemic since much of the population was immune and little disease ensued.

In 2009, the most recent pandemic strain emerged as a complex mixture of genes of avian, human, and swine derivation. It was again of the H1N1 subtype, but was most antigenically similar to the 1918 strain among viruses that circulated in the twentieth century. Because of this, only elderly persons who experienced influenza in the 1930s and 1940s had any cross-reactive immunity. Sero-archaeologic evidence suggests that as far back as the mid-1850s, H1, H2, and H3 subtype viruses have successively replaced each other as pandemic strains. It is not known whether this recycling phenomenon is limited to these subtypes due to factors presently not understood, or whether other subtypes are also capable of causing pandemics. The repeated incursions of highly pathogenic avian influenza viruses of the H5N1 subtype into humans since 1997 have created significant concern that a truly novel pandemic strain could arise, but as of yet these viruses seem incapable of sustaining chains of transmission in humans.

The 2009 H1N1 pandemic was marked by a high clinical attack rate in children, severe disease in older children and young adults, and relative sparing of the elderly due to cross-reactive immunity. Most cases of severe disease were found in persons with preexisting comorbidities, especially asthma, chronic cardiac or respiratory disease, and obesity. Bacterial pneumonia complicated the clinical course of about 30% of severe or fatal cases. The phenomenon whereby the elderly experience relatively less disease during pandemics than young persons appears to be related to the recycling phenomenon; the repeating reintroduction of the three most common subtypes leads to protection in the oldest sections of the populations as they will have antigenic experience with these unadapted viruses. Most disease is thus seen in younger persons. This is the inverse of the pattern of disease during seasonal epidemics with adapted viruses. Because most epidemics occur with drift variants that have been selected for their ability to cause disease in an immune population, the elderly are susceptible, and the relatively higher prevalence of comorbidities with increasing age drives higher rates of hospitalization and mortality. In pandemics, more than 90% of deaths are typically in younger age groups in whom the clinical attack rate is highest. During seasonal outbreaks, although young persons remain the primary vectors of transmission and are most likely to be infected, persons over 65 years account for about 95% of all mortality.

Transmission of influenza viruses can occur by contact, large droplet, and aerosol routes. Since most viruses are expelled during coughing and sneezing, direct contact with infected secretions or contaminated objects is thought to dominate in most settings. Transmission is affected by both temperature and humidity, and is favored in cold conditions and significantly diminished in the setting of high humidity. It has been suggested that aerosol transmission is more efficient in cool, dry environments,

facilitating explosive outbreaks when conditions are right. Most outbreaks in temperate climes are seasonal and occur in cooler, winter months when transmission is favored. However, a low level of infection can be detected year-round. In tropical parts of the world, circulation of viruses occurs all year, with inconsistent peaks related to poorly understood climactic changes. Herd immunity plays some role in the seasonality of influenza as well, since pandemic strains appear to transmit efficiently in the summer in temperate climes. The increased availability of susceptible hosts may overcome the temperature and humidity barriers to transmission of seasonal strains. The relative ability of influenza viruses to transmit is expressed by a term called the reproductive number R_0, which represents the average number of persons an infected individual will themselves infect. Any value over 1.0 suggests that sustained transmission is possible and therefore an outbreak can occur. Pandemic viruses may have an R_0 in the 2–3 range, higher than the average seasonal virus which may be $\sim$1.4, but much lower than comparable viruses such as measles which may have an R_0 of about 10–15.

Pathogenesis

Influenza viruses are segmented RNA viruses that encode 10–11 proteins. There are two surface glycoproteins, HA and NA, which are involved in attachment and budding, respectively, and are the main targets of antibodies. In addition to structural and polymerase proteins, the virus also encodes nonstructural proteins PB1-F2, which is a cytotoxin, and NS-1, which is an interferon antagonist. The lack of proofreading mechanisms for the polymerase complex during replication leads to a high mutation rate, which generates a multitude of variants within any population of viruses, termed a quasispecies. In the presence of selective pressure, such as adaptation to a new host or upon encountering antibody-mediated immunity, this breadth of options allows selection of fitter viruses. In the context of seasonal epidemics, the resulting drift of the surface antigens allows new variants to arise that can escape immune pressure in an experienced population, generating new epidemics. In addition, the segmented genome allows reassortment between two viruses infecting the same cell, which can lead to the genesis of a pandemic strain if the nascent virus encodes a novel HA from the animal reservoir.

The first encounter of the virus with the host is typically at a mucosal surface in the upper respiratory tract, where infection is initiated in epithelial cells. Clinically, influenza can be limited to this site or may spread down to the trachea and major bronchi. Penetration into the lower lung is limited by innate defenses such as collagenous lectins, which can bind glycoconjugates on the major surface glycoproteins HA and NA and neutralize infectivity. However, poorly glycosylated viruses, such as those recently emerging from avian sources, can evade this barrier and cause pneumonitis. The epithelial damage influenza viruses cause during replication can expose basement membrane, allowing adherence of bacteria and facilitating secondary infections. Severity of disease is thus a combination of the effective site of infection, which modulates both the viral syndrome and the type of secondary bacterial disease that might occur, together with the host response. The host response can be either helpful, by clearing the virus, or detrimental by furthering lung damage. Primary influenza is cleared by a combination of innate host defenses, IgM antibody, and a CD8+ T-cell response, which recognizes and kills infected cells. During this resolution stage, CD4+ T-cells facilitate class-switching of antibodies to IgG and induction of long-term memory. Thus, on later rechallenge with a related strain, infection is prevented or rapidly cleared through antibody-mediated neutralization of infecting particles. In the event that the new virus has drifted sufficiently that antibodies no longer recognize the surface proteins, infection is not prevented, but again the CD8+ T-cell response will clear the virus. This reliance of cellular immunity can be problematic in a compromised host, such as the elderly, who cannot clear virus as well and may suffer more severe disease. Paradoxically, robust immunity in older children can also contribute to disease if the T-cell response is strongly induced but cross-reactive antibodies are not present. Most of the clinical symptoms of influenza are due to either direct viral damage or the immune response.

Pathology

The hallmark of pandemic influenza is pneumonitis with diffuse alveolar damage, since these viruses typically penetrate well into the lower respiratory tract. Hemorrhage, fibrin deposition, edema, and formation of hyaline membranes are common. In severe cases, typical features of acute respiratory distress syndrome (ARDS) are seen. Findings suggestive of bacterial pneumonia, primarily manifest as a neutrophilic infiltrate with consolidation, may be superimposed on this pathologic picture. Antigen testing for bacteria in autopsy cases has been useful in recent studies to define the differences between primary viral and secondary bacterial pneumonia. Seasonal influenza rarely presents as severe, primary viral lower

respiratory tract disease; a mild to moderate tracheobronchitis is a more common presentation. Infiltration of lymphocytes in a peribronchial and perivascular distribution is typical. The epithelial lining of the major airways is predominantly affected, with cell death and sloughing of epithelial cells exposing basement membrane elements, upon which extracellular matrix material is deposited. Ciliated cells may also be killed during infection or may merely be functionally disrupted so that beat frequency and coordination of beat direction are altered, reducing clearance of mucus secretions. Pathologic alterations in other affected organs (e.g., heart, brain) are most commonly nonspecific, with edema and inflammatory changes present.

Clinical Manifestations: Symptoms, Signs

Influenza is a disease of rapid onset with both respiratory and systemic symptoms appearing together after a short, 2–3-day incubation period. After the first several days of illness when systemic symptoms dominate the clinical course, a transition takes place and systemic symptoms subside and cough and other respiratory tract–related symptoms become more prominent. Systemic symptoms include fever, chills, malaise, headache, dizziness, gastrointestinal disturbances, and myalgias. An erythematous maculopapular rash may be present briefly but it is not a common or prominent sign of infection. Common respiratory symptoms include cough, sore throat, rhinitis, nasal congestion, and eye irritation. Cough may be productive or nonproductive and may persist for weeks or longer. Typical features of bacterial pneumonia may be superimposed on this clinical presentation. Disease in adolescents and older children is similar to that of adults, and is dominated by the triad of fever, cough, and myalgias (*Table 112.1*). Cough is less prominent in younger children, and is sometimes absent entirely in infants. Myalgias are much less frequent in children than adults. Gastrointestinal symptoms are frequent in young children, and can manifest as vomiting, diarrhea, or abdominal pain. Infants may have fever and diarrhea as their sole presenting signs. Gastrointestinal symptomatology was more common during the 2009 H1N1 pandemic than is typically observed in seasonal influenza, and commonly affected older children and adults. Apnea and a sepsis-like syndrome can also occur in neonates and infants. Most children with influenza have a normal white blood cell count, but both leukopenia and leukocytosis can be seen. Leukocytosis with a predominance of neutrophils can be a sign of secondary bacterial infection, but can also occur with uncomplicated influenza. Blood chemistries are typically normal unless dehydration or complications are present. Influenza A and influenza B are indistinguishable clinically, although specific strains may have a predilection for certain clinical syndromes, and influenza B is more likely to cause clinical disease in younger children than in adults. Influenza C viruses typically cause more limited illness, with less-severe clinical presentations and a shorter duration of illness.

Table 112.1
Clinical manifestations of influenza

Symptoms	Infants	Children	Adults
Fever	++	+++	+++
Cough	+	++	+++
Myalgias	–	+	++
Sore throat	–	+	++
Headache	–	++	++
Conjunctivitis	++	++	++
Cervical adenopathy	+	+	–
Anorexia	++	++	+
Diarrhea	++	+[a]	–[a]
Vomiting	++	+[a]	–[a]
Rhinitis	++	+	+
Malaise/lethargy	++	+	+
Neurological symptoms	+	–[a]	–

– Rare, + uncommon, ++ common, +++ very common
[a]Common (++) with 2009 pandemic influenza

Both viral and bacterial complications are common during childhood influenza. Otitis media, sinusitis, and pneumonia can all be due to either the primary viral infection or can be manifestations of coinfecting bacteria. Otitis media may present as a mild, serous exudate if it is solely due to the virus, but in young children mixed viral–bacterial infections are common and a painful, purulent exudate may result. Symptoms of sinusitis are common during acute influenza, and opacification of the sinuses can be seen on computed tomography in a significant proportion of affected persons. Bacterial sinusitis may result as a secondary complication, manifest as increased pain and a return of fever after an initial period of recovery. Laryngotracheobronchitis (croup) can be a manifestation of acute influenza in young children, and is often more severe than is typical for parainfluenzaviruses. An acute myositis manifest by severe pain and tenderness of both calves may occur during the early convalescence stage. This syndrome typically has an acute onset and is accompanied by elevations of serum creatine kinase and aspartate

aminotransferase and, occasionally, rhabdomyolysis in severe cases. Cardiac complications including myocarditis and pericarditis are associated rarely with influenza. The pathogenesis of these complications is unclear, as virus is rarely identified in affected tissues.

Neurological symptoms associated with influenza are confined almost exclusively to young children who are naive to the virus and have never received the influenza vaccine. Febrile seizures are relatively common and uncomplicated in this group, and up to 30% of all febrile seizures of childhood are due to influenza. Encephalopathy from influenza can present with a variety of symptoms and signs, but mental status changes ranging from delirium to behavioral disturbances to coma are most prominent. Cranial nerve pareses are unusual, as are meningitic presentations. Cerebrospinal fluid (CSF) examination is typically normal or reveals a mild pleocytosis, and virus can be detected in CSF by polymerase chain reaction (PCR) or in biopsy or autopsy material from affected brains in about 15% of cases. Electroencephalography (EEG) typically shows a general slowing without an acute focus, and computed tomography (CT) scans are either normal or demonstrate diffuse edema. A subset of patients present with a more fulminant course and have findings on CT suggestive of necrosis in the subthalamic regions, a syndrome termed "acute necrotizing encephalopathy." Influenza-associated encephalopathy is uncommon in much of the world, but was relatively common in Japan in the late 1990s and early 2000s for reasons that remain unclear. During the 2009 H1N1 pandemic, older children were affected more commonly than is typically seen with seasonal influenza, likely because of lack of preexisting cross-reactive immunity.

Diagnosis

Classically, influenza has been diagnosed on the basis of a compatible clinical presentation in the setting of supportive epidemiology. Local or regional data suggesting increased presentation to primary care centers coupled with an increased rate of laboratory diagnosis of influenza can usually be relied on to indicate the start of winter-time epidemics in temperate climes. Sentinel programs to track influenza are in place in many countries (e.g., through the Centers for Disease Control in the United States) and internationally through the World Health Organization. As an important epidemiologic clue, influenza will more frequently affect both adults and children together than other causes of similar clinical syndromes. In this context, an age-appropriate clinical presentation can usually be assumed to be influenza and appropriate measures taken without specific diagnostic testing. Chest radiographs may be employed to confirm lower respiratory tract involvement or define a complicating bacterial pneumonia. Recently, two factors have altered the utility of clinical diagnosis alone. First, co-circulation of viruses with disparate antiviral susceptibility patterns has created a need to not only to definitively diagnose, but also determine the subtype of an infecting influenza virus so that treatment can be targeted with specific antivirals, and unnecessary drug use can be avoided. Second, during circulation of the 2009 H1N1 pandemic strain, infection control measures in hospitals differed for this strain compared to seasonal influenza. Strain identity had to be established to provide appropriate health-care worker protections. These factors, coupled with increased use of antiviral medications with their associated expense, have led to an increased demand for accurate, point of care diagnostic methodologies.

Three methods of diagnosis of influenza are in widespread use at present. Point of care testing in outpatient settings is typically limited to antigen based testing. This is accomplished through the use of inexpensive kits that utilize colorimetric changes upon antibody recognition of virus in nasal swab material to rapidly demonstrate the presence of antigen. Some tests can distinguish type A from type B influenza, but none can currently subtype influenza A strains or distinguish specific strains within an influenza A subtype or between the two major influenza B lineages. These kits uniformly have a low sensitivity, so while a positive result is useful for directing care, a negative result does not rule out influenza. Rapid antigen testing is also commonly employed in hospitals as a point of care diagnostic in acute care settings such as emergency rooms, but typically with a more sensitive and specific test as a backup, performed in a central laboratory. Two methods are commonly employed. A fluorescent antibody test, where clinical material from a nasal swab or nasal wash is incubated in susceptible cell culture, and the presence of virus is determined by microscopy to detect fluorescence of dyes bound to antibodies which recognize the virus, has been in common use for decades. This method is more sensitive and specific than rapid antigen tests, but may take several days to achieve a result. This is being replaced in many centers by the use of PCR-based testing, particularly using rapid and sensitive real-time PCR assays. These assays have the advantages of quick turn-around times, improved sensitivity and specificity compared to all other methods, and can be designed to differentiate viruses by type, subtype, and even strain. In parallel, similar methods are now available to rapidly sequence portions of the viral genome to provide

indicators of the most common resistance mutations. Other potential methods to diagnose influenza, such as virus isolation or acute and convalescent serology, are now confined to research settings.

Differential Diagnosis

Because influenza can manifest as a variety of clinical syndromes, the differential diagnosis is broad. This is particularly true in infants, who may not have common signs of infection such as cough. Depending on the particular disease manifestations, many other pathogens can either be the primary cause or a co-pathogen. Other respiratory viruses such as parainfluenzaviruses, respiratory syncytial virus, human metapneumovirus, rhinoviruses, and coronaviruses should be considered in the differential diagnosis for upper respiratory tract infections, otitis media, and laryngotracheobronchitis (croup). Bacterial causes of epiglottitis, such as *Haemophilus influenzae*, *S. aureus*, and *S. pneumoniae*, must also be considered in the child with croup, particularly if acutely ill. *S. pneumoniae*, *S. aureus*, and *S. pyogenes* are common lower respiratory tract co-pathogens with influenza, but must also be considered in the differential diagnosis as primary agents of disease along with other common causes of community-acquired pneumonia such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Numerous viral and bacterial pathogens can also present with fever and diarrhea, although gastrointestinal symptomatology with influenza is generally mild and the diarrhea non-bloody. The encephalopathy syndrome associated with influenza can mimic either bacterial meningitis or a viral encephalitis, so multiple causes must be considered. Finally, neonates with influenza can present with lethargy, poor circulation, and apnea, so other causes of sepsis must be considered.

Treatment

There are two classes of antiviral drugs approved for use against influenza viruses (*Table 112.2*). The adamantanes amantadine and rimantadine act by blocking the M2 ion channel, which prevents acidification of the virion during uncoating early in infection. Adamantanes have been in clinical use since the late 1960s for both prophylaxis and treatment of symptomatic influenza. Insomnia and difficulty concentrating are common side effects of amantadine that are less problematic with rimantadine due to its extensive metabolism in the liver. The NA inhibitors (NAIs) act by binding to and blocking the enzymatic activity of NA. This prevents budding of newly produced virions from infected cells, enhances aggregation at cell surfaces, and blocks escape from sialylated mucins. The NAIs oseltamivir and zanamivir were first licensed in the United States in 1999 and are now in widespread use throughout most of the world. Oseltamivir is available in a form that can be taken orally, while zanamivir is administered as a powder that must be inhaled with the use of a device. An intravenous form of zanamivir was made available in 2009 through an investigational new drug process to provide an alternative form of the drug for patients severely affected by pandemic H1N1 and unable to take oral or inhaled medications. A second NAI that can be administered intravenously, peramivir, was also made available during the recent pandemic through an emergency use authorization from the US Food and Drug Administration, and was licensed for clinical use in Japan. However, both of the US authorizations were withdrawn during the summer of 2010 at the conclusion of the pandemic, so licensed intravenous agents are not currently commercially available in any countries except Japan.

The primary clinical utility of existing antiviral agents is to halt progression of disease by preventing new host cells from being infected. If this intervention is administered early in the clinical course, it may alter the tempo of infection, allowing normal immune mechanisms to clear the virus. Earlier treatment works better in most cases because the infection is not yet widespread. Thus, the major effects of treatment are symptom reduction and a more rapid recovery, not immediate clinical cure. In clinical trials of NAIs, illness severity, ancillary medication use, and the frequency of prescriptions for lower respiratory complications were all reduced. The time to cessation of fever, alleviation of illness, and return to normal activity was decreased by about 24 h. Treatment of critically ill patients is complicated by lack of data regarding duration of therapy (all published data from prospective trials use short courses with a goal of symptom alleviation in acute, uncomplicated influenza) and by lack of a licensed intravenous formulation. Resistance has been a clinically significant issue for the adamantanes for years, limiting their utility. Widespread resistance to oseltamivir appeared in H3N2 viruses in 2007, and sporadic resistance in both seasonal and pandemic H1N1 viruses has been reported. Clinically significant resistance has not been seen with zanamivir, but viruses resistant to oseltamivir are typically also resistant to peramivir. Thus, while both zanamivir and peramivir could be considered for patients in need of intravenous therapy if they can be obtained, only zanamivir is currently an option for those with resistance

Table 112.2
Antiviral drugs available for treatment of influenza

Characteristics	Adamantanes[a]	Zanamivir	Oseltamivir	Peramivir
Licensure	1966, 1973	1999	1999	2009[b]
Target	M2 ion channel	Neuraminidase	Neuraminidase	Neuraminidase
Activity	Influenza A virus	Influenza A and B virus	Influenza A and B virus	Influenza A and B virus
Route	Oral	Inhaled, intravenous[c]	Oral	Intravenous
Effective against secondary bacterial infections	No	Yes	Yes	No data
Resistance[d]				
Seasonal H3N2	Resistant	Susceptible	Susceptible	Susceptible
Seasonal H1N1	Susceptible	Susceptible	Resistant	Resistant
Pandemic H1N1	Resistant	Susceptible	Susceptible	Susceptible

[a]Amantadine and rimantadine
[b]Emergency use authorization during 2009 pandemic only in United States; licensed in Japan
[c]Intravenous formulation available through investigational new drug (IND) application during 2009 pandemic only
[d]Based on 2008–2009 data

to both adamantanes and oseltamivir. The disparate resistance patterns of multiple viruses co-circulating over the last several years have made utilization of diagnostic PCR methodologies which can subtype viruses critical for appropriate management of severely ill patients. Combination therapy with multiple drugs within or across classes has been modeled in animals, and may improve effectiveness. However, these findings have not yet been proved in clinical trials.

Importantly, the effects on resolution of symptoms and the recommended duration of therapy (5 days) are based on studies in healthy persons with mild disease. It is not clear whether the dose, duration of therapy, and expectation of benefit should be the same in immunocompromised patients or in patients who have severe or complex disease manifestations. In regard to complications, oseltamivir both decreases the incidence of secondary bacterial pneumonia and reduces the severity of complications in animal models. Similar data are not available from a single, well-powered trial in humans, although a meta-analysis of data from multiple trials including unpublished data suggests these results can be extrapolated at least to healthy adults. In children, however, oseltamivir was shown to reduce the occurrence of otitis media by 44% compared to placebo. Retrospective reviews of insurance claims databases suggest that NA inhibitors reduce the risk of otitis media, pneumonia, respiratory illnesses other than pneumonia, and hospitalization in both adults and children, including in some at-risk groups such as diabetics. The best treatment for encephalopathy associated with influenza infection is uncertain. If viral replication in the brain is involved, effective antiviral treatment may not be possible, since neuraminidase inhibitors do not cross the blood–brain barrier (as do the adamantanes), and resistance to the adamantanes and lack of effect against influenza B viruses generally precludes their use. Reduction of virus titer in the lung with a neuraminidase inhibitor and supportive care may be the best available options.

The majority of clinically apparent cases of influenza can be managed as outpatients. The systemic symptoms that are prominent in the first several days of the acute infection often limit normal activity, causing missed school or work. General supportive care is often recommended, including antipyretics, rest, and hydration. Care must be taken in use of analgesics in children due to a past association of aspirin with an unusual manifestation of influenza known as Reye's syndrome and due to a concern that specific antipyretics or other herbal remedies in widespread use in Japan in the 1990s contributed to that country's high rate of influenza-associated encephalopathy. There is currently disagreement over the most appropriate use of antiviral medications. Most expert groups providing guidance have suggested that, at a minimum, persons at high risk for complications of influenza should receive early treatment with antivirals active against circulating strains of influenza. This guidance is tempered by a lack of study of these drugs in these specific groups. Clinical trials of these

compounds have typically been conducted in healthy persons, and clinical outcome measures have focused on reductions in symptoms and in duration of illness. Thus, whether these drugs are as active in persons with chronic medical conditions or are capable of preventing complications such as hospitalization and death are unclear. Duration of therapy and effective dose in critically ill patients and immunocompromised patients who may exhibit prolonged shedding are similarly unclear. There is currently little consensus on the issue of antiviral use in healthy persons including children, who have higher rates of hospitalization than adults. Some experts advocate withholding antivirals from healthy, well-appearing children on the basis of limited effectiveness data for significant outcomes such as hospitalization, coupled with the economic consideration of cost. However, the strategy of waiting to treat until complications develop may limit the effectiveness of therapy since early treatment has been proved to be superior to later treatment. In addition, many deaths in children are in otherwise healthy young persons of school age, and it has been argued that early intervention may prevent some of this mortality.

Numerous antiviral drugs directed against multiple targets of the influenza virus life cycle have progressed to preclinical or early clinical stages. As described above, intravenous formulations have seen some limited clinical use and at least one is now licensed in Japan. A long-acting drug in the NAI class has advanced through Phase III clinical trials, and may offer a single-dose option for uncomplicated influenza. Inhibitors of the HA, the polymerase complex, and combination chemotherapy approaches are also in various stages of clinical development and testing. Because of the prominent involvement of host immune responses in generation of symptoms and in the pathogenesis of severe influenza, immunomodulatory approaches have also been contemplated. Systemic steroids have been utilized to treat ARDS from H5N1 or pandemic H1N1 influenza, but the results have been generally disappointing, including some evidence that the disease may have been worsened by immunosuppression in some cases. Nonspecific anti-inflammatory therapies such as statins have also been utilized clinically, but no definitive, positive results have been reported. Use of antimicrobials is generally reserved for the treatment of complicated influenza when there is evidence of a secondary bacterial infection present. However, many pediatric deaths have been reported in recent years due to necrotizing *S. aureus* pneumonia, and this often presents as a fulminant disease. Early, directed anti-staphylococcal therapy should be considered in any critically ill child who presents with influenza-like illness or a confirmed diagnosis of influenza.

Prognosis

Viral disease from seasonal influenza is typically a self-limited illness in all but the most severe cases. Hospitalization and death are mainly due to complications, such as secondary bacterial infections, unusual non-pulmonary presentations (e.g., encephalopathy), or exacerbation of underlying illness. Bacterial disease when it accompanies influenza is often more severe than primary bacterial illness, and more difficult to treat. In particular, necrotizing staphylococcal pneumonia in association with influenza is considered an emerging disease in children. It presents as fulminant pneumonia progressing rapidly to respiratory failure, often with accompanying sepsis and multisystem organ failure, and may not respond to antibiotic therapy. Influenza-associated encephalopathy carries a high mortality rate. The severity of the initial presentation is considered a prognostic factor, with cases presenting in a comatose state carrying a high mortality rate and similarly high rate of severe neurologic deficit in survivors. Outcomes in immunocompromised children or in persons with chronic diseases are dependent on the severity of underlying illness and response to treatment. Need for hospitalization and the clinical course from influenza in the setting of preexisting cardiac or pulmonary disease is more often related to the underlying disease than to the inciting infection. Most children with cancer who contract influenza have a clinical course similar to that of immunocompetent children, but serious complications such as respiratory failure are more common. Disruptions of chemotherapy and hospitalization for fever in the setting of neutropenia are major problems in this group of patients. Prolonged viral shedding can occur, and in this setting prolonged antiviral therapy often leads to induction of resistance.

Prevention

Children experience the highest clinical attack rates, have the highest social contact rates to facilitate spread, and are the main vectors of transmission into vulnerable populations. Although mortality is unusual in children, more than 50% of rare complications and deaths are in healthy children without typical risk factors for hospitalization from influenza. For these reasons, universal influenza vaccination against children has been strongly advocated by most experts for many years. Current guidelines for vaccination of children vary widely between countries, but have been generally moving over time toward more inclusive recommendations. Vaccination of all children is now recommended in the

United States, as well as in many central European states, and is being considered in other countries. Prevention of influenza is clearly a cost-effective strategy compared to any currently available treatment options.

There are two basic types of influenza vaccines presently in use in children. Chemically inactivated, split-antigen vaccines grown in eggs (the "flu shot") are the standard vaccines that have been in use for more than 50 years and are licensed for children greater than 6 months of age. A cold-adapted, live, attenuated vaccine was introduced within the last decade and is licensed for use in children greater than 2 years of age. Both vaccines contain three antigens, one from the dominant, circulating type B strain, and the latest drift variants of each of the H1N1 and H3N2 subtypes of influenza A. The trivalent, inactivated vaccine (TIV) typically requires multiple exposures to achieve acceptable immunogenicity, efficacy, and durability in children under the age of 9 years, so current recommendations suggest two doses in anyone within this age group with fewer than two previous lifetime exposures. TIV is safe, with mild to moderate local soreness at the injection site the only common side effect. Guillaine–Barre syndrome does occur at a very low frequency after TIV, but at a lower rate than it does in association with influenza virus itself, the infection that the vaccine prevents.

The live, attenuated influenza vaccine (LAIV), which is administered as a nasal spray, appears to induce better initial immunity than TIV in young children who lack prior exposure, leading to better efficacy, longer durability, and improved cross-protection against drifted strains. It is unclear whether these advantages extend out of early childhood since available data suggest that LAIV has inferior efficacy in adults in some circumstances. This may be due to cross-protective antibody responses in more immunologically experienced hosts limiting replication of the vaccine virus. LAIV appears to be safe, with no evidence of reversion to wild type or transmission from vaccinated hosts. LAIV has been shown in one clinical trial to increase wheezing in children under 2 years of age, so administration to children with asthma or to those under 5 years of age with a history of wheezing is not currently recommended. Safety and efficacy have not been established in high-risk groups, so TIV is typically used for children with underlying chronic medical conditions.

Multiple alternative methods of producing influenza vaccines are either in clinical trials or already in use in adults. High-dose versions of standard TIV with four times the amount of each antigen show modestly increased immunogenicity in elderly adults, in whom vaccine effectiveness is generally poor, and are now licensed for this age group in many European countries and, more recently, in the United States. Adjuvanted vaccines, typically containing oil-in-water emulsions and lipids such as squalene or tocopherol, have also been extensively used in elderly adults in Europe to increase immunogenicity. Several of these vaccines that are in use in the elderly are in clinical trials in children, and may be available in the coming years as alternatives, where they might be particularly useful in at-risk groups where standard vaccine approaches are poorly immunogenic.

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