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ADVANCES IN PEDIATRICS

Seasonal and Pandemic Influenza

An Overview with Pediatric Focus

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Keywords
• Influenza • Children • Antiviral • Vaccination

Key Points

- Influenza viruses are constantly changing their antigenic structure. These changes allow the influenza viruses to escape from the host immunity and are responsible for the ability of these viruses to cause annual epidemics.
- Influenza viruses can cause disease among persons in any age group, but rates of illness are highest among children and those with underlying chronic medical conditions.
- The clinical presentation of influenza is variable in children at different age groups and may be atypical in infants.
- Annual influenza vaccination is the most effective strategy for the prevention and control of influenza and is recommended for all individuals 6 months of age or older.
- Influenza antiviral therapy is effective for the prevention of influenza, and, when used for treatment, can reduce the duration and severity of illness.

Influenza is a globally important respiratory pathogen, which causes nearly annual epidemics and occasional pandemics. Although influenza viruses can cause disease among persons in any age group, rates of illness are highest among children and those with conditions that increase their risk for developing influenza-related complications [1]. Annual influenza vaccination is the most effective strategy for the prevention and control of influenza and its complications, and is recommended for all individuals aged 6 months or older [2]. Antiviral therapy is effective for the prevention of influenza, and, when used for treatment, can reduce the duration and severity of illness [3–5]. This article reviews the biologic, epidemiologic, and clinical aspects of seasonal and pandemic influenza A (H1N1) infection in pediatric patients, and discusses antiviral therapy and disease prevention.

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BIOLOGY OF INFLUENZA

Structure

Influenza viruses belong to the family Orthomyxoviridae (from the Greek *myxa*, meaning mucus). They are enveloped negative-stranded, segmented RNA viruses with an average diameter of 120 nm. Currently, 3 types of influenza viruses are described (A, B, and C), which are distinguished by antigenic differences in 2 of their internal proteins, nucleoprotein (NP) and matrix protein 1 (M1). Influenza A (Fig. 1) and B viruses each contain 8 viral RNA segments, whereas influenza C has 7 viral RNA segments. In influenza A viruses, these segments encode for the 11 viral genes: hemagglutinin (HA), M1, matrix protein 2 (M2), NP, nonstructural protein 1 (NSP 1), nonstructural protein 2 (NS2), polymerase acidic protein (PA), polymerase basic protein 1 (PB1), and polymerase basic protein 2* (PB2). The viral envelope is made up of a lipid bilayer derived from the plasma membrane of the host and contains 3 of the viral transmembrane proteins: HA, NA, and M2 [6]. Sitting just underneath the viral lipid membrane is M1, which forms a matrix holding the viral ribonucleoproteins (vRNPs). These vRNPs are the core of the virus and are made up of the viral negative-stranded RNAs, which are wrapped around NP. At one end of the vRNPs are the 3 polymerase proteins (PB1, PB2, and PA) that make up the viral RNA polymerase complex [6].

Aquatic birds are the natural reservoir for type A influenza viruses, which are also found in a wide variety of other warm-blooded animals, including pigs, horses, whales, and humans. Types B and C influenza are predominantly

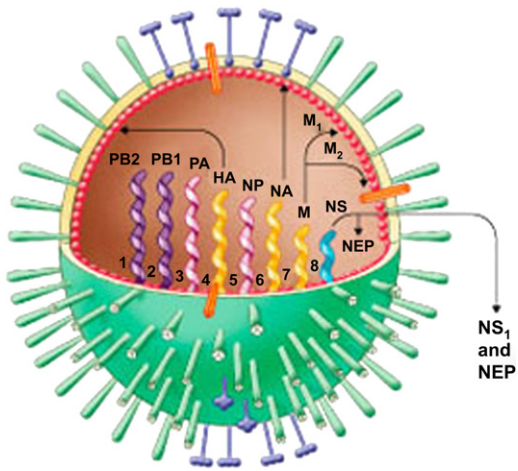

Fig. 1. Influenza virus structure. Eight segments of viral RNA are contained within the envelope and matrix (M1) shell. Each codes for 1 or 2 proteins that form the virus or regulate its intracellular replication. (*From* Hayden FG. Influenza. In: Goldman L, Schafer AI, eds. Cecil Medicine, 24th edition. Philadelphia: Saunders, 2011. *Courtesy of* Robert G. Webster, MD, Memphis, TN; with permission.)

human pathogens. Influenza A viruses are subdivided further into subtypes based on the surface antigens, HA and neuraminidase (NA). Fifteen subtypes of HA (H1–H15) and 9 subtypes of NA (N1–N9) have been described in influenza A viruses [6].

Influenza life cycle

The influenza virus binds to the cell surface by fixing the outer top of the HA to the sialic acid, the receptor for HA found on the surface of the membrane of the host cell. The sialic acid linkage to the penultimate galactose, either α2, 3 (in birds) or α2, 6 (in humans), determines host specificity. Influenza viruses from swine recognize both bird and human receptors, which explains why swine are a good mixing vessel for avian and human influenza viruses. After attachment, the virus enters the host cell in an endosome. The endosome has a low pH (around 5–6), which triggers the fusion of the viral and endosomal membranes. The acidic environment inside the endosome also opens up the M2 ion channel that acts as a proton-selective ion channel. Opening the M2 ion channels acidifies the viral core, allowing release of the vRNPs into the cytoplasm of the host cell. The vRNPs are subsequently transported to the nucleus, where transcription and replication of the viral genome take place. The newly formed RNPs leave the nucleus, then viral particles are formed, which subsequently leave the cell. Because influenza is an enveloped virus, it uses the plasma membrane of the host cell to form the virions that leave the cell and go on to infect neighboring cells. The viral NA facilitates virus release from infected cells by removing sialic acid from the viral HA protein [6,7].

IMMUNITY TO INFLUENZA INFECTION

Immunity to influenza infection is mediated by systemic and local antibodies, as well as cytotoxic T-cell responses. The first line of defense is mediated by the innate immune system. Infiltration of neutrophils and monocytes/macrophages into the lungs occurs during the initial stages of infection, followed by the recruitment of influenza-specific B and T cells [8].

Immune B cells secrete antibodies to neutralize the virus. Secretory immunoglobulin A is a major factor in resistance to natural infection in the upper respiratory tract [9,10]. Serum antibody production against HA is critical for viral neutralization, whereas antibodies against the viral NA are responsible for inhibiting virus release from the cell, thus preventing spread of the infection [11,12]. Influenza-specific CD8+ cytotoxic T lymphocytes (CTL) are believed to promote the elimination of the virus and host recovery via the production of proinflammatory cytokines, including interferon γ, and the direct killing of virus-infected cells. Once infectious virus is cleared, the CTL population contracts, leaving a pool of long-lived, antigen-specific memory CD8+ T cells capable of rapid recall to perform as effectors. This enhanced secondary response forms the basis for vaccination strategies based on priming CD8+ T-cell memory to promote early virus clearance [13].

ANTIGENIC DRIFT AND ANTIGENIC SHIFT

Influenza is continuously undergoing antigenic changes in the viral HA and, to a lesser extent, in the viral NA. These changes allow the influenza viruses to escape from the acquired immunity of the host and are responsible for the ability of these viruses to cause annual epidemics.

Antigenic drift results from point mutations that lead to a minor change in the HA or NA antigens, without resulting in a change in the viral subtype. It is responsible for the annual influenza epidemics. Antigenic shift occurs when there is a major change in the HA or NA antigens, resulting in the generation of a new influenza viral subtype. It occurs at infrequent and unpredictable intervals and occurs only with influenza A, because antigenically distinct subtypes of HA and NA occur only among influenza A viruses. Antigenic shifts have the potential to cause pandemics if the new virus subtype can be transmitted efficiently from person to person in a population with little or no preexisting immunity [14].

The 2009 pandemic H1N1 virus (2009 H1N1) has a unique combination of genes from both North American and Eurasian swine lineages that has not been identified previously in either swine or human populations [15]. The HA gene of the 2009 H1N1 belongs to the classic swine lineage and is antigenically and genetically distinct from HAs of contemporary human seasonal influenza H1N1 viruses. Because the H1 seasonal influenza subtype is currently circulating in humans, swine-origin influenza virus H1 is not a subtype new to humans; it is a virus that jumped species (from a nonhuman animal host to humans) and did not arise from previously circulating human viruses by mutation (ie, by antigenic drift) [16]. However, because most humans had no preexisting antibody to key pandemic influenza A (H1N1) virus HA epitopes, widespread transmission was possible [17].

IMPACT AND EPIDEMIOLOGY OF INFLUENZA IN CHILDREN

Annual influenza epidemics usually occur in the winter months in temperate zones. Influenza peak activity can occur any time from November to May, but most often it occurs during January or February [18]. Within a given community, an influenza epidemic may last 4 to 8 weeks or longer. Influenza A (H1N1, H3N2) usually causes annual epidemics, whereas influenza B circulates every 3 to 4 years, but both viruses can circulate during a single season. The severity of each influenza season varies and the level of mortality is highest when influenza A (H3N2) viruses predominate [19].

The most common mode of natural influenza transmission is from person to person through close contact, during which large respiratory droplets are produced during coughing or sneezing. Indirect contact transmission via hand transfer of influenza virus from contaminated surfaces or objects to mucosal surfaces of the face (eg, nose and mouth) or airborne transmission can also occur [20]. However, the relative contribution of the different modes of influenza transmission is unclear [21]. In 1 reported case, aerosol transmission is believed to have been a possible source of nosocomial transmission

from a patient receiving noninvasive ventilation to other patients on a medical ward [22].

The incubation period ranges from 1 to 4 days (average: 2 days) [23]. Influenza viral shedding in the respiratory mucosa occurs 1 day before the first symptoms and after resolution of the symptoms. In adults, the virus shedding lasts 5 to 10 days after the illness onset. In young children, viral shedding may last more than 10 days after resolution of symptoms. The peak level of virus in the respiratory secretions occurs 1 to 3 days after inoculation and correlates with the degree of fever [23,24].

Influenza infection affects 5% to 10% of the US population every year. Annual peaks of pediatric and adult acute respiratory disease (including ambulatory cases and hospital admissions) coincide with the peak activity of influenza in the community [1,25–28]. In addition, antibiotic prescriptions for children are estimated to increase by 10% to 30% during the winter months because of influenza and its complications [26].

During community-based outbreaks of influenza, the highest attack rates of infection occur in school-age children (5–18 years old), with rates reaching 70% (range 15%–70%) in some communities [29]. Children have the highest attack rates, and for this reason play a significant role in introducing and spreading influenza virus into households and throughout the community. Cases among school-age children and school absenteeism peak in the early stage of an epidemic. As the epidemic progresses, the proportions of infected adults and preschool children increase, whereas the proportion of infected school-age children decreases [30].

Young children have the highest risk of hospitalization [26,28]. Hospitalization rates among children 2 years of age or younger are similar to hospitalization rates among other groups considered at higher risk for influenza-related complications, including persons aged 65 years and older [31]. Annual hospitalization rates for laboratory-confirmed influenza decrease with increasing age, ranging from 240 to 720/100,000 children aged less than 6 months to approximately 20/100,000 children aged 2 to 5 years. Hospitalization rates for children less than 5 years of age with high-risk medical conditions are approximately 250 to 500/100,000 children [32].

Although children have the highest rates of influenza infection; older adults have the highest mortality. Previous studies report an estimated annual average of 92 influenza-associated deaths (0.4 deaths/100,000 persons) among children less than 5 years of age during the 1990s versus 32,651 deaths (98.3 deaths/100,000 persons) among adults aged 65 years or older [32]. However, half of all influenza-related deaths occur in groups with other risk factors for influenza-related complications (see later discussion) [33].

Most illnesses caused by the 2009 H1N1 influenza virus were acute and self-limited, with the highest attack rates reported among children and young adults. Also, hospitalization rates were highest among the youngest group, especially those 4 years of age or younger, and 90% of the deaths occurred in those 65 years of age or older [17]. Deaths among persons aged 65 years or older traditionally

have accounted for 90% or more of seasonal influenza-related deaths [34]. The relative sparing of adults older than 60 years of age is presumably because of the exposure of persons in this age group to antigenically related influenza viruses earlier in life, resulting in the development of cross-protective antibodies [17].

Underlying conditions that are associated with complications from seasonal influenza also are risk factors for complications from 2009 H1N1 influenza virus infection. Pregnant women (especially those in the second and third trimester) and women less than 2 weeks post partum are overrepresented among those with severe disease [35]. In addition, some studies report that obesity (body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters] $\geq$30 kg/m^2) and particularly morbid obesity (BMI $\geq$40 kg/m^2) are risk factors for hospitalization and death [17]. Additional studies are needed to determine whether obesity is a risk factor specific to the pandemic influenza A (H1N1) or a previously unrecognized risk factor for influenza-related complications caused by other influenza viruses.

CLINICAL MANIFESTATIONS

Influenza is difficult to differentiate from other acute respiratory diseases in children because the symptoms of influenza overlap with many other respiratory virus infections. In general, influenza is more commonly associated with nonspecific febrile and lower respiratory tract illnesses than other respiratory viruses [36]. The clinical presentation of influenza varies among children of different age groups [23]. In neonates and infants, influenza infection often mimics bacterial septicemia and may present only with fever without localizing signs, poor feeding, and lethargy or with nonspecific respiratory symptoms such as apnea [37]. Young children are more likely to manifest fever and upper respiratory symptoms (rhinorrhea, congestion) in addition to cough. The classic presentation of sudden onset of fever and chills accompanied by headache, sore throat, myalgia, malaise, anorexia, and nonproductive cough is more common among older children. The cough is described as a dry, hacking cough that peaks after 3 to 4 days and persists for more than 1 week after resolution of the other symptoms. Sore throat occurs in more than half of the cases and usually is associated with nonexudative pharyngitis. Ocular symptoms including tearing, photophobia, and burning also can occur [23,38,39].

Gastrointestinal symptoms, including vomiting, abdominal pain, and diarrhea, are more common in children than in adults [40]. Influenza infection can cause febrile seizures in infants and young children, with a reported rate of approximately 5% [39,41]. Other clinical manifestations of influenza infection include a crouplike syndrome that may be more severe than the croup caused by parainfluenza viruses, with a higher fever and more tenacious secretions. Airway compromise is often more severe and is sometimes complicated by bacterial superinfection [42].

Bronchopneumonia secondary to influenza occurs in 10% to 50% of cases, but most episodes are mild and associated with complete recovery. Rarely, influenza pneumonia can be fatal in previously healthy individuals [43].

Influenza-associated otitis media occurs in 3% to 5% of cases annually. Acute otitis media typically manifests 3 to 4 days after the onset of upper respiratory tract symptoms [44]. Concurrent viral and bacterial middle-ear infection significantly worsens the course of acute otitis media [44,45].

There is little published information about the differences in clinical presentations between influenza A and B infections. A recent study suggested that children with influenza B are older, and appear less ill than those with influenza A. This study also reported a higher incidence of myalgia and myositis with influenza B [39].

In most children without underlying risk factors for severe influenza, the pandemic influenza A (H1N1) causes an uncomplicated respiratory tract illness, signs, and symptoms similar to those associated with influenza B, and no more severe than seasonal influenza [46]. Similar to previous pandemics, secondary bacterial infection with *Streptococcus pneumoniae* and *S pyogenes* were associated with the 2009 H1N1 outbreak [17,47].

DIAGNOSIS

The nonspecific clinical presentation of influenza in children emphasizes the importance of laboratory diagnosis. A rapid diagnosis of influenza reduces the use of unnecessary tests and antibiotics in pediatric patients, and allows rational use of antivirals, early discharge from the hospital, and appropriate infection control measures. In addition, isolation and identification of circulating strains are critical to the preparation of annual vaccines [48–50].

Respiratory specimens should be obtained during the first 72 hours of illness because the amount of virus shed decreases rapidly beyond this point. False-negative results occur, especially for samples collected very early or late after the onset of symptoms. Nasopharyngeal aspirates and washes, followed by nasopharyngeal swabs and miniturbinate swabs, are preferred over throat swabs for detection of influenza. Combining 2 swabs, 1 from each nostril, into 1 vial further enhances viral load [51].

Conventional viral cell culture remains the gold standard for diagnosis of influenza infection, but time to detection ranges from 2 to 14 days, with a median of 3 to 5 days. Diagnosis by cell culture relies on infectious virus and is less sensitive than polymerase chain reaction (PCR) tests. Rapid cultures have replaced conventional cultures in many laboratories because they are simpler to master and faster to complete, with results available in 1 to 3 days [52].

Antigen detection assays are based on the detection of viral proteins by specific antibodies. They are simple to perform and provide results in 10 to 30 minutes; for this reason, these tests are the most commonly used diagnostic tests for influenza. However, although their specificity is generally high (96%–99%), their sensitivity varies by kit, ranging from 60% to 83% for seasonal influenza and 40% to 59% for novel H1N1 [53]. Because of the high false-negative results, the US Centers for Disease Control and Prevention (CDC) advise that antiviral therapy should not be withheld because of a negative rapid antigen detection assay [54].

Direct fluorescent assay (DFA) detects viral antigens in exfoliated respiratory epithelial cells applied to microscope slides, allows assessment of sample quality, and is more sensitive than rapid antigen detection tests. Results are available within 2 hours, and DFA detects 85% to 95% of culture-positive results. However, DFA requires expertise for accurate interpretation, and sensitivities and specificities vary between laboratories [55].

With a sensitivity of 98% and positive predictive value of 100%, reverse transcriptase PCR (RT-PCR) test is one of the most accurate and sensitive tests for detecting influenza viruses, including the pandemic influenza A (H1N1) [21]. The time required for testing and the limited availability of RT-PCR capable of subtyping limit the usefulness of this test for medical management of individual patients. RT-PCR tests for seasonal influenza are unable to provide subtyping information when used to test specimens from patients with 2009 H1N1 virus infections. RT-PCR tests for the detection of 2009 H1N1 virus were developed by the CDC and distributed to state public health and other reference laboratories. One RT-PCR test that can distinguish 2009 H1N1 from other influenza A viruses has been approved by the US Food and Drug Administration, and this test seems to have similar sensitivity and specificity compared with the test developed by the CDC [21].

COMPLICATIONS

Children at higher risk of complications from influenza include children with underlying chronic illness such as cardiac, pulmonary, immunologic, or neurologic disease [32]. However, influenza-associated deaths occur in both children with underlying medical conditions and healthy children. In 2003 to 2004, 47% of influenza-associated pediatric deaths occurred in previously healthy children [56].

Bacterial infections of the respiratory tract, particularly pneumonia and otitis media, are the most common complication of influenza [45]. The incidence of complicating bacterial infections in community studies, including children of all ages, is approximately 10%, and otitis media is the most frequent finding [57]. Studies of vaccine effectiveness support reports that influenza-associated acute otitis media occurs in 30% to 40% of children in day care during the respiratory disease season [58]. The proposed mechanisms for the development of acute otitis media after influenza infection include eustachian tube dysfunction, direct invasion of middle-ear epithelium, alteration of leukocyte function, enhanced adherence of bacteria to respiratory tract epithelial cells, and decreased mucociliary clearance [5].

Secondary bacterial pneumonia is characterized by fever and a productive cough during convalescence, along with radiologic evidence of lobar consolidation [41]. Although most cases of bacterial pneumonia as a complication of influenza are pneumococcal [59], the 2 most severe pulmonary complications are progressive primary viral pneumonia and staphylococcal pneumonia. Progressive primary viral pneumonia has been observed most frequently in adult patients with preexisting rheumatic heart disease, but it may occur in previously healthy children as well [26,28]. Staphylococcal pneumonia may occur as

a postinfluenza lobar pneumonia progressing to pneumatoceles and empyema. Necrotizing pneumonitis with microabscesses and positive lung cultures for both influenza A virus and *Staphylococcus aureus* are characteristic [34].

Among children at high risk for complications of influenza, most have asthma; children with a history of stable asthma can experience an acute exacerbation, with progression to status asthmaticus during an influenza infection [33].

Acute myositis occurs in the setting of early convalescence from a typical influenza illness [60]. The onset of severe pain and tenderness in the calves of both legs is sudden, and the patient often refuses to walk. The gastrocnemius and soleus muscle groups are affected in virtually all cases. Increased levels of serum creatine kinase and aspartate aminotransferase are characteristic. This complication occurs more commonly after infection with influenza B versus influenza A [60]. The condition generally is self-limited, but rhabdomyolysis with myoglobinuria and acute renal failure have been described [61].

Pericarditis and myocarditis with electrocardiographic changes and increased levels of cardiac enzymes are rarely noted in association with influenza A and B infection. It has been described in healthy adults and children as well in those with preexisting heart disease [62,63].

Influenza infection has been associated with a variety of neurologic complications, including seizures, Reye syndrome, Guillain-Barré syndrome, transverse myelitis, and encephalopathy. Seizures are the most frequently reported neurologic complication, with most believed to be febrile seizures in young children [45]. Influenza encephalopathy manifests with sudden onset of fever, convulsion, and rapid progression to coma. Radiologic imaging reveals bilateral thalamic necrosis and brainstem involvement in some cases. In most reported cases, influenza infection was not shown in the cerebral fluid or brain. There is a high fatality rate, with severe neurologic damage in survivors. The pathogenesis of this illness remains uncertain but may result from direct viral invasion of the central nervous system or from high levels of proinflammatory cytokines that breach the blood-brain barrier, or from another factor such as medications used to treat influenza [31]. Reye syndrome (encephalopathy and fatty degeneration of the liver) has become uncommon since the association between concomitant influenza infection and the use of aspirin was recognized [64].

Although influenza can cause severe disease in pregnant women, and evidence of the transplacental passage of influenza virus to a 30-week-old male fetus has been reported [65], there is no epidemiologic evidence of influenza virus teratogenicity.

TREATMENT

Two classes of antiviral agents are licensed for treatment and prophylaxis of influenza infection in the United States: adamantanes (rimantadine and amantadine) and the NA inhibitors (NI) oseltamivir and zanamivir. The adamantanes are effective only against influenza A viruses; they block the influx of H^+ ions through the M2 ion channel, interfering with viral uncoating inside the cell. The NIs have activity against influenza A and B viruses and they

inhibit the enzyme NA, thus preventing the release of new virions from the infected cell surface [66]. Currently, all circulating influenza A viruses are resistant to the adamantanes and these agents are therefore not recommended for the treatment of influenza infections in the United States [2]. The pandemic influenza A (H1N1) that is currently circulating is susceptible to the NIs oseltamivir and zanamivir, but is almost always resistant to amantadine and rimantadine [17]. However, antiviral resistance can emerge from one season to the next and resistance patterns of influenza strains might lead to new guidance. Clinicians should verify susceptibility information at the start of the influenza season and monitor it during the season through either the American Academy of Pediatrics (AAP) Web site (http://www.aap.org) or the CDC Web site (http://www.cdc.gov/flu).

The AAP recommends antiviral treatment of: all children hospitalized with presumed influenza or with severe, complicated, or progressive illness, regardless of influenza immunization status; all children with presumed influenza at high risk for influenza-associated complications regardless of influenza severity; and any otherwise healthy child with influenza for whom a decrease in duration of clinical symptoms is warranted [2]. Treatment may also be considered for previously healthy outpatients with confirmed or suspected influenza if treatment can be initiated within 48 hours of illness onset [21]. From epidemiologic studies of patients with seasonal influenza or pandemic influenza A (H1N1), persons at higher risk for complications from influenza include:

Children younger than 2 years
Adults 65 years of age or older
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic (including diabetes mellitus) disorders or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, or any condition that compromises respiratory function or handling of secretions or that can increase the risk of aspiration
Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus (HIV) infection
Women who are pregnant or in the postpartum period (within 2 weeks after delivery)
Persons younger than 19 years who are receiving long-term aspirin therapy
American Indian/Alaska Native persons
Persons who are morbidly obese (ie, BMI $\geq$40 kg/m^2)
Residents of nursing homes and other chronic care facilities [2].

There is emphasis on the use of early (<48 hours) empiric antiviral therapy for suspected influenza, because earlier treatment provides more optimal clinical responses and should not be delayed while waiting for a definitive influenza test result. However, treatment initiated later than 48 hours after the onset of symptoms in children with moderate to severe disease or with progressive disease may still be beneficial [2].

Table 1 summarizes the dosage and schedule of influenza antiviral medications for treatment and chemoprophylaxis for the 2011 to 2012 influenza season in the United States [2]. Oseltamivir was the drug of choice to treat seasonal and pandemic influenza A (H1N1) during this past season. In a randomized, double-blind, placebo-controlled study that evaluated oseltamivir in 452 children 1 to 12 years of age with influenza, oseltamivir treatment was associated with rapid resolution of the fever when given within 48 hours of the onset of illness. There was also a 44% reduction in the number of patients with otitis media, resulting in a concomitant 40% reduction in antibiotic use [67]. Oseltamivir has been reported to be less effective against influenza B in young children (≤5 years of age) compared with older children, probably because of the low sensitivity of influenza B viruses to oseltamivir [68].

The incidence of oseltamivir resistant virus has been described to be approximately 5% to 6% in children [67] and 1% to 2% in adults [69]. Because renal clearance of the active carboxylate metabolite of oseltamivir is significantly higher in younger than in older children and adults, the dose must be adjusted based on age [70]. The most common adverse effects of oseltamivir are nausea and vomiting. Postmarketing reports, mostly from Japan, have noted self-injury and delirium associated with approximately 1 in 100,000 oseltamivir prescriptions, primarily in adolescents [31]. Recent data suggest that these events were related to influenza disease rather than antiviral medication [71]. Zanamivir is licensed for the treatment of influenza in children 7 years of age or older. This drug is not orally active and is administered by inhalation, which consequently limits its potential for use in children aged 5 years or younger. Zanamivir use has been associated with bronchospasm in some people and is not recommended for use in patients with underlying airway disease such as asthma [2]. For patients who are intubated, use of the zanamivir disk inhaler is not possible because the licensed powder formulation contained in the disk inhaler can clog ventilator tubing [2]. Zanamivir does not require dosing adjustment for renal insufficiency, given that it is administered as an inhalant.

The recommended duration of antiviral therapy is 5 days. Longer treatment regimens might be necessary in severely ill hospitalized patients or persons with immunosuppression [31].

No antiviral agent is approved for use in infants younger than 12 months of age. During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children aged less than 1 year were developed from limited pharmacokinetic data. Although the recommendation for this indication expired on June 23, 2010, recommendations for the use of oseltamivir in this young age group can still be followed and are provided in Table 1 [2].

Weight-based dosing recommendations for full-term infants are believed to be inappropriate for premature infants, who might have slower clearance of oseltamivir as a result of immature renal function, resulting in excessively high plasma concentrations of the drug. Therefore, the data currently available are insufficient to recommend a specific dose of oseltamivir for premature infants [72].

Table 1
Recommended dosage and schedule of influenza antiviral medications for treatment and chemoprophylaxis for the 2011 to 2012 influenza season: United States

Medication	Treatment (5 d)	Chemoprophylaxis (10 d)
Oseltamivir[a]		
Adults	75 mg bid	75 mg qd
Children >12 mo		
Body weight		
≤15 kg (≤33 lb)	30 mg bid	30 mg qd
>15–23 kg (33–51 lb)	45 mg bid	45 mg qd
>23–40 kg (>51–88 lb)	60 mg bid	60 mg qd
>40 kg (>88 lb)	75 mg bid	75 mg qd
Children 3 to <12 mo[b]	3 mg/kg per dose bid	3 mg/kg per dose qd
Children 0 to <3 mo[c]	3 mg/kg per dose bid	Not recommended unless situation judged critical, because of limited data on use in this age group
Zanamivir[d]		
Adults	10 mg (two 5-mg inhalations) bid	10 mg (two 5-mg inhalations) qd
Children (≥7 y for treatment, 5 y for chemoprophylaxis	10 mg (two 5-mg inhalations) bid	10 mg (two 5-mg inhalations) qd

[a]Oseltamivir is manufactured by Roche Laboratories (Nutley, NJ) and is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu in 30-mg, 45-mg, and 75-mg capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL. The volume of oral suspension is being changed from 12 mg/mL to 6 mg/mL this year to reduce frothing when shaken. Oral suspensions in 12-mg/mL concentrations remain available until supplies run out. For the 6-mg/mL suspension, a 30-mg dose is given with 5 mL of oral suspension, 45-mg dose is given with 7.5 mL oral suspension, 60-mg dose is given with 10 mL oral suspension, and 75-mg dose is given with 12.5 mL oral suspension. If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste, or a suspension can be compounded by retail pharmacies (final concentration: 15 mg/mL). For patients with renal insufficiency, the dose should be adjusted by creatinine clearance rate. For treatment of patients with a creatinine clearance rate of 10 to 30 mL/min: 75 mg once daily for 5 days. For chemoprophylaxis of patients with a creatinine clearance rate of 10 to 30 mL/min: 30 mg once daily for 10 days after exposure or 75 mg once every other day for 10 days after exposure (5 doses). (See http://www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm.)

[b]Weight-based dosing is preferred: however, if weight is not known, dosing according to age for treatment (2 doses per day) or prophylaxis (1 dose per day) of influenza in term infants younger than 1 year may be necessary: 0 to 3 months (treatment only), 12 mg (2 mL of 6 mg/mL commercial suspension); 4 to 5 months, 17 mg (2.8 mL of 6 mg/mL of commercial suspension); 6 to 11 months, 24 mg (4 mL of 6 mg/mL commercial suspension). Although Emergency Use Authorization recommendations for use of oseltamivir in children younger than 1 year expired on June 23, 2010, this drug remains appropriate for use when indicated.

[c]Current weight-based dosing recommendations are not intended for preterm infants. Preterm infants may have slower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to high drug concentrations in this age group. Limited data from a cohort of preterm infants who received an average dose of 1.7 mg/kg twice daily revealed drug concentrations higher than those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among preterm infants. These data are insufficient to recommend a specific dose of oseltamivir for preterm infants.

[d]Zanamivir is manufactured by GlaxoSmithKline (King of Prussia. PA) and is administered by inhalation using a proprietary Diskhaler device distributed together with the medication. Zanamivir is a dry powder (not an aerosol) and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for persons with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease that increase the risk of bronchospasm.

Data from Fiore AE, Fry A, Shay D, et al. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza–recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(RR-1):1–24; *From* American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2011–2012. Pediatrics 2011;128:822; with permission.

PROPHYLAXIS

Influenza vaccines

Annual influenza vaccination is the most effective method for preventing influenza infection and its complications. Two influenza vaccines are currently available in the United States to prevent infection in the pediatric population: injectable trivalent inactivated influenza vaccine (TIV) and intranasally administered live-attenuated influenza vaccine (LAIV). Both LAIV and TIV contain strains of influenza viruses that are equivalent antigenically to the annually recommended strains: 2 influenza A viruses (H3N2 and H1N1) and 1 influenza B virus. The 2011 to 2012 vaccine contains A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The vaccine composition for the 2011 to 2012 season was unchanged from the 2010 to 2011 influenza season. A comparison between the 2 influenza vaccines recommended to prevent influenza infection during the 2011 to 2012 season is summarized in Table 2.

Current recommendations for influenza vaccination

Routine influenza vaccination is recommended for all persons aged 6 months or older. Efforts should be made to vaccinate people in the following groups [2]:

- All children, including infants born prematurely, 6 months of age and older with conditions that increase the risk of complications from influenza
- All household contacts and out-of-home care providers of children with high-risk conditions (see earlier discussion) and children younger than 5 years
- All health care personnel
- All women who are pregnant, considering pregnancy, or breastfeeding during the influenza season

The number of trivalent seasonal influenza vaccine doses to be administered depends on the child's age at the time of the first administered dose and their vaccine history:

- No influenza vaccine is licensed for infants younger than 6 months.
- Children 6 months to 8 years who did not receive any dose of vaccine last season require 2 doses of vaccine administrated at least 4 weeks apart.
- For children 6 months to 8 years of age who had received at least 1 dose of the 2010 to 2011 trivalent seasonal influenza vaccine (regardless if it was the first time receiving influenza vaccine or not), only 1 dose of the 2011 to 2012 influenza vaccine was recommended. The first vaccine dose primes the immune system and the second dose gives the adequate protection [73]. Because the vaccine strains for the 2011 to 2012 season were unchanged from the last season, 1 dose this season coupled with 1 dose of last season provides adequate protection.
- Children 9 years of age and older need only 1 dose.

Although the above recommendations were made to the 2011-2012 influenza season, it is recommended use them as a guide to vaccination until recommendations to the 2012-2013 season are available from the CDC.

Table 2
LAIV compared with TIV

Vaccine characteristic	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular or intradermal injection[a]
Type of vaccine	Live virus	Killed virus
Product	Attenuated, cold-adapted	Inactivated subvirion or surface antigen
Number of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration[b]	Annually	Annually
Approved age groups	All healthy persons aged 2–49 y	All persons aged >6 mo (intradermal 18–64 y)
Interval between 2 doses in children	4 wk	4 wk
Can be given to persons with medical risk factors for influenza-related complications	No	Yes
Can be given to children with asthma or children aged 2–4 y with wheezing in the previous year	No[c]	Yes
Can be simultaneously administered with other vaccines	Yes[d]	Yes[d]
If not simultaneously administered, can be administered within 4 wk of another live vaccine	No, prudent to space 4 wk apart	Yes
Can be administered within 4 wk of an inactivated vaccine	Yes	Yes

[a]The preferred site of TIV intramuscular injection for infants and young children is the anterolateral aspect of the thigh.
[b]See Fig. 3 for decision algorithm to determine the number of doses of 2011 to 2012 seasonal influenza vaccine recommended for children this year [2].
[c]LAIV is not recommended for children with a history of asthma. In the 2-year to 4-year age group, there are children who have a history of wheezing with respiratory illnesses in whom reactive airways disease is diagnosed and in whom asthma may later be diagnosed. Therefore, because of the potential for increased wheezing after immunization, children 2 to 4 years of age with recurrent wheezing or a wheezing episode in the previous 12 months should not receive LAIV. When offering LAIV to children in this age group, a clinician should screen those who might be at higher risk of asthma by asking the parents/guardians of 2-year-olds, 3-year-olds, and 4-year-olds (24-month-olds to 59-month-olds) the question, ''In the previous 12 months, has a health care professional ever told you that your child had wheezing?'' If the parents answer ''Yes'' to this question, LAIV is not recommended for these children.
[d]LAIV coadministration has been evaluated systematically only among children 12 to 15 months of age with measles-mumps-rubella and varicella vaccines. TIV coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide and zoster vaccines.

Data from American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2010–2011. Pediatrics 2010;126(4):816–26; and Fiore AE, Fry A, Shay D, et al. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza–recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(RR-1):1–24. *From* American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2011-2012. Pediatrics 2011;128:822; with permission.

Vaccination begins in September or whenever the vaccine becomes available and should continue through the influenza season, which can have more than 1 disease peak and often extends into March or later.

This approach provides opportunity to administer a second dose of vaccine, because children younger than 9 years might require 2 doses to confer optimal protection. Annual influenza immunization is recommended because immunity decreases during the year after immunization and because in most years, at least one of the vaccine antigens is changed to match ongoing antigenic changes in circulating strains.

Influenza vaccine to egg-allergic children

The influenza vaccine contains small but variable amounts of egg protein, therefore severe egg allergy has long been considered a contraindication to administration of the influenza vaccine [4]. However, new data suggest that a single, age-appropriate dose of an influenza vaccine with an ovalbumin content up to 0.7 μg/0.5 mL of a vaccine dose has been well tolerated by nearly all recipients who have egg allergy [2]. More conservative approaches, such as skin testing or a 2-step graded challenge, are no longer recommended. Influenza vaccine can be given to children with a history of mild allergic reaction to eggs that is defined as hives alone. Appropriate resuscitative equipment must be readily available and the vaccine recipient should be observed in the office for 30 minutes (the standard observation time after receiving immunotherapy). If a second dose is needed, the same product brand, but not necessarily the same lot as the first dose, is preferred. Children with a history of severe allergic reaction to eggs (defined as severe reactions with systemic cardiovascular, respiratory, and gastrointestinal changes, or reactions that require the use of epinephrine) should have an allergist consult before influenza vaccine is given. No data are available to support the use of LAIV in children with a history of egg allergy [2].

Influenza chemoprophylaxis

Chemoprophylaxis should be considered during periods of influenza activity in children 1 year or older who are at high risk of developing influenza-associated complications and in whom vaccination has not been received or is contraindicated. It should be considered in high-risk children during seasons when the influenza vaccine is documented to have low clinical effectiveness in preventing infection. It also should be considered in high-risk patients during the first 2 weeks after vaccination when antibody immune response is still inadequate. In children who were not previously vaccinated and require 2 doses, the period of inadequate immune response extends to 6 weeks from the first vaccine dose, and chemoprophylaxis should be continued through this period in high-risk patients. In these circumstances, only the inactivated influenza vaccine should be administered because antiviral medications can reduce the effectiveness of the live, attenuated influenza vaccine [31]. In household members exposed to influenza, the efficacy of preventing infection in individuals was 68% to 89% with oseltamivir [74,75] and 79% to 82% with zanamivir [76,77].

SUMMARY

Influenza is an important cause of respiratory illness in children, who have the highest attack rates during the annual influenza outbreaks [60]. Clinical infection ranges from subclinical illness to complicated disease that affects multiple organs. Annual vaccination remains the most effective strategy for the prevention and control of influenza [2]. Recently developed antiviral drugs offer new approaches to the prevention and treatment of influenza.

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