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RELIAS MEDIA

# Viral Influenza Infection and Complications: A Pediatric-focused Review

*As influenza season approaches, it is important that clinicians prepare themselves with the current literature on clinical presentation, best and most rapid diagnostic testing, and treatment strategies in pediatric patients. The literature shows that antiviral agents are underutilized in children, a critical issue for this vulnerable population. The authors provide insight and evidence for diagnostic and therapeutic practice for the upcoming influenza season.*

*— Ann M. Dietrich, MD, FAAP, FACEP, Editor*

Influenza is one of the most common viral respiratory pathogens to infect infants and children and leads to significant morbidity and mortality. It is caused by a virus of the Orthomyxoviridae family and has three known serotypes — A, B, and C. The term comes from the Greek *myxa* meaning mucus,[1] and clinical presentation commonly includes acute febrile illness with myalgia, headache, and cough.[2] Influenza occurs in annual outbreaks mostly during the winter season, and activity varies depending on antigenic drifts of the virus along with the susceptibility of the population. It is estimated that nearly one in every 1,000 children younger than 5 years of age will be hospitalized each year with seasonal influenza, and for every child admitted to a hospital, another 50 are seen in an outpatient setting.[3] The total economic burden of annual influenza-related illnesses was estimated at $87.1 billion in direct medical expenses in 2003,[4] and likely has increased since that time.

## Virology

Hosts for type A influenza viruses vary and include aquatic birds and other animals, such as pigs, horses, and whales, in addition to humans. Types B and C influenza predominantly are human pathogens.[1] Although influenza A naturally infects hundreds of bird species, human infection and transmission has been limited to three hemagglutinin (HA) glycoproteins and two neuraminidase (NA) enzymes in three combinations: H1N1, H2N2, and H3N2.[5] Since swine are susceptible to infection from both avian and human strains, they function as mixing vessels for pathogenic and, occasionally, pandemic strains of influenza that infect humans, such as the one that occurred in 2009, known as "swine flu" involving the H1N1 strain.

The influenza virus undergoes two types of changes — antigenic drift and antigenic shift. Each year, influenza virus undergoes small mutational changes known as antigenic drifts, leading to the seasonal variation of influenza A and varying annual outbreaks. Over time, these small changes can result in a new viral strain that is antigenically different from the virus recognized by the host immune system, resulting in seasonal epidemics.[1] Antigenic shifts occur less commonly, but more abruptly, resulting in a new surface HA and NA combination due to mixing of surface antigens from two or more different viral strains, often of a different subtype. The risk of influenza pandemic is greater after antigenic shifts, particularly because the population has no

## EXECUTIVE SUMMARY

- Influenza is caused by a virus of the Orthomyxoviridae family and has three known serotypes — A, B, and C. During community-based outbreaks of influenza, the highest rates of infection occur in children 5-18 years of age.
- The incubation period for influenza has been shown to be between one and four to seven days. Viral shedding in the respiratory mucosa occurs approximately one day before the onset of symptoms and lasts at least until symptoms resolve (between four to 8.5 days). Children and younger adults may shed and transmit influenza for more than 10 days after symptoms resolve, while immunosuppressed persons may shed the virus for weeks.
- Although influenza vaccine effectiveness can range widely from season to season, it is the most effective method to prevent influenza. Influenza vaccination reduced the likelihood of influenza-associated death in children by 65%.
- Symptoms of influenza include fever, cough, dyspnea, tachypnea, conjunctivitis, epistaxis, acute otitis media, headache, myalgia, arthralgia, and fatigue. A recent study suggested that children with influenza B are older, appear less ill than those with influenza A, and present with a higher incidence of myalgia, myositis, and pharyngitis.
- The incidence of influenza-associated otitis media is 3-5% of cases annually and may be as high as 30-40% in children who attend daycare during respiratory disease season. Symptoms typically present three to four days after the onset of upper respiratory infection symptoms.
- The incidence of influenza-associated pneumonia hospitalizations was estimated to be highest in children younger than 2 years of age. Children with asthma were more likely to have a pathogen found than those without asthma.
- The most frequently reported neurologic complication is seizures, which occur in approximately two-thirds of patients hospitalized for influenza, of which febrile seizures make up the majority.
- Studies show that oseltamivir was associated with a 39-44% decrease in risk of otitis media, 53% decrease in risk for pneumonia, and 28% decrease in risk for respiratory illness as well as reduced incidence of sinusitis and bronchitis. In a separate retrospective study, children from 1 to 12 years of age who received oseltamivir within 24 hours of diagnosis had a 52% reduction in subsequent medical encounters and fewer outpatient and ED visits.

or minimal pre-existing immunity against the novel influenza strain.[6] In addition, although clinical symptoms are similar, the severity is greater in novel strain infections compared to seasonal strains. This is evidenced by higher viral load, more exuberant cytokine response, and mortality of approximately 60% for infection with the novel strain of H5N1 after it reemerged in 2003.[7]

## Epidemiology

Each year, the spread of influenza depends on multiple factors, including the occurrence of antigenic shifts, the transmissibility of the virus, and the susceptibility of the population. The population-based risk for influenza-related hospitalizations in the United States is as high as 150 per 100,000, with as many as 125 deaths annually.[8] During peak season, it is estimated that incidence of influenza in children with influenza-like-illness (ILI) is as high as 40%.[8] During community-based influenza outbreaks, the highest rates of infection occur in school-age children (5-18 years of age), with rates reaching up to 70% in some communities.[1] Because children have the highest infection rates and shed the virus for longer periods than adults, they play a large role in introducing and spreading influenza virus throughout the community.[9]

**Activity.** The timing of influenza activity varies and can occur any time between November and May, with peak activity in the United States occurring most commonly between December and February.[1,6,10,11] In temperate zones, annual influenza epidemics usually occur in the winter months and may last one to two months. Influenza may circulate year-round in equatorial regions.[5] Influenza A (H1N1, H3N2) usually causes annual epidemics, whereas influenza B circulates every three to four years, although both may be present during any given season. Seasonal severity varies, with the highest mortality reported when influenza A (H3N2) viruses predominate.[1] In the 2017-2018 influenza season, influenza A (H3N2) viruses predominated.

Influenza affects between 5-20% of people in all age groups each year, leading to an estimated cost burden of $26.7 billion.[12] A study that categorized 1,737 influenza-positive patients by age showed that 9.4% of patients were 0-4 years, 27.3% were 5-24 years, 33.2% were 25-64 years, and 30.1% were ≥ 65 years, with influenza A (H3N2) viruses dominating across all age groups.[10] Almost 80% of influenza-associated hospitalizations were due to influenza A.[13] The largest proportion of reported influenza B viruses occurred in persons 5-24 years of age, accounting for 16.6% of the viruses reported for that age group.

From 2010 through 2016, the incidence of symptomatic influenza among U.S. residents, both vaccinated and unvaccinated, was approximately 8% and varied from 3-11% between seasons, with the majority of infections in children 0-17 years (9.3%), followed by adults 18-64 years (8.9%), then adults older than 65 years (3.9%).[14] Despite similar infection rates, children who were unvaccinated were at increased risk of mortality in the 2017-2018 season. Among 171 laboratory-confirmed pediatric deaths secondary to influenza, of 138 children who were eligible for influenza vaccination (age ≥ 6 months at date of onset) and for whom vaccination status was known, only 22% had received at least one dose of influenza vaccine before illness onset, indicating that 78% of pediatric deaths were in children who did not receive the influenza vaccine.[15]

## Transmission

The primary mode of natural influenza transmission is through close contact from person to person, and it is spread via large respiratory droplets produced during coughing or sneezing.[6] Indirect contact transmission occurs via hand transfer of influenza virus from fomites (contaminated surfaces or objects) to mucosal surfaces of the face (e.g., nose and mouth); airborne

transmission also can occur.[1] Furthermore, fecal oral transmission via fecally contaminated fomites also is possible, particularly in patients who present with diarrhea.[6] Patients with suspected influenza infection should be placed on standard and droplet precautions to decrease transmission.

In general, the incubation period for influenza has been shown to be between one and four to seven days.[5,16] Viral shedding in the respiratory mucosa occurs approximately one day prior to symptom onset and lasts at least until symptoms resolve — on average between four to 8.5 days.[1,16] Children and younger adults may shed and transmit influenza for more than 10 days after symptoms resolve,[1,11] while patients who are immunosuppressed may shed the virus for weeks. Viral shedding is greatest during periods of high fever.[6] The viral load peak occurs on the day of symptom onset and may correlate with the degree of fever,[5] usually one to three days after inoculation, then decreases gradually thereafter.[1,16] Patients are most infectious during the 24 hours prior to symptom onset and during the first three to seven days of illness.[6]

## Burden of Disease

Seasonal influenza is an important cause of morbidity and mortality in children, leading to an estimated 600,000 to 2.5 million influenza-associated outpatient medical visits.[17] Annual peaks of pediatric and adult acute respiratory disease coincide with the time of peak influenza activity in the community, both in ambulatory and hospital settings.[1] Most children with mild uncomplicated forms of influenza are treated in the outpatient setting.[18] Studies have shown that an additional seven to 12 medical examinations and an additional five to seven antibiotic prescriptions are needed for every 100 children during the influenza season.[9] In a retrospective review of nearly two decades of Medicaid data, researchers found that influenza accounted for up to 35% of excess outpatient visits in young children and up to 30% of excess antibiotic use in children during the winter,[6] a well-known burden of the disease. Influenza leads to significant increases in school and work absences after initial outpatient presentation.[1,18] Still, the overall burden of pediatric influenza may be underestimated because of possible underutilization of rapid influenza tests.[18]

In the United States, influenza is associated with an estimated 54,000 to 430,000 hospitalizations and 3,000 to 49,000 deaths annually,[19] with infants and children younger than 5 years of age at higher risk. Infants and children younger than 5 years of age account for an estimated 6,000 to 26,000 hospitalizations per year in recent U.S. seasons.[17] One study in England found that healthy children younger than 5 years of age had the highest hospital admission rate of 1.9 per 1,000,[20] and other studies have shown a rate of hospitalization of approximately 2.5 to five per 1,000 children younger than 5 years of age with high-risk medical conditions.[1] Hardelid et al found that 85% of influenza-related hospital admissions in children ages 6 to 23 months occurred in those who were not known to be in a clinical risk group; however, prematurity increased the risk of influenza-associated hospitalizations by 47%.[21] More than half of children hospitalized for influenza between October 2017 and March 2018 had at least one underlying medical condition, with asthma, neurologic disorders, and obesity among the most commonly reported.[13] In 2009, neurologic disorders were the most commonly reported high-risk condition at 33%, followed by asthma at 16%, chromosomal/genetic abnormality at 12%, congenital heart diseaseat 11%, and pulmonary disorder at 6%.[19] In addition to contributing to high rates of hospitalization in children 17 years of age or younger, a study identified pneumonia and influenza as major causes of death for children 29 days to 9 years of age.[22]

Although children have the highest rates of influenza infection, mortality is highest in older adults.[1] Globally, influenza is associated with up to 500,000 deaths annually, with estimates ranging between 291,243 to 645,832.[20,23] An estimated 9,243 to 105,690 influenza-associated respiratory deaths occur worldwide each year among children younger than 5 years of age.[23] Influenza-associated pediatric deaths likely are underreported. Since mortality from influenza became a nationally notifiable condition in 2004, influenza testing may not be performed routinely, and clinical data are limited, missing many deaths that occur outside the hospital setting.[24] In the United States, there are more than 100 influenza-associated deaths among children younger than 18 years reported per year during non-pandemic seasons, with 358 deaths reported during the 2009 pandemic.[17,19,25] During the 2014-2015 to 2017-2018 influenza seasons, there were 93-148 pediatric deaths per season based on the Centers for Disease Control and Prevention (CDC) influenza surveillance report.[13] In the United States, pediatric deaths peak in February-March at a median age of 6-7 years in primarily undervaccinated children; these deaths primarily were attributed to influenza A virus infections.[19,25,26]

## Vaccination

Every year brings variability in influenza activity, strain virulence, and population immunity to circulating strains, which makes assessing the effect of vaccination policy problematic.[27] Nonetheless, vaccination has been shown to have a positive effect on influenza infection and can reduce costs.[20] Vaccination of otherwise healthy daycare and school-aged children directly and indirectly can reduce influenza-related costs associated with the children and their unvaccinated household contacts. This supports the recommendation to expand influenza vaccinations in healthy children of any age to reduce the burden of the infection on the community.[9] Although the effectiveness of the influenza vaccine can vary widely from season to season, influenza vaccination is the most effective method currently available to prevent influenza and its complications.[10] Despite this, less than half of the U.S. population was vaccinated in recent influenza seasons.

Inactivated vaccines and live attenuated vaccines reduce the proportion of confirmed influenza cases in children by at least 19% and 14%, respectively.[2] In a study examining effectiveness of seasonal vaccination against pediatric intensive care unit (PICU) admission in the 2010-2011 and 2011-2012 seasons, children 6 months through 18 years of age who were fully vaccinated with either inactivated influenza vaccine (IIV) or live attenuated influenza vaccine (LAIV) were 74% less likely to be admitted to the PICU for influenza than unvaccinated children. In addition, vaccination reduced the likelihood of influenza-associated death among children by 65%.[17]

Recommendations for vaccination are based on previously identified risk factors for serious outcomes in people with influenza virus infection and vary by country.[28] Experts in Canada and the United States recommend universal influenza vaccination, while the primary focus in most European countries is on vaccinating individuals at greatest risk.[21] Vaccination rates vary from 24-52% among both universal

and targeted vaccination strategies, and only a few countries outside of North America recommend influenza vaccines for healthy children, regardless of the World Health Organization (WHO) Advisory Committee on Immunization Practices (ACIP) recommendations.[21,29] The main barriers to vaccination include lack of knowledge and awareness of influenza and its severity, uncertainty about the safety and efficacy of the vaccine, negative publicity regarding influenza vaccination, costs incurred because the vaccine was not part of the immunization schedule, decreased caregiver priority for influenza vaccination, perception of decreased importance/utility of vaccination, missed opportunities in outpatient visits, and reluctance to increase the number of immunizations for young children.[20,21]

Uncertainty regarding the vaccine's safety and efficacy is largely a result of periodic antigenic drifts and shifts that then affect vaccine production and procurement. At the beginning of each new influenza season, new vaccines matching the antigenic composition of the circulating strains must be produced. Early identification and isolation of viral strains circulating worldwide, made possible by the WHO influenza surveillance program, help predict which influenza strains will circulate during the upcoming season.[2] Influenza vaccines must contain both influenza A and B viruses because of antigenic drifts.[6]

After vaccination, protective antibody titers originate from naïve B cell differentiation into antibody secreting cells in adults and memory B cells in infants.[30] The majority (80-95%) of children 6 months of age or older develop protective antibody levels after two doses of vaccine.[5] Studies involving seasonal IIV among young children indicate that two doses are needed for optimal benefit among younger children who are influenza vaccine-naïve.[17] Overall, based on culture-confirmed studies, vaccine efficacy ranges from 56-100%, varying based on season, patient age, and type of vaccine.[5]

Multiple studies have demonstrated significant burden of influenza in young children with or without high-risk conditions. This led to new recommendations for vaccination by the CDC ACIP beginning in 2010, which recommended vaccination for all persons 6 months of age or older who do not have contraindications. [19,27,31,32]

The American Academy of Pediatrics (AAP) agrees with the recommendation for seasonal influenza vaccination for all children older than 6 months of age. Annual vaccination is especially important for children with high-risk medical conditions, their household contacts, care providers, and especially family members younger than 5 years of age.[6] This is particularly important for infants younger than 6 months of age who are ineligible for influenza vaccination or antiviral prophylaxis.[6] Although vaccination is not indicated in infants younger than 6 months of age, preliminary studies have found that influenza vaccines are safe and immunogenic in infants as young as 6 to 12 weeks with protective antibody titers similar to levels in 6-month-old infants.[5] Pre-existing maternal antibodies appear to blunt the immune response in vaccines, indicating that vaccination of mothers during pregnancy may protect infants, as maternal antibodies have been found to be protective up to 6 months. The vaccination of mothers was more than 90% effective in preventing influenza-related hospitalizations of their infants. However, prior vaccination does not affect significantly the antibody protections conferred to neonates, indicating the need for vaccination against influenza in each pregnancy.[33] Unfortunately, rates of maternal influenza vaccination vary widely.[34] As children serve to disseminate infection, prioritization of influenza vaccination of daycare children may help decrease influenza-related morbidity among members of the household and the community.[5]

Children aged 6 months to 8 years who have not received a total of two or more doses of any trivalent or quadrivalent influenza vaccine in any previous season(s) require two doses at least four weeks apart.[10] Influenza vaccine should be administered as soon as it is available, typically in September, and throughout the influenza season into March and April, since it is possible to have more than one peak caused by different influenza virus strains.[1,6]

Since 2003, two influenza vaccine types (LAIV and IIV) have been recommended for children 2 to 17 years of age in the United States. Although both LAIV and IIV contain antigenically equivalent strains, they differ by type, route of administration (intranasal vs. intramuscular, respectively), population eligible for use, and efficacy. Subsequently, the U.S. ACIP recommended not to use LAIV for the 2016-2017 and 2017-2018 seasons because of a decreased efficacy compared to IIV. The cause of decreased effectiveness of LAIV is not known, and multiple hypotheses are being evaluated.[17,31] Detailed information for currently available vaccines for the 2017-2018 influenza season may be found on the CDC website.

**Contraindications, Precautions, and Adverse Reactions.** Influenza vaccination should not be administered to children younger than 6 months of age and should be avoided in children who developed Guillain-Barré syndrome (GBS) with past influenza vaccines and who are not at high risk of severe complications from the influenza virus. The risk for post-influenza vaccination-associated GBS is considered low, at an observed rate of one to two additional GBS cases per 1 million patients.[5,6]

Precaution must be taken in children with egg allergy, who should be able to receive specific age-recommended influenza vaccination under certain circumstances depending on level of severity. Although egg allergy previously was considered a contraindication, new studies have shown that a single age-appropriate dose of influenza vaccine with an ovalbumin content up to 0.7 mcg/0.5 mL of a vaccine dose has been well tolerated in this population. For patients reporting mild reactions to egg, such as hives, no other measures are recommended. Patients reporting reactions with other symptoms should be vaccinated under the supervision of a healthcare provider who can recognize and manage severe allergic reactions. Severe allergic reactions, which include systemic, cardiovascular, respiratory, or gastrointestinal (GI) involvement, or reactions that involve the use of epinephrine, require allergist consultation prior to vaccination. Personnel and equipment needed to treat severe allergic reactions always should be available in vaccination settings.[1,17]

LAIV is not recommended for children younger than 2 years of age, those at high risk of developing severe complications from influenza infection, children receiving salicylate therapy, children younger than 5 years of age with a history of wheezing in the last 12 months, or those with asthma because of an increased risk of bronchospasm. LAIV also is not recommended in children with nasal congestion, which may affect intranasal absorption of the vaccine.[6] Currently, there are no data available to support using LAIV in children who have a history of egg allergy.[1]

The most common immunization reactions are fever, malaise, irritability,

**Table 1. Frequency of Influenza Symptoms**

| Symptom | Frequency |
|---|---|
| Fever | 63-100% |
| Cough | 66-85% |
| Sore throat | 19-74% |
| Runny nose | 48-78% |
| Muscle aches | 13-86% |
| Headache | 39-84% |
| Fatigue | 48% |
| Gastrointestinal | 6-35% |

drowsiness, localized pain, myalgia, and headache. Both observational and randomized, controlled trials demonstrated short-term outcomes, including localized erythema, swelling, induration, pain, and tenderness after vaccination. One review article noted there were fewer visits for acute respiratory infections, otitis media, and asthma episodes in the weeks after influenza vaccination based on large post-licensure, population-based studies.[5] However, based on a Cochrane review, there were wide-ranging, similar rates of adverse effects, including fever, nasal congestion, and upper respiratory tract infections (URI), after receipt of inactivated vaccines in children 6 months to 18 years of age when compared to control groups.[2] Of note, fever more commonly was associated with receipt of whole virus IIVs in children, which now are replaced by split-virus and subunit vaccines in the United States. Oculorespiratory syndrome was reported to be an acute, self-limited reaction to IIV, occurring two to 24 hours after vaccination and consisting of red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling. Febrile seizures can occur.

## Uncomplicated Influenza

**Clinical Features.** Influenza and many acute respiratory illnesses have similar symptoms that circulate during the same seasons.[1,5] Symptoms include fever, cough, dyspnea, tachypnea, conjunctivitis, epistaxis, acute otitis media, headache, myalgia, arthralgia, and fatigue.[2,16] There is no significant difference in signs or symptoms between children with influenza A or B.[35] However, a recent study suggested that children with influenza B typically are older, appear less ill than children with influenza A, and have a higher incidence of myalgia, myositis, and pharyngitis.[1,18]

Neonates and infants may present with nonspecific symptoms such as isolated fever without localizing signs, poor feeding, apnea, or lethargy that may mimic sepsis, often with minimal respiratory findings.[1,6] Young children are more likely to manifest fever, cough, rhinorrhea, and congestion. The classic presentation of sudden onset of fever and chills, myalgia, malaise, headache followed by sore throat, nasal congestion, rhinorrhea, and dry, hacking, nonproductive cough is seen among older children.[1,6] Sore throat is associated with nonexudative pharyngitis and occurs in more than half of cases. Ocular symptoms, such as tearing, photophobia, and burning, also can occur. GI symptoms, such as vomiting, abdominal pain, and diarrhea, are more common in children than in adults.[1] Approximately 20% of young children have diarrhea and up to 25% had emesis and diarrhea during the 2009 influenza H1N1 pandemic.[6] Table 1 includes the most common symptoms associated with acute influenza infection.[32,35-37]

**Clinical Course.** Influenza generally is an acute, self-limited, and uncomplicated respiratory illness lasting approximately one week with a median duration of nine days. The median duration of days with fever ≥ 100.4° F, plus either cough or rhinitis, was four days.[18] Influenza viral load typically peaks within the first three days. The cough peaks after three to four days, and persists for more than one week after resolution of the other symptoms.[1] Rhinitis occurs for a median of 10 days.

## Risk Factors

Recent studies highlight the severity of influenza in both children with severe chronic underlying disease and healthy children.[1,5,6,28,36] (*See Table 2.*) Many influenza deaths are an exacerbation of an underlying medical conditions or invasive coinfection with another infectious pathogen. Compared to children aged 13-17 years, infants younger than 6 months of age were more than six times as likely to have an influenza-associated death, and children between 6-23 months of age were more than three times as likely to have an influenza-associated death in the six seasons that were studied.[26] Native Hawaiian or Pacific Islander, American Indian, and Alaskan native children had higher mortality rates compared to white, African American, or Asian American children. The children who died suffered a range of complications such as sepsis, shock, and respiratory complications. More than 50% of pediatric patients who died reportedly received antiviral or antibiotic treatment; however, information on the timing of treatment relative to death was unavailable.[26]

Obesity may predispose individuals to worse disease, as obese hosts appear to have increased baseline levels of inflammation and expression of both bacterial and viral receptors that may affect bacterial and viral virulence negatively, especially when coinfection occurs.[38] With an influenza infection, those with a history of asthma, even if stable, are at a higher risk for pneumonia and may have an acute asthma exacerbation that progresses to status asthmaticus.[1] Chronic conditions, such as diabetic ketoacidosis, are reported to have increased risks associated with flu.[16] Approximately 30-50% of affected children did not have high-risk medical conditions and appeared to have a shorter interval between symptom onset and death (median, five days) compared to children with high-risk conditions.[9,19,26]

## Complications of Influenza

**Otitis Media.** The incidence of influenza-associated otitis media is 3-5% of cases annually and may be as high as 30-40% in children who attend daycare during respiratory disease season. Symptoms typically present three to four days after the onset of URI symptoms. Simultaneous viral and bacterial middle ear infection significantly worsens the course of otitis media. Development of otitis media following influenza infection is hypothesized to be caused by several mechanisms, including eustachian tube dysfunction, direct invasion of middle ear epithelium, leukocyte function alteration, enhanced adherence of bacteria to respiratory tract epithelial cells, and decreased mucociliary clearance.[1] In one study, acute otitis media and stenosing laryngotracheitis were reported more in patients with influenza B infection.[18] Since the introduction of the trivalent influenza vaccine in 2004, the incidence of seasonal acute otitis media decreased in children younger than 2 years of age from 98.4 per 1,000 person-seasons to 66.1 per 1,000 person-seasons. Subsequent influenza seasons had fewer outpatient visits for acute otitis media.[39]

**Pneumonia.** Secondary bacterial pneumonia typically presents with fever and

productive cough, with radiologic evidence of lobar consolidation. Etiology is most frequently pneumococcal; however, staphylococcal pneumonia and progressive primary viral pneumonia, which is seen mostly in adults with rheumatic heart disease, also can occur.[1,5] Staphylococcal pneumonia due to influenza A and *Staphylococcus aureus* may progress to pneumatocele, empyema, and necrotizing pneumonitis.[1]

Influenza-associated bronchopneumonia occurs in 10-50% of cases, and although most are mild with complete recovery, it rarely has been fatal in previously healthy individuals[1] and has been identified as a major cause of mortality during influenza pandemics.[24] The Etiology of Pneumonia in the Community study estimated the incidence of influenza-associated pneumonia hospitalizations to be highest in children younger than 2 years of age (3.7 per 10,000 child-years). Children with asthma were more likely to have a pathogen found than those without asthma. Sixty percent of pneumonia hospitalizations in adults were not associated with a pathogen compared to 20% of children.[40]

***S. aureus* and *Streptococcus pneumoniae* Infection.** During the 2009 H1N1 outbreak, many influenza-related deaths were related to secondary bacterial infection with *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Between the 2004-2005 and 2006-2007 influenza seasons, the proportion of children with bacterial coinfection increased more than fivefold, with *S. aureus* coinfections accounting for the majority. In 2007, the CDC reported increased reports of pediatric deaths associated with *S. aureus* coinfection.[26] The main clinical presentation is pneumonia,[41] followed by parapneumonic effusions and empyema.[5] There are several hypothesized mechanisms by which influenza virus infection increases the risk for secondary bacterial coinfection — namely, damage to the epithelial cell layer of the tracheobronchial tree by the influenza virus enhances adherence of staphylococcus. This increased adherence might be mediated by the neuraminidase activity of the virus. Additionally, the virus suppresses the phagocytic function of neutrophils and macrophages, which facilitates the development of a subsequent bacterial infection.[41]

Several studies have found that a recent history of staphylococcal soft tissue infection in the patient or family members may precede invasive infection. This invasive infection may cause overwhelming sepsis that is reported in infants and younger children, and family clusters of invasive staphylococcal infection have been described. Nasal carriage with methicillin-resistant *S. aureus* (MRSA) has increased and was as high as 22% among new admissions to a pediatric hospital. With the increase of MRSA, there is evidence that many of these isolates are the USA300 strain and are associated with the Panton-Valentine leukocidin toxin. This toxin is an important virulence factor associated with necrotizing pneumonia and necrotizing skin lesions.[24]

**Respiratory Failure.** Patients with influenza infection that progresses to acute lung injury and shock have the highest mortality. It often presents with profound hypoxia and respiratory failure, or with systemic infection that leads to septic shock requiring vasopressors.[41] There have been previous case reports of successful prolonged extracorporeal membrane oxygenation (ECMO) for respiratory failure associated with influenza H1N1; however, those requiring ECMO for more than 14 days had lower survival.[38]

**Central Nervous System.** Neurologic complications of influenza include seizures, encephalitis and encephalopathy, hemiplegia, quadriparesis, ataxia, acute myelopathy, GBS, Reye's syndrome, stroke, and transverse myelitis. In general, these patients make a full recovery; however, some have continued residual seizures and significant cognitive deficits associated with necrotizing encephalitis, involvement of the basal ganglia, and significant cerebral volume loss. Neurologic complications have been observed at a low rate ranging from one to four per 100,000 person-years.[1,16,42]

The most frequently reported neurologic complication is seizures, which occur in approximately two-thirds of patients hospitalized for influenza, of which febrile seizures make up the majority. The reported rate of febrile seizures in infants and young children is approximately 5%. They also have been reported in older children beyond the age range of typical febrile seizures, children with previous diagnosis of epilepsy, and children with more severe neurologic complications. For patients diagnosed with seizure exacerbation with a previous diagnosis of epilepsy, the outcome is good, and most return to their previous neurologic baseline. For patients with encephalopathy or encephalitis, the prognosis is variable. Many diagnostic tests, such as cerebrospinal fluid and electroencephalogram, do not distinguish between severity and long-term outcomes.[1,42]

The second most reported neurologic complication in children is influenza-associated encephalopathy, which causes severe neurologic disease with high mortality and results in severe neurologic deficits in survivors. Most of these studies originated in Japan, where there are more cases with severe encephalopathy with poor outcomes (approximately 30% overall mortality prior to the year 2000, with a subsequent decrease to 15% thereafter). The reason for this greater incidence is unknown. Influenza-associated encephalopathy often manifests with sudden onset of fever, seizures, and rapid progression to coma, with radiologic imaging revealing bilateral thalamic necrosis and brainstem involvement. Other symptoms include mild confusion, disorientation, "Alice in

## Table 2. Risk Factors for Serious Outcomes

- Prematurity
- Age ≤ 0-59 months or ≥ 65 years
- Long-term aspirin therapy (e.g., Kawasaki)
- Pulmonary disease
- Immunosuppression (e.g., HIV)
- Metabolic and hepatic disease
- Morbid obesity
- Hemodynamically significant cardiac disease
- Hemoglobinopathies (e.g., sickle cell disease)
- Chronic renal disease
- Malignancy
- Neurologic disorders (e.g., cerebral palsy)
- Residents of nursing homes/long-term care facilities
- Persons of American Indian/Alaska native descent
- Household contacts and care providers of children younger than 5 years of age
- Pregnant women in second or third trimester or women less than two weeks postpartum

Wonderland" syndrome, hallucinations, behavioral changes, meaningless speech, mutism, aphasia, delirium, lethargy, and somnolence. The pathogenesis is uncertain but may be a result of direct viral invasion to the central nervous system, high levels of pro-inflammatory cytokines that cross the blood brain barrier, or medications used to treat influenza.[1,42]

A study reported 385 cases of influenza-associated encephalopathy during the 2010-2015 influenza seasons. Children accounted for 74% of cases, with the largest percentage among patients 5-12 years of age. The overall case fatality proportion was 9% and the median duration from influenza-associated encephalopathy to death was one day.[43] In a more recent case study, a child presented with encephalitis progressing to obstructive hydrocephalus, with viral RNA detected in the cerebrospinal fluid.[44] Reye's syndrome is no longer common since the link between the use of aspirin and concomitant influenza infection was discovered.[1,42]

**Musculoskeletal.** Influenza-associated myositis has been reported since 1957 and almost always is benign. It is more common in children and usually affects boys. It occurs most often with influenza B virus, theoretically because of the greater potential for influenza B to invade the muscle cells directly, which results in greater damage. Symptoms generally include severe calf tenderness, pain, and sudden onset of difficulty walking after an influenza infection.[5,37] Symptoms typically occur in the setting of early recovery from a typical influenza illness. The gastrocnemius and soleus muscle groups almost are always affected. In laboratory studies, elevated serum creatinine kinase and aspartate aminotransferase are seen. This complication generally is self-limited, but there have been reports of rhabdomyolysis with myoglobinuria and acute renal failure.[1]

**Cardiac.** Pericarditis, myocarditis, and heart failure rarely have been associated with influenza A and B. These have been found mostly in healthy adults and in children with pre-existing heart disease.[1,16]

**Gastrointestinal.** GI symptoms include diarrhea and have been associated with an acute abdomen and intussusception. Diarrhea appears to be more prominent with A(H1N1)pdm09 infection compared to seasonal influenza and is thought to be caused by extensive local viral replication or indirect injury to the GI tract.[16,36]

## Diagnosis

**Clinical Suspicion.** Studies have cited the sensitivity of the clinical exam to diagnose influenza to be around 30%. ILI often presents as the presence of fever in addition to cough and sore throat in the absence of an alternative cause. Young preverbal children are challenging to assess for influenza because of the subjective nature of myalgia, headache, and sore throat. There has not been a specific combination of clinical signs or symptoms to diagnose influenza consistently and accurately. Seattle Children's Hospital developed a diagnostic tool called SPIRA to predict high influenza positivity based on clinical symptoms. In patients presenting with fever and ILI, those younger than 2 years of age have a higher likelihood of having influenza if they have a laboratory-confirmed positive contact, high influenza prevalence, unimmunized status, or a cough. For those between age 2 and 18 years of age, the factors shown to predict influenza positivity include high influenza prevalence, unimmunized status, myalgia, and absence of diarrhea.[4]

**Whom to Test and Approach to Testing.** Quickly diagnosing influenza has been shown to decrease unnecessary tests and antibiotics in pediatric patients, and allows better use of antivirals and early discharge from the ED and inpatient wards.[35]

Multiple modalities of influenza testing are available. These include rapid antigen testing, immunofluorescence, viral culture, and molecular assays.[4] Viral cell culture used to be the gold standard for diagnosis of influenza; however, the time to detection ranges from two to 14 days, with a median of three to five days. Several studies have shown no statistically significant difference between viral culture, antigen detection, or reverse transcriptase polymerase chain reaction (RT-PCR) in children < 24 hours from onset of symptoms, between vaccinated or unvaccinated children, or in children younger than 3 years of age. Ideally, the specimen for testing should be obtained within the first 72 hours of illness. After 72 hours, there is a significant decrease in the amount of virus shedding. There are also several studies that show that viral titers may be low in the first 12-24 hours. False-negative results may occur, especially if the specimen is collected too early (< 12 hours) or very late (> 5 days) after onset of symptoms. False-positive results are most common during periods of low influenza activity (early and late in the season). During these time periods, a confirmatory PCR or viral culture may be needed. Nasopharyngeal aspirates and washes provide the best results, followed by nasopharyngeal and mid-turbinate swabs. In one study, the mid-turbinate swab had higher sensitivity for detecting influenza than a nasal swab, although there was no difference in specificity.[32] Nasopharyngeal and mid-turbinate swabs are preferred over throat swabs for detection. Other factors that affect interpretation of the test include the prevalence of influenza in the community during the time of testing and the likelihood of infection based on clinical symptoms. A positive influenza test does not exclude the possibility of bacterial coinfection.[1,6,35]

**Testing Modalities.** RT-PCR is one of the most accurate, reliable, and sensitive tests for detecting influenza, with sensitivity of 98% and positive predictive value of 100%, and currently is considered the gold standard and preferred method of detection by the Infectious Diseases Society of America. It is FDA-approved and has been available since 2008. RT-PCR transcribes single-stranded RNA into double-stranded DNA, which then is amplified for detection. The test can distinguish between various serotypes of the influenza virus, including A, B, H1, H3, and avian H5. Results generally take between four to six hours, but may take up to 24 hours. Rapid multiplex reverse transcriptase polymerase chain reaction (mRT-PCR) has a better sensitivity of 99%, but it is costly and generally only available in large academic centers.[1,4,6] Rapid viral testing has been shown to decrease the rates of chest X-ray performed in the ED significantly but does not influence antibiotic usage. If the test is positive for respiratory virus, decreased length of hospital stay and time in isolation is seen. In one study, mRT-PCR was found to be the most cost-effective testing method (based on quality-adjusted life years) compared to other modalities, such as traditional PCR, direct fluorescent antibody, and rapid antigen testing.[45]

Real-time assays combine the amplification and detection steps, shorten the assay time, reduce cross-contamination, and provide an indicator of viral load. These have increased the sensitivity of viral detection drastically over other methods, such as rapid antigen testing and viral culture. The test speed is faster because of the removal of an external extraction step before testing; thus, results can be available in 30-60 minutes. It has greater sensitivity than viral

culture, may be used as a confirmatory test, and distinguishes between different influenza types and subtypes. Testing can be performed year-round regardless of the prevalence of influenza because of high sensitivity and specificity of molecular tests. However, false-negative results have been seen in critically ill patients when upper instead of lower respiratory tract samples were tested.[35,45]

Antigen detection assays are based on the detection of viral proteins by specific antibodies that bind to the nucleoprotein of influenza. It is the most widely available option for testing. Rapid immunoassays that detect viral antigens are relatively insensitive, ranging from 40-70%, and do not distinguish between subtypes of influenza, especially compared with RT-PCR and viral culture. Factors that influence the sensitivity include the rapid antigen test used, the specimen collection technique, the influenza type tested, and the patient's age. Specificity generally is high, ranging between 96-99%. With the pandemic H1N1 strain, the sensitivity varied widely from 10-99% depending on the kit used. Results generally are available in 10-30 minutes. Rapid influenza antigen detection tests require $10^4$-$10^6$ infectious influenza particles for a positive result. There is a high rate of false-negative results, so the CDC advises that antiviral therapy should not be withheld because of a negative rapid detection assay.[1,4,6,35]

Direct fluorescent assay (DFA) and indirect fluorescent antibody (IFA) staining detect viral antigens in exfoliated respiratory epithelial cells applied to microscope slides. For the DFA test, antibodies are attached to fluorescein, which binds to influenza surface antigens and can be detected under a fluorescent microscope. In the IFA test, unlabeled antibodies first bind to the influenza surface antigen and then are bound by secondary antibodies attached to fluorescein, which can be detected under the microscope. These techniques allow assessment of sample quality, and are more sensitive than rapid antigen detection tests, generally around 40-90% with a specificity of 86-100%. It has a lower sensitivity and specificity than cell culture. Results generally are available within two to five hours. However, DFA requires expertise for accurate interpretation, sensitivities and specificities vary between laboratories, and the tests do not distinguish between subtypes of influenza A.[1,6,35]

The viral culture is the criterion standard for diagnosing influenza infection.[6] In a conventional cell culture, the time to detection usually ranges from two to 14 days and does not yield results in a timely manner. It relies on infectious virus and is less sensitive than PCR tests. Rapid influenza cultures have replaced conventional cultures in most laboratories, with results available in one to three days. These cultures have similar sensitivity to conventional cell cultures. Although results take days to obtain, during influenza season, viral culture should be performed for routine surveillance purposes and for confirmation of negative test results from rapid antigen and immunofluorescence testing, especially if there is an institutional outbreak. Additionally, it is useful for providing diagnosis in times of low influenza activity and provides antigenic information and antiviral susceptibility.[1,6,35]

Serologic testing is not recommended for detection of influenza virus for either acute or convalescent phase antibody titers. Single serum specimens cannot be interpreted reliably. Paired serum specimens are collected 10-14 days apart, and results rarely are helpful in acute disease management. If there is a four-fold or greater increase in antibody titers, the diagnosis can be made retrospectively.[6,35]

## Treatment

**Antiviral Treatment.** According to the CDC guidelines, early empiric treatment with antiviral medication is recommended during peak influenza season for any child with suspected influenza or ILI who is at high risk for influenza-related complications. The AAP recommends antiviral treatment of all hospitalized children with presumed influenza or severe, complicated, or progressive illness, regardless of whether they have received the vaccine previously. Like the CDC, it also recommends immunization of any child with symptoms who is at risk for complications, regardless of illness severity, including children younger than 2 years of age and those with underlying chronic medical conditions. Empiric treatment also is recommended to shorten illness duration in older previously healthy children if they present within 48 hours of illness onset and also should be considered for children with a sibling or household contact younger than 6 months of age or who have other risk factors for severe influenza.[1,4] In children with more severe or progressive disease, treatment after 48 hours of illness onset still may provide clinical response and should be initiated even if the rapid antigen-detection influenza diagnostic test results are negative.[10]

Both the CDC and AAP have emphasized that treatment with an antiviral medication such as oseltamivir reduces risks of hospitalization, ambulatory service use, severity of illness, duration of illness, antibiotic use, need for mechanical ventilation, and risk of death, as well as secondary complications such as otitis media, asthma exacerbations, and pneumonia. It also has been shown to reduce viral shedding. Earlier use of antiviral therapy for suspected influenza provides better clinical responses, and confirmatory testing should not delay treatment initiation. For those children hospitalized in the PICU, early treatment also was reported to reduce the risk of death and length of hospitalization.[1,4,6,8,18,19] In healthy children between 1 and 12 years of age with uncomplicated influenza, a 36-hour decrease in illness duration was seen if treatment was initiated within 48 hours of illness onset. Studies show that oseltamivir was associated with a 39-44% decrease in risk of otitis media, 53% decrease in risk for pneumonia, and 28% decrease in risk for respiratory illness as well as reduced incidence of sinusitis and bronchitis. In a separate retrospective study, children from 1 to 12 years of age who received oseltamivir within 24 hours of diagnosis had a 52% reduction in subsequent medical encounters and fewer outpatient and ED visits.[6] Early treatment with antiviral medication is not meant to replace influenza vaccination, which remains the first line of defense against influenza.[11,17] Antiviral treatment with oseltamivir currently is approved by the FDA for children 2 weeks of age or older.[19]

A study of patients over five influenza seasons found that antiviral treatment in children was lower than in adults (72% vs. 86%, respectively).[17] It was reported in less than half of the children who died during the 2010-2011 and 2011-2012 seasons.[19] Among outpatient children for whom treatment is recommended, the rate is even lower. During the 2013-2014 influenza season, one study found that only 28% of patients 6 months to 2 years of age who sought outpatient medical care for acute respiratory illness received antiviral treatment, with 0 of 66 children younger than 2 years of age with chronic medical

## Table 3. Age and Weight-based Oseltamivir Dosing

| Age | Dose |
|---|---|
| Premature infants | • 28-38 weeks PMA: 1 mg/kg/dose PO BID<br>• 38-40 weeks PMA: 1.5 mg/kg/dose PO BID<br>• > 40 weeks PMA: 3 mg/kg/dose PO BID |
| Term infants-8 months of age | • 3 mg/kg/dose PO BID |
| Babies 9-11 months of age | • 3.5 mg/kg/dose PO BID |
| 12 months and older | • ≤ 15 kg: 30 mg PO BID<br>• 16-23 kg: 45 mg PO BID<br>• 24-40 kg: 60 mg PO BID<br>• > 40 kg: 75 mg PO BID |
| Adults | • 75 mg PO BID |

Infant dosing based on American Academy of Pediatrics recommendations. 12 months and older dosing based on U.S. manufacturer's labeling. Capsules are available as 30 mg, 45 mg, and 75 mg, and suspension is available as 6 mg/mL.

conditions prescribed an antiviral despite presenting less than two days into illness and having a confirmed RT-PCR positive influenza result.[17]

Several studies highlight the effectiveness of influenza antiviral treatment to prevent secondary complications by inactivating viral neuraminidase, which decreases the influenza virus's ability to facilitate bacterial adherence.[24] Studies show that treatment of influenza with oseltamivir was associated with rapid resolution of the fever if given within 48 hours of onset of illness and reduction in acute otitis media, duration of illness, and antibiotic use.[1,46]

There are two main classes of antiviral drugs against influenza — neuraminidases and adamantanes. The recommended length of treatment is five days; however, longer courses may be indicated in patients with immunosuppression or in severely ill hospitalized patients. Antiviral resistance may emerge from one season to the next and is monitored closely by the AAP and CDC.[1]

**Neuraminidase Inhibitors.** Neuraminidase inhibitors include oseltamivir, zanamivir, and peramivir, all of which currently are approved for use in treatment of influenza. They prevent infection and viral replication, and thus prevent viral spread to respiratory secretions. Neuraminidase inhibitors have activity against influenza A and B viruses; however, reportedly they are less effective against influenza B in children younger than 5 years of age compared to older children, which is likely because of the low sensitivity of influenza B viruses to oseltamivir.[1,11,47] The most widely available option is oral oseltamivir. Inhaled zanamivir also currently is available.[5]

Oseltamivir phosphate is an ethyl ester prodrug that has a good oral bioavailability. It is metabolized by the liver and converted to the active inhibitor oseltamivir carboxylate. It has a half-life of six to 10 hours and is excreted by the kidney, requiring dose adjustment in patients with renal impairment.[11,47] The dose also must be adjusted based on age because of higher renal clearance of active carboxylate metabolite in younger children than in older children and adults.[1,11] See Table 3 for treatment dosing.[13]

Oseltamivir currently is licensed for children as young as 2 weeks of age.[46] The FDA expanded this in December 2012; prior to this time, oseltamivir was approved only for children 1 year of age and older. In prior testing with rats, toxic levels of the drug were found in neonatal brain tissue; however, later this was proven to be erroneous, and further animal studies have shown no such effects. In a retrospective study, researchers reviewed charts of infants who were administered oseltamivir phosphate "off label" and found no safety concerns.[11] Oseltamivir also may be used for chemoprophylaxis for children 3 months or older. It can be used in both term and preterm infants from birth for treatment of influenza, according to existing safety information.[5] There are no known significant drug-drug interactions with oseltamivir.[6,11]

The main adverse side effects of oseltamivir are GI complaints, such as nausea, vomiting, and diarrhea.[1,47] Oseltamivir phosphate's manufacturer states that for infants 2 weeks of age to less than 1 year of age, the most common adverse reactions are vomiting, diarrhea, and diaper rash. Other reported side effects for children 1 to 12 years of age are epistaxis, conjunctivitis, ear disorder, and abdominal pain. Taking the medication with food may decrease the GI side effects in some patients. If provided as a suspension, the medication should be refrigerated between 2-8 degrees Celsius and needs to be shaken prior to taking a dose. It must be discarded 10 days after it is constituted. Care must be taken in patients with hereditary fructose intolerance, as the oseltamivir phosphate oral suspension contains 2 g of sorbitol per 75 mg, which can cause diarrhea and dyspepsia. Blood glucose and renal function also must be monitored closely in patients with diabetes mellitus.[1]

Oseltamivir is contraindicated in patients with known hypersensitivity to it or its components. Anaphylaxis and other serious skin conditions have been reported post-marketing of oseltamivir phosphate. Oseltamivir should not be given to children with severe renal dysfunction (creatinine clearance of ≤ 10 mL/min), as oseltamivir is excreted renally. The dose should be adjusted for patients with creatinine clearance of 10-30 mL/min.[6,11] Oseltamivir phosphate should not be given two weeks before or 48 hours after vaccination with LAIV. It has not been shown to affect the use of trivalent IIV.[11]

A rare neuropsychiatric event with fatal outcomes was reported from studies in Japan. These events included self-injury and delirium, especially in adolescents, with a rate of approximately one per 100,000 oseltamivir prescriptions. These reports were found to be inconclusive, as these events also were reported in children with influenza who were not receiving oseltamivir and likely were related to influenza disease rather than the medication. The FDA concluded that there was insufficient evidence to restrict the use of oseltamivir, but recommended closely monitoring children for unusual behavior, especially on the first day of starting treatment.[1,47] Another rare but fatal toxicity, known as "gasping syndrome," occurs from the metabolite of benzyl alcohol sodium benzoate in neonates.[11]

Zanamivir currently is licensed for children older than 7 years of age. The dosage is 10 mg inhaled twice daily for five days.[47] Because of its administration by inhalation, its use for children younger

than 5 years of age is limited. It can be used for prophylaxis in children 5 years of age and older. Approximately 14% of the inhaled dose distributes to the airways and lungs, where it has a local antiviral effect. Between 4-17% of the dose is absorbed systemically and then excreted by the kidneys. Unlike oseltamivir, dosing does not have to be adjusted in patients with renal impairment.[1,5,47] Intravenous (IV) zanamivir currently is being investigated and is available only through clinical trials or emergency investigational new drug requests for patients hospitalized for severe influenza. The dose is 14 mg/kg/dose every 12 hours for children 6 months to 6 years of age, and 12 mg/kg/dose every 12 hours for children 6 to 18 years of age for five to 10 days, with a maximum dose of 600 mg. The IV dose was adjusted for renal function in these patients.[47]

The main adverse side effect of zanamivir is bronchospasm. This risk is increased in patients with pulmonary disease such as asthma and should be avoided in these patients. Zanamivir also may not be used in patients who are intubated, as the disk inhaler contains a powder formulation that can clog the ventilator tubing.[1] There were no safety events reported regarding the use of IV zanamivir.[47]

In October 2017, the CDC's WHO Collaborating Center (CC) for Surveillance, Epidemiology and Control of Influenza found that 291 influenza virus specimens, including 41 influenza A(H1N1)pdm09, 50 influenza B viruses, and 200 influenza A (H3N2), were sensitive to all three neuraminidase inhibitors.[10] Reported resistance to oseltamivir is approximately 5-6% in children and 1-2% in adults.[1] A recent study documented a resistance rate of 4.4% among young infants in the United States. This resistance occurs as a result of mutation in the neuraminidase gene.[47]

**Adamantanes.** Adamantanes, which include rimantadine and amantadine, block the influx of hydrogen ions through the M2 ion channel, which interferes with viral uncoating inside the cell. These drugs are ineffective against influenza B viruses. According to the CDC's WHO CC for Surveillance, Epidemiology and Control of Influenza, high levels of resistance were found among adamantanes in currently circulating influenza A viruses, including the pandemic influenza A (H1N1) and the H3N2 viruses. Thus, adamantanes currently are not recommended for the treatment of influenza infections in the United States.[1,10]

**Chemoprophylaxis.** Chemoprophylaxis should be considered in children older than 1 year of age who are at high risk of influenza-associated complications and who have a contraindication for vaccination or have not yet received the vaccine. Other indications for chemoprophylaxis include high-risk patients in seasons in which the influenza vaccine is reported to have low clinical effectiveness. It also may be considered in the first two weeks after vaccination when antibody immune response still is inadequate. In children who previously were not vaccinated and require two doses, antibody immune response is inadequate six weeks from the first vaccine dose, and chemoprophylaxis is recommended throughout this period.[1,6]

Oseltamivir prophylaxis dosing is the same weight-based dosing as the treatment dosing, except it is given once daily instead of twice and for 10 days instead of five. Zanamivir prophylaxis dosing is 10 mg inhaled once daily for 10 days for household contacts and 28 days for community outbreaks. Chemoprophylaxis is not recommended in children younger than 3 months of age because of variability of pharmacokinetics.[47]

The reported efficacy is 68-89% with oseltamivir and 79-82% with zanamivir in household members exposed to influenza.[1,6] Overall, these drugs are effective for prophylaxis of households against both seasonal and pandemic influenza. A systematic review of published clinical trials found a modest effect of neuraminidase inhibitors for post-exposure prophylaxis of influenza in healthy children, with a number needed to treat of 13.[48]

**Supportive Care.** Supportive care options include watch-and-wait and symptomatic treatment with antipyretics. Other prevention methods include personal hygiene measures, such as covering coughs and sneezes, handwashing, and staying home when sick.[14] In the United Kingdom, one study found variability among their practitioners regarding the management of influenza. The suspicion of potential influenza infection and influenza status were not described as important factors affecting assessment or management.[49] Another study in Germany looking at outpatient care for influenza found most children received only symptomatic treatment with antipyretics and there was low administration of antiviral and antibiotic medication.[18] One proposed method to prevent further influenza spread includes school closure, especially during a pandemic. It is thought to be a possible nonpharmaceutical way to delay the peak, reduce the epidemic effect, and reduce transmission of influenza. Children often have limited prior immunity, which increases their vulnerability to infections. Additionally, at school, they have high contact rates with other children which increases the rate of transmission. However, despite a large volume of literature on this topic, no consensus exists due to contrasting evidence with no clear effect of school closure on epidemic burden and the transmission of influenza.[48]

## Conclusion

Influenza is one of the most common viral respiratory pathogens to infect infants and children. Clinical presentation commonly includes acute febrile illness with myalgia, headache, and cough. Influenza occurs in annual outbreaks mostly during the winter season, and activity varies depending on antigenic drifts of the virus and the population's susceptibility. A critical issue is that antiviral agents are underutilized in children. Clinicians need to be knowledgeable about presentation, best and most rapid diagnostic testing, and appropriate treatment strategies in pediatric patients.

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## CME/CE Questions

1. Which of the following does *not* place pediatric patients at increased risk of influenza complications?
   a. Prematurity
   b. Sickle cell disease
   c. Vaccination
   d. Asthma

2. Classic presenting symptoms of influenza in older children include all of the following *except*:
   a. hemoptysis.
   b. myalgia.
   c. fever.
   d. cough.

3. A mother brings in her fully vaccinated 2-year-old child to the ED following a convulsive episode lasting two minutes in the setting of an acute rise in fever to 103° F and one day of cough, congestion, and rhinorrhea. What is the quickest modality used to diagnose influenza in the ED?
   a. Reverse transcriptase polymerase chain reaction
   b. Rapid antigen testing
   c. Viral culture
   d. Serologic testing

4. For the 2-year-old child above, who weighs 11.3 kg, what would be the most appropriate influenza treatment dose if you prescribe oseltamivir?
   a. 3 mg/kg/dose PO daily × 10 days
   b. 30 mg PO BID × five days
   c. 45 mg PO daily × 10 days
   d. 45 mg PO BID × five days

5. Which of the following antiviral drugs would need renally adjusted dosing for treatment in patients with severe renal impairment?
   a. Oseltamivir
   b. Inhaled zanamivir
   c. Intravenous zanamivir
   d. Both a and c

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