Influenza and Parainfluenza Viral Infections in Children

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Practice Gaps

1. Because influenza and parainfluenza viruses are responsible for significant morbidity and mortality in young infants and children, especially those with chronic conditions, clinicians must learn to recognize, treat, and prevent infections caused by these viruses.
2. Disease caused by influenza virus can be prevented through the vaccination of all persons 6 months or older. Special attention should be given to pregnant women and persons with chronic medical conditions, such as asthma, congenital heart disease, and neuromuscular disorders.

Objectives   After completing this article, readers should be able to:

1. Describe the epidemiology of influenza and parainfluenza virus infections.
2. Recognize the clinical features of influenza infections.
3. Select the most appropriate vaccines for the prevention of influenza.
4. Differentiate clinically between influenza and parainfluenza virus infections.
5. Order the most appropriate test for the diagnosis of respiratory viral infections.

Introduction

Influenza and parainfluenza viruses (PIVs) are among the most common respiratory pathogens that affect infants and children worldwide. Infections and their complications are responsible for a significant number of hospitalizations and fatalities on a yearly basis. In most temperate climate countries, seasonal patterns of disease are observed. In warmer climates, disease can be observed year round. The fear of an influenza pandemic looms when new strains are discovered. Recognition and prevention become pressing priorities. In recent years, a greater emphasis in preventing influenza through vaccination has emerged within the United States. Many health care systems have mandatory vaccinations programs for health care professionals. In addition, vaccination is now recommended for all persons 6 months or older. Available antiviral agents are effective not only as therapy but also as preventive agents.

PIVs are the most common cause of laryngotracheitis or croup in children. In recent years, these viruses have become recognized as important pathogens in the immunocompromised host. Unfortunately, an effective antiviral regimen or vaccine still eludes us. In this review, we summarize the key aspects of what is known about influenza and PIVs, including their clinical manifestations, treatment, and prevention.

Abbreviations

IIV:	inactivated influenza vaccine
LAIV:	live attenuated influenza vaccine
LRI:	lower respiratory tract infection
PCR:	polymerase chain reaction
PIV:	parainfluenza virus
URI:	upper respiratory tract infection

Influenza Virus

Historical Aspects

The avian origin H1N1 influenza pandemic of 1918–1919 (Spanish flu) has been described as the single most fatal event in human history, responsible for more than 50 million deaths worldwide. (1) Subsequent pandemics occurred in 1957 (H2N2 Asian flu) and 1968 (H3N2 Hong Kong flu). The emergence of swine-origin novel H1N1 influenza in March 2009 heralded the fourth influenza pandemic in

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the last 100 years. Influenza epidemics can be traced back at least 2000 years, and the first true pandemic (intercontinental disease) occurred in 1580.

Influenza Biology

Influenza viruses are classified as orthomyxoviruses and contain a negative sense single-stranded RNA genome. There are 3 major influenza types: A, B, and C. The individual virus is spherically shaped and studded with 2 major proteins: hemagglutinin and neuraminidase. Differences in the hemagglutinin and neuraminidase antigens form the basis for the nomenclature of influenza A subtypes (eg, H1N1 vs H3N2). Influenza strains are further categorized according to type, location, and year and are given a strain number (eg, A/California/7/2009 [H1N1]).

Hemagglutinins facilitate attachment of the virus to the columnar epithelial cell in the respiratory tract. After uptake of the virion by endocytosis, an influx of protons through the virus M2 channel allows release of viral RNA, which is then imported to the nucleus. The virus hijacks the host's cellular machinery to produce the proteins and genetic material needed for viral progeny. Neuraminidases function in the budding of the newly formed virion to aid in its release from the host cell. (2)

Influenza Genetics and the Pandemic Threat

The genetic characteristics of influenza viruses facilitate the generation of novel strains with the potential to cause human disease. The influenza genome is composed of 8 RNA segments that can rearrange if more than one influenza subtype infects the same host. The virus contains its own RNA polymerase, which, in contrast to DNA polymerase, lacks proofreading functions. Consequently, point mutations occur with regular frequency during genome replication. The accumulation of these point mutations is known as *antigenic drift* and is responsible for the seasonal variation of influenza A strains that cause annual epidemics. Antigenic shift occurs when an influenza A strain with a novel hemagglutinin (and sometimes a novel neuraminidase) enters the human population. A pandemic occurs if this newly generated strain causes disease in humans and can efficiently spread from person to person and throughout the world. To date, 17 unique hemagglutinin antigens and 10 unique neuraminidase antigens have been identified. (2) Many of these influenza subtypes naturally infect the hundreds of bird species susceptible to influenza. Birds can be infected by multiple different strains simultaneously and serve as a genetic pool for the generation of new influenza strains. The human population has so far been susceptible to a limited number of influenza subtypes. Human infection and effective human-to-human transmission has been achieved by only 3 hemagglutinins and 2 neuraminidases in 3 combinations: H1N1, H2N2, and H3N2. (3) Because of differences in preferred cellular binding sites, different influenza strains preferentially infect birds and humans. However, pigs (swine) are susceptible to infection from both avian and human strains. Swine can serve as mixing vessels to produce novel strains that subsequently infect humans. In recent years, 2 influenza A strains of avian origin, H5N1 and H7N9, were responsible for several clusters of human disease in Asian countries, resulting in many hospitalizations and a high fatality rate. (4)(5)

2009 Novel H1N1 Pandemic

In March 2009, a new strain of influenza A was identified that caused significant disease in humans and could efficiently spread from person to person, leading to the fourth influenza pandemic of the last 100 years. This virus was a novel combination of 2 individual swine viruses, hence the term *swine-origin H1N1* or *swine flu*. From April 2009 to March 2010, novel H1N1 was responsible for an estimated 60 million illnesses, 270,000 hospitalizations, and 12,270 deaths in the United States. (6) As seen in previous pandemics, novel H1N1 disproportionately affected young adults and children, as well as pregnant and postpartum women. There were 317 confirmed pediatric deaths during the pandemic, significantly higher than prior years. The excess childhood deaths are probably explained by the increased attack rate in the young rather than enhanced virulence in this age group. (7)

Epidemiology and Transmission

Epidemics of influenza occur annually during the winter months in temperate regions of the world, typically peaking in January or February in the Northern hemisphere. There is no clear influenza season in equatorial countries, where influenza can circulate year round. Children are important vectors of disease because of higher attack rates and more prolonged viral shedding compared with adults. The peak incidence of infection occurs earlier in the pediatric population. An increase in missed school days in children sick with influenza often precedes increased work absenteeism in adults.

Influenza virus is transmitted primarily by large particle droplets, although contaminated surfaces can also spread disease. The incubation period is 1 to 4 days (mean, 2 days). Viral shedding correlates with fever intensity and begins 24 hours before symptom onset, peaks at day 3, and resolves by day 7. (8) However, young

children and individuals with compromised immunity can shed virus for extended periods. The severity of disease may also correlate with duration of shedding.

Hospitalization rates for influenza are highest in children younger than 2 years and adults older than 65 years. Children with certain comorbidities are at increased risk of hospitalization and influenza complications. These complications include hemoglobinopathies, diabetes mellitus, neuromuscular disorders, chronic kidney disease, and congenital heart disease. Children with underlying pulmonary disease, such as asthma and cystic fibrosis, are at risk for more severe disease.

Clinical Manifestations

Classic influenza infection is characterized by the sudden onset of fever, chills, and myalgias followed by prominent upper respiratory tract symptoms, such as rhinorrhea, cough, and sore throat. It is critical to recognize that younger children are less likely to present with this flulike syndrome. This is especially true in infants, who can present with fever and irritability with minimal respiratory findings. It is difficult in younger children to distinguish clinically influenza infection from infections due to other respiratory viruses (eg, respiratory syncytial virus and PIV) that circulate in communities during the same periods, and the manifestations of disease can be identical. Table 1 provides a comparison of clinical features between influenza

and PIVs. Upper respiratory tract infection (URI), laryngotracheitis (croup), bronchiolitis, and pneumonia are all possible presentations of influenza in the younger child. Gastrointestinal symptoms are uncommon in adults but can be the primary symptoms in children with influenza.

Complications

Bacterial infection of the respiratory tract is the most common complication of influenza infection and includes otitis media, sinusitis, and tracheitis. Pneumococcal pneumonia is a relatively common complication and should be suspected in the child who develops fever and a lobar infiltrate during the convalescent period. Less common than *Streptococcus pneumoniae*, staphylococcal infection can complicate acute influenza and lead to a diffuse necrotizing pneumonia with a high mortality rate, especially if caused by methicillin-resistant *Staphylococcus aureus*. Parapneumonic effusions and empyemas are common complications.

Acute myositis can occur during convalescence but is almost always benign. It occurs more commonly with influenza B. The typical presentation is a child who has sudden onset of severe pain in the calves and refusal to walk. The serum creatine kinase level is usually elevated. Severe encephalopathy and encephalitis have been reported with influenza infection. Reye syndrome is a rare form of encephalopathy that has been associated with influenza infection and salicylate (eg, aspirin) use.

Table 1. Clinical Comparison of Influenza and Parainfluenza Viral Infections

Clinical Condition	Influenza	Parainfluenza	Comments
Afebrile URI	+	+ +	Coryza and pharyngitis are common with PIV infections.
Febrile URI	+ + +	+	Flulike illness
Acute otitis media	+ +	+ + +	
Pneumonia	+	+ +	
Laryngotracheobronchitis (croup)	+	+ + +	Croup by influenza virus is more severe: thicker secretions, higher temperatures, more severe airway obstruction, and more bacterial superinfections.
Bronchiolitis	+	+ + +	PIV is third most common cause of bronchiolitis.
Sepsis–like syndrome	+	Rare	
Myositis	+	Rare	Mostly observed with influenza B virus. Myositis associated with PIV infection tends to be milder and of shorter duration.
Myocarditis	Rare	Rare	
Encephalopathy, aseptic meningitis, Guillain–Barré syndrome	Rare	Rare	Necrotizing encephalitis reported with influenza virus.

PIV=parainfluenza virus; URI=upper respiratory tract infection.

Laboratory Diagnosis

Laboratory testing is the mainstay in the diagnosis of influenza infection. Clinical findings alone are insufficiently sensitive or specific, especially in younger children who less often have classic findings. Accurate and rapid diagnosis of influenza infection can allow prompt initiation of antiviral therapy while simultaneously limiting antibiotic use. A variety of testing modalities exist, and each has its merits. Serologic (antibody) testing for influenza infection is important in the epidemiologic study of disease but does not play a role in clinical management. Similarly, although laboratory culture of influenza virus is essential for vaccine development and antiviral resistance testing, other methods have proven more clinically useful. (9)

Regardless of the diagnostic method used, proper sampling is paramount. Nasopharyngeal specimens are preferred over throat swabs. (9) The timing of specimen collection will also affect the validity of the result. A sample obtained in a patient with an influenza-like illness on days 2 to 3 of symptoms (when influenza virus shedding is at its peak) will yield a more reliable result compared with one obtained later in the disease course. (9)

Rapid Antigen Testing

Rapid antigen testing is the most commonly used method in the laboratory diagnosis of influenza infection and plays a vital role in high-volume patient settings, such as emergency departments, especially during epidemics of disease. In fact, the first case of 2009 pandemic influenza infection in the United States was diagnosed using a rapid antigen test. These assays work by measuring the immunologic reaction between influenza antigens from the patient's secretions with a specific influenza antibody. The advantages of rapid antigen tests include quick results (≤15 minutes), bedside or point-of-care testing, and distinguishing influenza type A from B.

Rapid antigen testing can be part of treatment algorithms in the management of patients with suspected influenza. (10) Rapid antigen tests for influenza are highly specific, allowing for efficient allocation of antivirals during peaks of activity. The major disadvantage of rapid tests is their low and highly variable sensitivity, ranging from 20% to 90%. (9) Therefore, a negative rapid test result in a patient presenting with sudden onset of high fever, myalgias, and cough during peak influenza activity could be falsely negative. One important aspect of rapid influenza testing—and rapid viral tests in general—is that the accuracy of the test result is directly correlated with the prevalence of disease in the community. As stated in the above example, during periods of peak viral activity, a negative rapid test result in a patient with an

influenza-like illness could be falsely negative. If that same patient presents during a period with minimal circulating influenza but has a positive rapid antigen test result, the test result is likely to be falsely positive. However, influenza strains can cause infections in out-of-season times of the year like in the case of an influenza A (H3N2) variant that initially circulated in the United States during the summer months with outbreaks associated with contact with swine at state and county fairs in the Midwest. (11)

Molecular Tests

Molecular methods of detection are replacing viral culture as the gold standard in the diagnosis of many viral infections, including influenza. Polymerase chain reaction (PCR)–based assays offer superior sensitivity and turnaround time compared with viral culture and are becoming more widely available in many laboratories. The PCR-based tests for influenza are often part of multiplex assays that can concomitantly detect influenza and other important viruses, aiding in the diagnosis of noninfluenza respiratory infections. Most PCR-based influenza assays can distinguish influenza types (A from B). Some tests reliably determine specific subtype (eg, H1N1 vs H3N2), which proved valuable in guiding antiviral therapy during the 2009 H1N1 pandemic. None of the currently available rapid antigen tests can discriminate influenza A subtypes.

Other Testing Choices

Direct and indirect fluorescent antibody testing can be performed on patient secretions and provide results within a few hours. These tests are highly specific but have variable sensitivities. The reliability of the results can vary, depending on the skill of the performing technician. They are more expensive than rapid antigen tests.

Treatment

Influenza infection is a benign self-limited disease in most children and adults, regardless of whether treatment is provided. However, influenza infection can cause severe disease and death in both high-risk patients and healthy individuals. The administration of active antiviral therapy early in the course of disease has been found to shorten symptom duration and prevent the spread of virus. It may also be beneficial in hospitalized patients and in those with severe disease, even if started later in the disease course. Treatment should optimally be initiated within 48 hours of symptom onset.

The decision to provide antiviral therapy as treatment or prophylaxis should be based on the duration of symptoms and the individual's risk of progression to severe disease. Hospitalized patients with suspected or confirmed

influenza should receive therapy. Patients at high risk for severe disease and complications should also be provided therapy and prophylaxis (Tables 2 and 3). (10)

Table 2. **Candidates for Antiviral Treatment**

Antiviral treatment is recommended as soon as possible for any person with confirmed or suspected influenza in any of the following categories:

- Is hospitalized
- Has severe, complicated, or progressive illness
- Is at higher risk for influenza complications

Persons at higher risk for influenza complications:

- Children younger than 2 years
- Adults 65 years or older
- Persons with chronic pulmonary (including asthma and cystic fibrosis), cardiovascular, renal, hepatic, hematologic, metabolic disorders, or neurologic and neurodevelopmental conditions (including cerebral palsy, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression
- Women who are pregnant or post partum (within 2 weeks after delivery)
- Persons younger than 19 years who are receiving long-term aspirin therapy
- American Indians or Alaska Natives
- Persons who are morbidly obese
- Residents of nursing homes and other chronic care facilities.

There are 2 classes of antivirals available for the treatment and chemoprophylaxis of influenza: the adamantanes and the neuraminidase inhibitors. The adamantanes include amantadine and rimantadine and work by interfering with the viral M2 ion channel to prevent the release of viral RNA into the host cell after endocytosis. The adamantanes do not have activity against influenza B. Furthermore, because of widespread resistance among influenza A strains, their use in the treatment and chemoprophylaxis of influenza A is not recommended at this time. The neuraminidase inhibitors have activity against both influenza A and B, and although resistant strains of influenza A have been found, most circulating influenza strains are susceptible. Neuraminidase inhibitors block viral neuraminidase, which prevents the budding and release of viral progeny. Oral oseltamivir and inhaled zanamivir are 2 neuraminidase inhibitors currently available for clinical use. Intravenous formulations of zanamivir and a third agent, peramivir, are being investigated. Oseltamivir is approved for the treatment of influenza in children older than 2 weeks and for chemoprophylaxis down to age 3

months. However, according to existing safety information, oseltamivir can be used to treat influenza in both term and preterm infants from birth. (12) Zanamivir is approved for use in the treatment of children 7 years and older and as prophylaxis in children 5 years and older. Oral oseltamivir can cause gastrointestinal distress but in general is well tolerated. Cough and bronchospasm have been associated with the use of inhaled zanamivir. It should be used with caution in patients with underlying pulmonary dysfunction (eg, asthma). For antiviral indications and dosages, see Tables 2 and 3. (10)(12)

Prevention

Yearly vaccination is the main strategy of prevention against influenza. All persons 6 months and older should be vaccinated. Influenza is responsible for its greatest morbidity in young infants, children younger than 5 years, and individuals 65 years and older. In addition, persons with chronic medical conditions, such as asthma, heart disease, cystic fibrosis, diabetes mellitus, neuromuscular disorders, cancer, and other immunodeficiencies, are at an increased of severe disease and death. In recent years, a significant number of infants and children have died of the disease. Although many had underlying medical conditions, close to 50% of fatalities were in previously healthy children. Unfortunately, only approximately 50% of children with cognitive, neurologic, and seizure disorders received the vaccine. (13) Infants younger than 6 months are at risk for severe disease. Although vaccination is not indicated in this age group, preliminary studies have found that influenza vaccines are safe and immunogenic in infants as young as 6 to 12 weeks. (14) In an open-label study, vaccination of influenza-seronegative infants induced levels of antibody similar to levels in 6-month-olds. Preexisting maternal antibodies appear to blunt the immune response in vaccinees. (15) One strategy that will protect these young infants is the vaccination of mothers during pregnancy because maternal antibodies in the infants have been found to be protective up to 6 months. (16)(17) The vaccination of mothers was more than 90% effective in preventing influenza-related hospitalizations of their infants. (18) More mothers need to be vaccinated. When vaccination is not proactively recommended, only 16.1% of pregnant women receive the vaccine. (19) If vaccination is recommended to the pregnant woman by a health care practitioner, 70.5% will receive it. The vaccination of children in daycare has been found to reduce influenza-related morbidity among members of the household. (20)

Multiple vaccines are distributed within the United States (Table 4). Most are inactivated products, but a live

Table 3. Antiviral Agents for Treatment and Chemoprophylaxis of Influenza

Agent	Age Group	Treatment	Chemoprophylaxis
Oseltamivir	Adults	75 mg twice daily	75 mg once daily
	Children ≥12 months		
	≤15 kg	30 mg twice daily	30 mg once daily
	>15–23 kg	45 mg twice daily	45 mg once daily
	>23–40 kg	60 mg twice daily	60 mg once daily
	>40 kg	75 mg twice daily	75 mg once daily
	Infants 9–11 months	3.5 mg/kg per dose twice daily	3.5 mg/kg per dose once daily
	Term infants 3–8 months	3 mg/kg/dose twice daily	3 mg/kg per dose once daily
	Term infants 0–3 months[a]	3 mg/kg per dose twice daily	Not recommended unless situation is judged critical. Limited safety and efficacy data. Consult pediatric infectious disease specialist.
	Preterm infants	Dosing based on postmenstrual age[b]	Not recommended unless situation is judged critical. Limited safety and efficacy data. Consult pediatric infectious disease specialist.
		<38 weeks: 1.0 mg/kg per dose twice daily. 38–40 weeks: 1.5 mg/kg per dose twice daily. >40 weeks: 3 mg/kg per dose twice daily	
Zanamivir	Adults	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
	Children	≥7 years: 10 mg (two 5-mg inhalations) twice daily	≥5 years: 10 mg (two 5-mg inhalations) once daily

[a]Approved by the Food and Drug Administration down to age 2 weeks. However, on the basis of existing safety information, oseltamivir can be used to treat influenza in both term and preterm infants from birth.
[b]Postmenstrual age is gestational age plus chronological age.

attenuated intranasal vaccine (LAIV) and a recombinant vaccine are available. The antigenic composition of the various vaccines is determined on a yearly basis based on worldwide and national surveillance of current and past influenza seasons. The composition of the 2013–2014 trivalent influenza vaccine is A/California/7/2009 (H1N1)–like virus, A/Victoria/361/2011 (H3N2), and B/Massachusetts/2/2012–like virus. The quadrivalent vaccine contains an additional influenza B strain, B/Brisbane/60/2008–like virus, which will cover both the Victoria and Yamagata lineages. This year, quadrivalent vaccines that contain antigens for 2 strains each of influenza A and B are also available in addition to trivalent vaccines.

Healthy individuals 2 years or older can receive either an inactivated influenza vaccine (IIV) or LAIV. The LAIV is licensed for healthy persons ages 2 to 49 years. It is contraindicated in persons with underlying medical and immunosuppressive conditions. Administration of the vaccine to young infants has also led to wheezing. Although caution is merited, high-risk individuals with impaired immune systems do not appear to have significant adverse events or prolonged viral shedding after the inadvertent exposure to LAIV. Several studies have found superior efficacy of LAIV compared with IIA. (21) In children 6 years or older and adolescents with asthma, the LAIV provided a 32% increase in protection against culture-proven influenza infections when compared with IIA. (22) Viral shedding from the nasopharynx occurs after vaccination, which peaks approximately 2 days after vaccination. Postvaccination symptoms, such as runny nose, headache, and sore throat, do not correlate with viral shedding. Mean duration of shedding was approximately 2.8 days. Viral shedding can be observed with LAIV recipients up to 6 to 8 days after vaccination. With this in mind, practitioners should exercise caution when deciding who should receive this vaccine. Persons caring for persons with

Table 4. **Influenza Vaccines, 2013–2014**

Vaccine Trade Name (Manufacturer)	Presentation and Route of Administration	Mercury Content μg /0.5 mL)	Age Indications
Inactivated, trivalent			
Afluria (CSL Limited)	0.5 mL single-dose prefilled syringe or single-dose vial, IM	0	≥9 years[a]
	0.5 mL, IM (5.0 mL multidose vial)	24.5	≥9 years
Fluarix (GlaxoSmithKline)	0.5 mL single-dose prefilled syringe, IM	0	≥3 years
Flucelvax (Novartis Vaccines and Diagnostics)	0.5 mL single-dose prefilled syringe, IM	0	≥18 years
Flulaval (ID Biomedical Corporation of Quebec)	0.5 mL, IM (5.0 mL multidose vial)	<25.0	≥3 years
Fluvirin (Novartis Vaccines and Diagnostics)	0.5 mL single-dose prefilled syringe, IM	≤1.0	≥4 years
	0.5 mL, IM (5.0 mL multidose vial)	25.0	
Fluzone (Sanofi Pasteur)	0.25 mL, single-dose prefilled syringe, IM	0	6–35 months
	0.5 mL single-dose prefilled syringe or single-dose vial, IM	0	≥36 months
	0.5 mL, IM (5.0 mL multidose vial)	25	≥6 months
Fluzone Intradermal (Sanofi Pasteur)	0.1 mL prefilled microinjection system, ID	0	18–64 years
Inactivated quadrivalent			
Fluarix Quadrivalent (GlaxoSmithKline)	0.5 mL single-dose prefilled syringe, IM	0	≥3 years
Fluzone Quadrivalent (Sanofi Pasteur)	0.25 mL, single-dose prefilled syringe, IM	0	6–35 months
	0.5 mL single-dose prefilled syringe or single-dose vial, IM	0	≥36 months
Flulaval Quadrivalent (ID Biomedical Corporation of Quebec)	0.5 mL, IM (5.0 mL multidose vial)	<25.0	≥3 years
Inactivated, trivalent, high dose			
Fluzone High-Dose (Sanofi Pasteur)	0.5 mL single-dose prefilled syringe, IM	0	≥65 years
Recombinant, trivalent			
FluBlok™ (Protein Sciences)	0.5 mL, single-dose vial, IM	0	18–49 years
Live attenuated, quadrivalent, intranasal			
FluMist Quadrivalent (MedImmune)	0.2 mL intranasal sprayer	0	2–49 years[b]

ID=intradermal; IM=intramuscular.
[a]The Advisory Committee on Immunization Practices recommends that this vaccine not be given to infants and children ages 6 months through 8 years because of an increased risk of febrile reactions. If no other influenza vaccine is available for children ages 5 to 8 years, the vaccine could be used only after discussing with parents or caregivers the risks and benefits of vaccination.
[b]Healthy, nonpregnant individuals.
Table modified from Centers for Disease Control and Prevention. (23)

immunosuppression need to practice caution to minimize the spread of attenuated virus. If caring for severely immunosuppressed persons who require protective environment, the caregiver should not receive this vaccine. (23)

Injectable IIVs are used in individuals who are not candidates for LAIV. Health care workers who work with immunocompromised persons should receive this vaccine. Vaccine effectiveness varies significantly among age groups and persons with various medical conditions. Because of this variability, it is critical that more persons receive their yearly vaccine. The higher the number of vaccinated individuals, the better protected the at-risk community is. This is critical in groups with a large number of infants younger than 6 months.

Antibodies against influenza viruses are type specific. Eighty percent to 95% of children 6 months or older develop protective antibody levels after 2 doses of vaccine. (24) In children ages 6 to 35 months, 50% will develop protective antibody levels, and in those ages 3 to 9 years, 75% will develop protective antibody levels. Vaccine efficacy varies according to season, patient age, type of vaccine, and study design. Using culture-confirmed studies, vaccine efficacy varies between 56% and 100%. Influenza vaccines have been found to be immunogenic and safe when given simultaneously with other vaccines. All infants and children younger than 9 years will require 2 doses of vaccine separated by 4 weeks if receiving the vaccine for the first time.

Most influenza vaccines have been derived from chicken embryo tissue cultures. In persons with documented allergies to egg, the administration of vaccines may be considered to be contraindicated. However, recently, cell culture and recombinant vaccines have become available, allowing for the vaccination of patients with allergies to eggs. Patients with a history of anaphylaxis to egg products should not be vaccinated with chick embryo–derived vaccines (Table 5). Skin testing by an allergist-immunologist is no longer recommended for children with a history of urticaria after the consumption of egg products. (12)(23) A recent retrospective medical record review study of egg-allergic children concluded that patients without a history of anaphylaxis to egg can receive the influenza vaccine without the need for skin testing. (25) Current recommendations of the Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend the use of the newer recombinant vaccine for individuals ages 18 to 49 years with a history of anaphylaxis or hives to egg. (12)(23) For individuals with a history of only hives, vaccination with an IIV can be performed safely.

For infants and children ages 6 to 36 months, a dose of 0.25 mL of the IIV is administered by the intramuscular route. Past age 3 years, 0.5 mL is administered. The intranasal vaccine delivers a dose of 0.1 mL into each nostril.

Recently, an intradermal vaccine became available, resulting in a less painful injection. This vaccine was found to be more immunogenic than vaccines administered via the intramuscular route. There is currently limited experience with this vaccine in young children.

Large postlicensure population-based studies have failed to demonstrate any increase in clinically important medically attended events in the 2 weeks after vaccination. Acute respiratory infections, acute otitis media, and asthma episodes are less common in the weeks after vaccination. Fever, malaise, pain at the site of injection, myalgias, and headaches have been reported after the receipt of influenza vaccines. Wheezing and rhinorrhea have been reported after LAIV. Febrile seizures can occur after vaccination. However, its risk appears to be related to a specific vaccine produced by CSL Biotherapies (Afluria). Because of the risk, this vaccine is not recommended for children younger than 9 years. In transplantation patients, vaccination did not alter allograft function or cause rejection episodes. Oculorespiratory syndrome, an acute, self-limited reaction to IIVs that consists of red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling, has been reported 2 to 24 hours after vaccination. It resolves spontaneously within 48 hours. This syndrome may represent a type of hypersensitivity reaction. Guillain-Barré syndrome has been described after influenza vaccination. The risk is considered low. After vaccination, 1 additional Guillain-Barré syndrome case per 1 million was observed.

Parainfluenza Virus
Biology and Epidemiology

PIVs are members of the Paramyxoviridae family. They are RNA viruses with a viral envelope covered with glycoproteins, such as hemagglutinins-neuraminidases and fusion proteins, that are responsible for the entry into respiratory epithelial cells, where they replicate exclusively.

Table 5. **Influenza Vaccination: Egg Allergy** (12)(23)

Symptom	Treatment
If tolerates lightly cooked eggs (scrambled eggs) without reaction	Vaccinate with LAIV, TIIV, or QIIV
Develops ONLY hives after eating eggs or egg-containing foods	If 18–21 years: administer RIV3 OR TIIV or QIIV (observe for reaction for at least 30 minutes after vaccination)[a]
After eating eggs or egg-containing foods, the child experiences hypotension, respiratory distress (wheezing or throat swelling), nausea or vomiting, and reactions requiring epinephrine and/or medical attention	If 18–21 years: administer RIV3 OR refer to allergist–immunologist

LAIV=live attenuated influenza vaccine (intranasal); QIIV=quadrivalent inactivated influenza vaccine; RIV3=recombinant influenza vaccine, trivalent; TIIV=trivalent inactivated influenza vaccine.
[a]RIV3 is licensed for persons ages 18–49 years.

Other members of this family include respiratory syncytial virus, mumps, measles, and human metapneumovirus. There are 4 antigenically distinct types of PIV (PIV-1, -2, -3, and -4). There are also 2 antigenic subtypes (PIV-4A and PIV-4B). Most of the disease caused by PIV occurs in children younger than 5 years and is responsible for 6% to 11% of hospitalizations due to respiratory infections. (26)(27) Most hospitalizations are in infants younger than 1 year. Parainfluenza viruses are responsible for approximately 4% of all respiratory tract infections. (28) Coinfections with other respiratory viruses are a common occurrence, with percentages as high as 40%. (29) Coinfected children tend to have a longer duration of symptoms and prolonged viral shedding. By age 5 years, all children have been infected by all types of PIV. (30)(31)

PIVs are a frequent cause of childhood disease, such as laryngotracheobronchitis (croup) and pneumonia. PIV-1 and -2 are the most common causes of croup, especially during the fall season, whereas PIV-3 is mostly responsible for lower respiratory tract infections (LRIs), such as bronchiolitis and pneumonia, occurring mostly in the spring and summer months. The epidemiology of PIV-4 has been less known, but it appears to be responsible for URIs and LRIs in infants younger than 6 months. In a recently published retrospective study, PIV-4 had a year-round prevalence with clinical features similar to those of PIV-3. (32) No patients with PIV-4 had croup.

PIV infections mostly involve the large airways of the lower respiratory tract of children. Tropism for this region is influenced by the large number of ciliated epithelial cells in the area. Many of the clinical features of PIV infections are indistinguishable from those observed with other viruses, such as influenza virus (Table 1). PIV-1, -2, and -3 are responsible for most pediatric disease, with PIV-3 being responsible for 50% of all PIV infections. (30)(31) In a study of children in China, PIV-3 was the most common PIV isolated (61% of children), followed by PIV-1 (21% of children). PIV-4 was detected in 10% of children with PIV infection. (33)

Clinical Aspects

The virus is transmitted through exposure to contaminated nasopharyngeal secretions by droplets or contact with contaminated surfaces. The usual incubation period is 2 to 4 days, with viral shedding that may last up to 1 week after onset of symptoms. Infected persons may shed virus up to 1 week before onset of symptoms. The duration of shedding may be serotype specific, with PIV-3 lasting 3 to 4 weeks. Acute otitis media is frequently preceded by infections caused by PIV. PIVs are responsible for 18% to 45% of all URIs. (34)(35) Coryza, rhinorrhea,

pharyngitis, and low-grade fever are common features of URI caused by PIV. Cervical lymphadenopathy is generally absent.

In contrast to influenza viruses, in most communities PIVs circulate all year. Cases of croup observed in the summertime are generally caused by PIVs. The clinical presentation of croup is distinctive. A sudden onset of a hoarse, barkinglike cough accompanied by laryngeal obstruction, dyspnea, and inspiratory stridor is common. Symptoms usually last 3 to 5 days. The presence of fever and recurrence helps differentiate it from spasmodic croup. In some young children, drooling, difficulty swallowing, and decreased appetite can be observed. However, excessive drooling, severe respiratory distress, and a child sitting quietly and still at the edge of a chair are highly suggestive of epiglottitis, an infection usually associated with *Haemophilus influenzae* type b, which now is rare thanks to routine vaccination. Children with croup generally do not require intubation. Children with croup caused by influenza virus tend to be more febrile, have tenacious thick secretions, and have more severe laryngeal obstruction. Subglottic stenosis is a common complication of croup. Subglottic stenosis may lead to prolonged intubation and/or symptoms of coughing and respiratory distress. A steeple sign is frequently observed on an anteroposterior radiograph of the neck and chest. The epiglottis appears normal on a lateral neck radiograph. PIV-1 is isolated in most children with croup. Laryngitis in children is frequently caused by a PIV.

All types of PIV, but especially PIV-1 and PIV-3, cause bronchiolitis, which is indistinguishable from disease caused by respiratory syncytial virus and human metapneumovirus. Five percent to 15% of bronchiolitis cases are caused by PIV. (36)(37) Fever, tachypnea, retractions, expiratory wheezing, rales, and air trapping are common features. Approximately 10% of outpatient LRIs are caused by PIV-1, -2, and -3. Young infants, especially those born prematurely, can experience apnea in the presence of an LRI. Most hospitalizations will occur in the first year of life. Conjunctivitis is observed in more than 35% of infected children. The most severe LRI will occur in chronically ill or immunocompromised children. Patients with weakened immune systems, such as those with T-cell deficiencies or who have undergone hematopoietic stem cell transplantation, are at risk of more severe disease, such as pneumonia. Pneumonia in this population can be life-threatening, with a fatality rate of approximately 30%. (38)(39) Patients undergoing HSCT have the highest mortality, especially in the first 100 days of the transplantation, when lymphopenia is common. Prolonged viral shedding is a common feature of children

with primary immunodeficiency. Reinfections are common but tend to be milder or asymptomatic in the otherwise immunocompetent host.

Diagnosis

With the exception of direct fluorescent and PCR assays, there are no rapid diagnostic assays, especially for point-of-care testing. Diagnosing PIV infection can be important because it may obviate the use of antibacterial therapy. Most laboratories consider nasopharyngeal aspirates and washes to be the most optimal specimens for the detection of respiratory viruses by reverse-transcription PCR and direct immunofluorescence. However, nasopharyngeal flocked swabs are easier to perform and are better tolerated by patients. The sensitivity of both methods was excellent (100%) for respiratory viruses other than adenovirus. (40) PCR-based testing from bronchoalveolar lavage has high sensitivity and specificity.

Treatment

There is no available licensed antiviral therapy for the treatment of PIV infections. Aerosolized or systemic ribavirin with and without intravenous immunoglobulin has been used as treatment in immunocompromised children and adults with severe disease. (41) Most of the gathered experience comes from uncontrolled trials or anecdotal reports. However, on the basis of the favorable results of these limited trials, this regimen should be considered in the compromised child with lower respiratory tract disease. Management of these infections is supportive.

Attention to proper hydration so the child can mobilize secretions appears to be reasonable However, the use of humidified inhaled air (cool mist) delivered in a tent or hood has no demonstrable benefit for the child with croup. (42)(43) In patients with croup, the use of epinephrine and dexamethasone is associated with a reduction of symptoms. The use of nebulized budesonide and intramuscular and oral dexamethasone has been found to be beneficial in patients with croup, resulting in shorter hospital stays and fewer return visits. (44) In comparative studies, they appear to be equally effective. (45)(46) Nebulized epinephrine is associated with a reduction in symptoms of croup. (47) Most practitioners will give this agent in combination with a corticosteroid.

Prevention

There are no available vaccines. Handwashing is an effective way of preventing the transmission of respiratory viruses. Transmission appears to be related to contact with infectious droplets.

Summary

- On the basis of strong epidemiologic evidence, influenza and parainfluenza viruses are responsible for significant morbidity and mortality in young infants and children and in persons with chronic medical conditions. (1)(4)(26)(27)(35)
- On the basis of research evidence, influenza vaccines are effective in preventing disease in high–risk individuals. (8)(17)(18)
- On the basis of strong research evidence, influenza vaccines are safe in young infants and children 6 months or older. (8)(15)
- On the basis of research evidence, the use of corticosteroids and epinephrine is beneficial in the treatment of laryngotracheitis caused by parainfluenza viruses. (44)(45)(46)(47)
- Strong evidence supports the use of influenza vaccines in pregnant mothers as a strategy to prevent disease in infants younger than 6 months. (17)(18)(19)

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1. A previously healthy 5-year-old boy has a 3-day history of high temperatures, sore throat, coughing, and malaise. He is diagnosed as having influenza A. Which of the following statements is correct about his condition?

   A. He is likely to benefit from oseltamivir.
   B. Oseltamivir is not likely to be beneficial.
   C. A prophylactic antibiotic would be beneficial.
   D. A chest radiograph is always indicated.
   E. Hospitalization is required.

2. Which of the following vaccine strategies would be most protective of an infant boy younger than 6 months?

   A. Vaccination of the infant in the first 6 months of life.
   B. Vaccination of the teachers of his siblings.
   C. Use of oseltamivir chemoprophylaxis during influenza season.
   D. Avoidance of state fairs.
   E. Vaccination of mother during pregnancy, caregivers, and school-age siblings.

3. A healthy 5-year-old girl gets an upset stomach when she eats eggs. The parents deny hives or respiratory distress. Which of the following statements would best describe her ability to receive the yearly influenza vaccine?

   A. She has a serious egg allergy and should not receive the vaccine.
   B. She can receive the live attenuated intranasal vaccine but not the inactivated type.
   C. She does not have a significant egg allergy and can receive the vaccine safely.
   D. Do not vaccinate. Use chemoprophylaxis instead.
   E. Give vaccine preceded by injection of epinephrine.

4. A 2-year-old boy has a croup-like illness. Which of the following statements is FALSE?

   A. Parainfluenza types 1 and 2 are common causes of croup.
   B. Previously healthy children should receive ribavirin as antiviral therapy.
   C. Child may benefit from receiving dexamethasone and epinephrine.
   D. Crouplike symptoms accompanied by high temperatures most likely represent an infection by influenza virus.
   E. Subglottic stenosis is a known complication.

5. Influenza vaccines are effective in preventing disease in high-risk children. Which of the following statements is/are CORRECT?

   A. Patients with asthma can receive live-attenuated intranasal vaccine.
   B. Recombinant influenza vaccine can be administered to a 5-year-old egg-allergic child.
   C. Yearly influenza vaccination of household contacts will diminish risk of acquiring infection.
   D. Intranasal quadrivalent vaccine is protective against 4 strains of influenza A.
   E. B and D

Cystic Fibrosis CME Quiz Correction

In the May 2014 article "Cystic Fibrosis" (Paranjape SM and Mogayzel PJ. *Pediatrics in Review.* 2014:35(5):194. DOI: 10.1542/pir.35-5-194), there was an error in Question 2 of the CME quiz. The query sentence before the answer options should read: "The most likely explanation for the normal newborn screen finding is that: … ." The correct answer option – E – remains unchanged. The online versions of the article and quiz have been corrected. The journal regrets the error.

Influenza and Parainfluenza Viral Infections in Children

Thomas G. Fox and John C. Christenson

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Pediatrics. Dr Nagan, a resident from Boston University School of Medicine and Harvard Medical School Pediatric Residency Program, wrote this case report. Choosing which case to publish involved considerations of the teaching value and excellence of writing, but also the content needs of the journal. Another case will be chosen from the finalists presented at this year's AAP National Conference and Exhibition and published in the September 2015 issue of Pediatrics in Review.

To view Suggested Reading lists for these cases, visit https:// pedsinreview.aappublications.org and click on the "Index of Suspicion" link.

Parent Resources from the AAP at HealthyChildren.org

Case 4:

- English: http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Celiac-Disease.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/abdominal/Paginas/Celiac-Disease.aspx

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Corrections

In the July Pediatrics in Review article "Pneumococcal Infections" (Maraq N. Peds in Rev. 2014;35(7):299–310, doi: 10.1542/pir.35-7-299), there is an error on page 301, column 2, line 2. The parenthetical phrase should read: " ... (82% reduction from 205 to 37 cases per 100,000 population ... "). The journal regrets the error.

The June 2014 article "Influenza and Parainfluenza Viral Infections" (Fox TG and Christenson JC. *Pediatrics in Review.* 2014;35(6):217–228, doi: 10.1542/pir.35-6-217) contained an abbreviation error on p. 22, column 2, lines 6 and 9. The abbreviation "IIA" should be "IIV." The sentences should read: "Several studies have found superior efficacy of LAIV compared with IIV. (21) In children 6 years or older and adolescents with asthma, the LAIV provided a 32% increase in protection against culture-proven influenza infections when compared with IIV. (22)" The journal regrets the error.

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Pediatrics in Review 2014;35;217
DOI: 10.1542/pir.35-6-217

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