THIS ACTIVITY IS SUPPORTED BY AN EDUCATIONAL GRANT FROM GENENTECH.

Reaching Out: The Benefit of Treating Influenza: The Role of the Pharmacist as Patient Educator and Advocate

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EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:
- Identify patients who may benefit from influenza treatment
- Examine influenza treatment strategies consistent with guidelines
- Explore currently available therapies for the treatment of influenza
- Illustrate the role of the pharmacist in treating influenza

TARGET AUDIENCE: Retail and health-system pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: April 15, 2019

EXPIRATION DATE: May 15, 2020

ESTIMATED TIME TO COMPLETE ACTIVITY: 3.0 hours

FEE: This lesson is offered for free at www.pharmacytimes.org.

OVERVIEW OF INFLUENZA

Influenza (also commonly called the flu) is an acute, contagious upper respiratory tract illness caused by influenza viruses A, B, or C that infect the nose, throat, and sometimes the lungs. It can range from a mild illness that does not require extensive medical care to a severe illness that requires hospitalization and can lead to death. In the United States, the highest rates of influenza illness occur during the fall and winter (October to May), and it typically peaks in February.[1]

Epidemiology

The incidence of influenza illness varies significantly each year and depends on a number of factors including antigenic changes of circulating viruses, timing of the season, vaccine match, and how many people received the vaccination.[2] A study by Nicholson et al estimated that 20% of children and 5% of adults worldwide are affected by influenza annually.[3] The FIGURE[2] provides estimates from the Centers for Disease Control and Prevention (CDC) since 2010 and highlights the annual burden of influenza.

For the 2017-2018 influenza season, the CDC estimated an overall 48.8 million cases of influenza-associated illness; 22.7 million health care provider visits; 959,000 hospitalizations; and 79,400 deaths from influenza.[4] The 2017-2018 influenza season was atypical in that it was severe for all ages and affected each age group differently. Influenza-associated illness was highest in the 50- to 64-year-old age group, with 24,558 cases per 100,000 individuals.[4] Health care provider visits were highest in the 0- to 4-year-old age group, with 13,389 per 100,000.[4] Hospitalization and mortality were highest for those 65 years and older at 1306 and 134 per 100,000, respectively.[4] The number of cases of influenza illness that occurred during the 2017-2018 influenza season was the highest since the 2009 H1N1 pandemic.[4]

Etiology

Influenza viruses are single-stranded RNA viruses that are members of the *Orthomyxoviridae* family. The 3 types of influenza viruses that infect humans are types A, B, and C.[5] Influenza A is responsible

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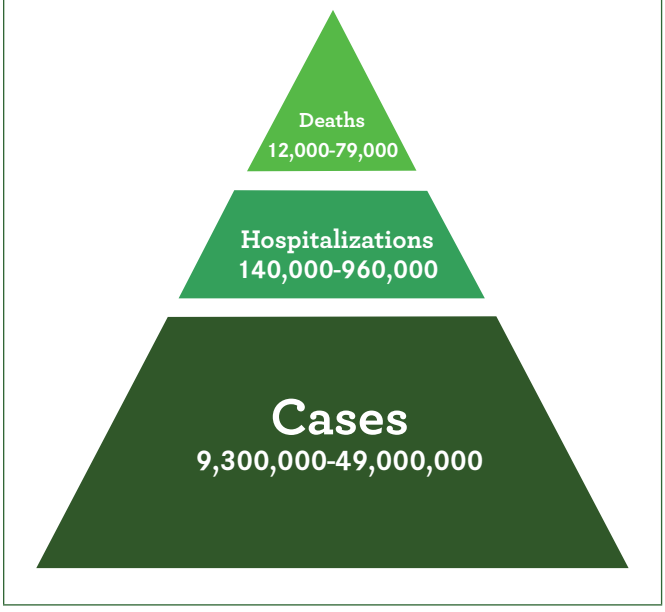
FIGURE. ESTIMATED RANGE OF ANNUAL BURDEN OF FLU IN THE UNITED STATES SINCE 2010[2]



for pandemics.[5] Influenza A and B are responsible for seasonal epidemics.[5] Influenza C is not associated with pandemics or epidemics.[5]

- **Influenza A:** Viruses are classified into subtypes based on the hemagglutinin (H) and neuraminidase (N) surface antigens. Hemagglutinin allows the influenza virus to attach and enter the host cells.[3] Neuraminidase allows the mature virus particles to be released from the host cells.[3] Although 18 different hemagglutinin subtypes (H1-H18) and 11 different neuraminidase subtypes (N1-N11) are known, types H1, H2, H3, N1, and N2 have circulated among humans.[3,5]
- **Influenza B:** Viruses are not classed as subtypes but rather by lineages (Yamagata and Victoria).[5]
- **Influenza C:** Viruses usually cause a mild illness and therefore do not represent a public health concern.[5]

Seasonal outbreaks and pandemics of influenza continue to occur because the virus is constantly evolving.[3] New influenza viral surface antigens arise from 2 processes: (1) gradual antigenic drift and (2) rapid antigenic shift. Antigenic drift leads to the emergence of a new viral strain because of point mutations that accumulate during viral replication. Seasonal outbreaks of influenza A and B are caused by gradual genetic changes due to antigenic drift, whereas influenza A pandemics are caused by the sudden acquisition of new genetic material due to antigenic shift. Together, antigenic drift and shift help explain why the burden of influenza changes within and between seasonal outbreaks.[3]

Pathophysiology

The influenza virus is transmitted from person to person via inhalation of respiratory droplets that become aerosolized through coughing, sneezing, or talking.[6] Transmission via self-inoculation with contaminated inanimate objects can also occur.[7]

The incubation period for influenza ranges from 1 to 4 days (average, 2 days).[7] Adults can be infectious beginning 1 day before and for up to 5 to 7 days after symptoms develop.[7] Children and people with compromised immune systems can shed virus and remain infectious for an even longer period of time. Uncomplicated influenza typically resolves in 3 to 7 days, although the cough and malaise can persist for more than 2 weeks.[7]

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What are examples of patients who are at increased risk for influenza-related complications?

**S = Stop; T = Think; A = Assess; R = Review*

Patients at High Risk for Complications

The groups of patients most likely to experience influenza-related complications are very young children, older adults, pregnant and postpartum women, persons with certain chronic medical conditions (ie, pulmonary, cardiovascular, renal, hepatic, hematologic, and metabolic disorders; neurologic and neurodevelopment conditions), persons with immunosuppression, children and adolescents taking aspirin (due to the risk of Reye syndrome), American Indians and Alaskan Natives, persons with extreme obesity, and residents of nursing homes or other long-term care facilities.[8,9]

Children younger than 5 years, especially those younger than 2 years, are a high-risk population.[10] The CDC estimates that since 2010, between 7000 and 26,000 children younger than 5 years have been hospitalized related to influenza illness and its complications.[10] Since the 2004-2005 influenza season, influenza-related deaths in children have ranged from 37 to 185 annually, depending on the severity of the season.[10]

Pregnant and postpartum women within 2 weeks of delivery are more susceptible to influenza and its complications due to physiologic changes in the heart, lungs, and immune system that happen during pregnancy.[11] In addition, influenza viral infection may be harmful to the developing fetus. Fever is a common symptom of influenza, and developing a fever early in the first trimester may increase the risk of a neural tube defect.[11] However, this risk may be reduced in pregnant women who are receiving 400 mcg of folic acid daily.

Adults 65 years and older represent another population at high risk for influenza and its complications. These patients account for 50% to 70% of influenza-related hospitalizations and 70% to 90% of influenza-related deaths.[12] In addition, members of the older adult population typically have chronic medical conditions, many of which are also risk factors for influenza and related complications. These can include chronic obstructive pulmonary disease (COPD), heart failure, kidney disease, liver disease, diabetes, and weakened immune system.[8] Patients with asthma or heart failure may experience an exacerbation of the condition that is triggered by influenza infection.

Economic Burden

Depending on the severity of the influenza season, the annual economic burden can be significant. Economic burden encompasses both direct costs, such as outpatient visits and hospitalizations, and indirect costs, such as lost productivity and earnings due to illness. Using 2003 US dollars, Molinari et al estimated direct medical costs to average $10.4 billion annually, which includes 3.1 million hospital-days and 31.4 million outpatient visits.[13] The same study estimated indirect costs at $16.3 billion annually; the overall economic burden of annual influenza was estimated at $87.1 billion.[13] Additionally, with an estimate of 41,008 deaths in case patients, the study calculated an average of 610,660 life-years lost annually.[13] These results highlight the large burden of annual influenza and also show that even though medical expenses are a contributing factor, lost productivity from missed workdays and lost lives make up the majority of the economic burden.

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What are the similarities and differences in symptom presentation of influenza versus those of the common cold?

Clinical Presentation and Symptoms

Influenza can be challenging to diagnose because the presentation is similar to several other respiratory illnesses (eg, rhinovirus, respiratory syncytial virus, parainfluenza, and adenovirus). Clinical diagnosis can be made more sensitive depending on the prevalence of circulating influenza viruses in the community.[14] The most common tests used in outpatient settings to detect influenza viruses to confirm infection are called rapid influenza diagnostic tests (RIDTs).[14] These tests detect influenza antigens and provide the results within 10 to 15 minutes.[14]

Common signs and symptoms of influenza include sudden onset of severe fatigue, malaise, myalgia, nonproductive cough, headache, sore throat, and rhinitis with or without fever.[7] Patients presenting with influenza often remember and can state the exact moment when they began to feel ill. This is in contrast to rhinovirus (eg, common cold), where patients initially present with a slow-onset, scratchy sore throat followed by rhinorrhea and nasal congestion symptoms.

Complications of Influenza

Complications of influenza include primary viral pneumonia, secondary bacterial pneumonia, or other respiratory illnesses (eg, bronchitis, otitis media, and sinusitis).[15] Less common but severe complications that can be triggered by influenza infection include myocarditis, encephalitis, myositis, and rhabdomyolysis; chronic medical conditions can also be exacerbated.[16]

Primary influenza viral pneumonia is a direct lung infection with the influenza virus. This infection primarily occurs in pregnant women and those with chronic cardiovascular disease.[15] Patients typically present with classic influenza symptoms that gradually progress to shortness of breath with productive cough with bloody sputum.[17]

TABLE 1. INFLUENZA VACCINES APPROVED FOR THE 2018-2019 INFLUENZA SEASON[20]

Category of Influenza Vaccine	Brand Name	Age Indication
Inactivated influenza vaccine (IIV)	Afluria Quadrivalent	≥5 years (needle/syringe) 18–64 years (jet injector)
	Fluarix Quadrivalent	≥6 months
	FluLaval Quadrivalent	≥6 months
	Fluzone Quadrivalent	≥6 months (depending on presentation)
	Flucelvax Quadrivalent	≥4 years
	Afluria [Trivalent]	≥5 years (needle/syringe) 18–64 years (jet injector)
	Fluzone High-Dose	≥65 years
	Fluad [Adjuvanted]	≥65 years
Recombinant hemagglutinin influenza vaccine (RIV)	Flublok Quadrivalent	≥18 years
Live-attenuated influenza vaccine (LAIV)	FluMist Quadrivalent	2–49 years

The most common complication of influenza is secondary bacterial pneumonia. In this case, pneumonia is thought to be due to the resolution of inflammation caused by the initial influenza viral infection.[18] The body's mechanisms to restore tissues damaged by the virus impair the natural host response to unrelated bacterial pathogens.[18] Pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*.[15] Patients typically present with fever, productive cough, and evidence of consolidation upon chest radiograph.[15] Pneumonia is seen in high-risk individuals as well as those with underlying pulmonary conditions. Factors associated with increased risk of pneumonia include age 75 years and older, nursing home residence, chronic lung disease, immunosuppression, and asthma.[19] Hospitalized patients with influenza and pneumonia were more likely to be admitted to the intensive care unit, require ventilation, and die.[19]

PREVENTION OF INFLUENZA

Vaccinations

The most effective treatment strategy for influenza is prevention utilizing one of the available vaccines.[9] There are 3 categories of influenza vaccine available: (1) inactivated influenza vaccine (IIV), (2) recombinant hemagglutinin influenza vaccine (RIV), and (3) live-attenuated influenza vaccine (LAIV). See TABLE 1.[20]

Current Vaccination Guidelines

The Advisory Committee on Immunization Practices (ACIP) of the CDC recommends that all persons 6 months and older without contraindications receive the influenza vaccine annually.[20] The ACIP has no preferential recommendation for any influenza vaccine over another.[20] Vaccination before the onset of influenza activity in the community is important as it takes 14 days following administration for the vaccine to be effective.[20]

Two recent changes were made with regard to influenza vaccine dosing. Fluarix Quadrivalent and FluLaval Quadrivalent received FDA approval for a 0.5-mL dose to be used for children aged 6 through 35 months, which is the same dose as that used for older children and adults.[20]

Current Coverage Provided by the Vaccine

Data suggest that the influenza vaccine reduces the risk of influenza infection by 40% to 60% in the general population when the vaccine is well matched to circulating viruses.[21] Older adults and immunocompromised individuals often have a lower protective effect from the vaccine. Although immune responses may be lower, vaccine effectiveness has been similar to that of healthy adults in these populations.[12]

Benefits of Vaccination

Below is a summary of benefits for receiving influenza vaccine annually.

- **Vaccination prevents influenza illness.** It is estimated that during the 2016-2017 influenza season, the vaccine prevented 5.3 million influenza illnesses and 2.6 million influenza-associated medical visits.[22]
- **Influenza vaccination reduces the risk of influenza-associated hospitalizations.** During the 2016-2017 influenza season, influenza vaccination prevented an estimated 85,000 influenza-related hospitalizations.[22] Results of a study conducted by Ferdinands et al found that the influenza vaccine reduced children's risk of influenza-related admission to the pediatric intensive care unit by 74%.[23] A 2017 systematic review and meta-analysis found the influenza vaccine to reduce the risk of influenza-associated hospitalizations among adults aged 18 to 64 years by 41% and among adults 65 years and older by 37%.[24]
- **Influenza vaccination helps prevent medical events associated with chronic medical conditions.** Results of a meta-analysis of randomized controlled trials found the use of influenza vaccine to be associated with reduced risk of cardiovascular events among high-risk patients who had a cardiac event in the previous 12 months.[25]
- **Influenza vaccination protects pregnant and postpartum women.** Vaccination reduces the risk of influenza-associated acute respiratory illness in pregnant women by 50%.[26] Results from a 2018 study found a 40% reduction in a pregnant woman's risk of being hospitalized with influenza.[27] Additionally, maternal influenza vaccination can protect the infant from influenza after birth because the mother passes antibodies to the baby during the pregnancy.
- **Influenza vaccination can be lifesaving for children.** A case-cohort analysis published in 2017 in *Pediatrics* reiterates the importance of routine influenza vaccination in all children 6 months and older. The results of the study showed that influenza vaccination reduced the risk of death by 51% in children with chronic medical conditions and by 65% among healthy children.[28]
- **Influenza vaccination provides herd immunity.** Influenza vaccination of healthy persons in the community can provide herd immunity, protecting those who are vulnerable to influenza illness, such as infants, young children, older adults, and those with certain chronic medical conditions.[29]

Vaccine Hesitancy

Common barriers identified that led adults to never receive an influenza vaccination included lack of health insurance, disliking shots, perception of low vaccine effectiveness, perception of low risk for influenza infection, and perception of adverse effects.[30]

Consequences of Low Vaccination Rates

In addition to the individual being susceptible to influenza infection due to low vaccination rates, the herd immunity protection for those who cannot receive vaccination is reduced. Those who would rely on herd immunity include children younger than 6 months and persons with severe, life-threatening allergies to the vaccine or a vaccine component.

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Which organizations develop clinical practice guidelines for the diagnosis, treatment, and prophylaxis of influenza?

CURRENT GUIDELINES FOR INFLUENZA

When prevention efforts are unsuccessful or fail, treatment of influenza with available antiviral agents is the next option. The Infectious Diseases Society of America (IDSA) and the CDC have clinical practice guidelines for the diagnosis, treatment, and chemoprophylaxis of seasonal influenza.[9,31] IDSA published updated guidelines in 2018, which was its first update since 2009. The CDC publishes annual recommendations. The CDC provides the following recommendations regarding the use of antiviral

drugs in the treatment of influenza:

- Antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who need hospitalization; or who are at high risk for influenza complications.[31]
- Decisions to initiate antiviral therapies should not wait for laboratory confirmation of influenza.[29] The greatest clinical benefit with antiviral treatment is seen when therapy is started as close to illness onset as possible.
- For patients with acute uncomplicated influenza, oseltamivir, zanamivir, peramivir, or baloxavir may be used for treatment.[31]
- Oseltamivir is the preferred treatment for pregnant women.[31]
- For nonhospitalized patients with severe or complicated influenza with or without laboratory confirmation, oseltamivir is recommended as soon as possible.[31]
- For hospitalized patients with or without laboratory confirmation, oseltamivir is recommended as soon as possible.[31]

Goals of Treatment

Goals of treatment of influenza are 4-fold: (1) control symptoms, (2) prevent complications, (3) decrease work and/or school absenteeism, and (4) prevent the spread of infection to others.[32]

Influenza Prophylaxis

Influenza prophylaxis can be either pre- or post-exposure. Neither the CDC nor IDSA guidelines recommend routine pre-exposure prophylaxis with influenza antiviral drugs.[9,31] Chemoprophylaxis with antivirals may be considered in the following patient populations:

- For high-risk patients during the 2 weeks following vaccination with exposure to influenza[31]
- For high-risk patients who cannot receive the vaccine due to a contraindication with exposure to influenza[31]
- In patients with immunosuppression who might not adequately respond to the influenza vaccine with exposure to influenza[31]

Postexposure prophylaxis is also not recommended by either the CDC or IDSA guidelines but may be considered to control institutional influenza outbreaks.[31] The rationale for this is to avoid subtherapeutic dosing resulting in antiviral resistance if the patient has already been infected with influenza.[31]

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Which influenza antiviral is a 1-dose treatment indicated for acute, uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours?

TREATMENT

Pharmacotherapy of influenza has evolved progressively since the first influenza antiviral agent, amantadine, received FDA approval in 1967.[33] An adamantane, either amantadine or rimantadine, was the only treatment option for the next 30 years. But, by 2005, widespread resistance had rendered adamantanes essentially obsolete. In 1999, the influenza armamentarium was bolstered by FDA approval of the neuraminidase inhibitors, oral oseltamivir and inhaled zanamivir.[33] Approval of peramivir in 2014 provided clinicians the first neuraminidase inhibitor for intravenous (IV) administration. Neuraminidase resistance is now a threat, as evidenced by the 2009 pandemic of oseltamivir-resistant influenza A(H1N1).[33] In 2018, the influenza armamentarium expanded again with the FDA's approval of baloxavir, the first endonuclease inhibitor.

Currently available treatment options for influenza in the United States include antiviral pharmacotherapy, adjunct agents, and nonpharmacologic therapies. This includes 6 prescription-only influenza antiviral drugs from 3 different pharmacologic classes, neuraminidase inhibitors, endonuclease inhibitor, and adamantanes. Just 4 of the available drugs are recommended for use during the 2018-2019 influenza season, the 3 neuraminidase inhibitors and 1 endonuclease inhibitor.[31]

Neuraminidase Inhibitors

Neuraminidase inhibitors include oseltamivir (Tamiflu), zanami-

TABLE 2. OSELTAMIVIR DOSING[34]

Age	Weight	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
2 weeks to <1 year	Any weight	3 mg/kg twice daily	Not indicated
1 to 12 years	≤15 kg	30 mg twice daily	30 mg once daily
	15.1–23 kg	45 mg twice daily	45 mg once daily
	23.1–40 kg	60 mg twice daily	60 mg once daily
	≥40.1 kg	75 mg twice daily	75 mg once daily
≥13 years[a]	Any weight	75 mg twice daily	75 mg once daily

[a]Dose adjustments suggested for patients with renal impairment who have a creatinine clearance less than or equal to 60 mL/minute. Please see package insert for additional information.

TABLE 3. ZANAMIVIR DOSING[35]

Indication	Dose	Duration
Treatment of influenza	10 mg twice daily	5 days
Prophylaxis		
• Household setting	10 mg once daily	10 days
• Community outbreaks	10 mg once daily	28 days

vir (Relenza), and peramivir (Rapivab). The mechanism of action is inhibition of the neuraminidase enzyme, which is responsible for cleaving the influenza virus particles just prior to release from the host cell. Neuraminidase inhibitors have activity against both influenza A and B viruses.[31]

Class adverse effects with neuraminidase inhibitors include serious skin reactions and neuropsychiatric events.[34-36] Although causality has not been established, sporadic transient neuropsychiatric events have been primarily reported among pediatric patients with a rapid onset and resolution.[34-36] Administering neuraminidase inhibitors in close proximity may potentially reduce the effectiveness of LAIV. The administration of neuraminidase inhibitors from 48 hours prior to and up to 2 weeks after LAIV should be avoided, unless medically required.[34-36]

Influenza viruses have demonstrated resistance to neuraminidase inhibitors, but the incidence is currently low. To date during the 2018-2019 influenza season, 99.4% and 99.7% of tested A/(H1N1)pdm09 viruses were susceptible to oseltamivir and peramivir, respectively, whereas 100% of the A/(H1N1)pdm09 viruses tested were susceptible to zanamivir.[37] Of the other viruses tested, including A(H3N2), B/Victoria, and B/Yamagata, 100% were susceptible to all 3 neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir).[37]

Oseltamivir

Oral oseltamivir is indicated for the treatment of acute, uncomplicated influenza in patients 2 weeks and older who have been symptomatic for no more than 48 hours.[34] In addition, oseltamivir is indicated for prophylaxis of influenza in patients 1 year and older.[34]

Oseltamivir dosing is based on indication (ie, treatment vs prophylaxis), age, weight, and renal function (see TABLE 2).[34] Although it can be taken with or without food, taking oseltamivir with food improves gastrointestinal tolerability.[34] Treatment for longer than 5 days can be considered for patients who remain severely ill after 5 days of treatment.[31] Oseltamivir is available as an oral capsule (30 mg, 45 mg, and 75 mg) and a suspension for reconstitution (6 mg/mL). When the suspension is not available, capsule contents can be mixed with a small amount of a sweetened liquid.[34] Common adverse effects with oseltamivir include nausea, vomiting, and headache.

Zanamivir

Inhaled zanamivir is indicated for the treatment of acute, uncomplicated influenza in patients 7 years and older who have been symptomatic for no more than 2 days.[35] It is indicated for the prophylaxis of influenza in patients 5 years and older.[35]

Dosing for inhaled zanamivir is based on indication (ie, treatment vs prophylaxis) (see TABLE 3).[35] Zanamivir is available as four 5-mg blisters of powder on a disk for inhalation via a specific inhaler device. Patients should be instructed how to use the blisters with the delivery device. Zanamivir is not recommended for patients with chronic lung disease (eg, asthma, COPD) because it can cause bronchospasm or a decline in respiratory function in this patient population. Common adverse effects of zanamivir during influenza treatment include sinusitis and dizziness.[35]

Peramivir

IV peramivir is indicated for the treatment of acute, uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days.[36] Peramivir is not indicated for prophylaxis.

Peramivir dosing is based on age and renal function (see TABLE 4).[36] It is given as a single IV infusion over a minimum of 15 minutes.[36] Peramivir is available as 200 mg in 20-mL single-use vials that must be diluted before administration. The most common adverse effect reported with peramivir is diarrhea.[36]

Data are insufficient to establish the role of IV peramivir in treating hospitalized patients with influenza.[9,31] Five days of treatment with peramivir failed to demonstrate superiority over placebo for time to clinical resolution in a clinical trial that enrolled adults and children, but appeared equivalent to oral oseltamivir for time to clinical stability in a phase 2 clinical trial of adults hospitalized for influenza.[37,38] The CDC and IDSA advise clinicians to consider IV peramivir when oral oseltamivir cannot be used.[9,31] However, the optimal dosing regimen for influenza in hospitalized patients has not been established.[9,31]

TABLE 4. PERAMIVIR DOSING[36]

Age	Dose (Normal Renal Function)	Dose (CrCl ≥50 mL/minute)	Dose (CrCl 30-49 mL/minute)	Dose (CrCl 10-29 mL/minute)
2 to 12 years	12 mg/kg (up to 600 mg)	12 mg/kg (up to 600 mg)	4 mg/kg (up to 600 mg)	2 mg/kg (up to 600 mg)
≥13 years	600 mg	600 mg	200 mg	100 mg

CrCl indicates creatinine clearance.

Endonuclease Inhibitor

Baloxavir marboxil

Approved by the FDA in 2018, baloxavir marboxil (Xofluza) is the first and only cap-dependent polymerase acidic endonuclease inhibitor available in the United States.[39] This novel agent is the first influenza antiviral agent in almost 20 years with a new mechanism of action.[39] By inhibiting endonuclease activity, which is required for viral gene RNA transcription, baloxavir inhibits influenza virus replication. Baloxavir has activity against both influenza A and B viruses, including strains resistant to current antiviral drugs.[31,40]

Baloxavir marboxil is a prodrug that is converted to the active form baloxavir. Baloxavir is indicated for the treatment of acute, uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours.[41] The clinical trials for baloxavir did not include patients 65 years and older, so it is unclear if older adult patients will respond differently.[41] Baloxavir is not indicated for prophylaxis.

Baloxavir efficacy and safety were evaluated in a phase 2 trial that compared it with placebo and a phase 3 trial (CAPSTONE-1) that compared it with placebo and oseltamivir in adults and adolescents with uncomplicated seasonal influenza.[40] An additional phase 3 trial (CAPSTONE-2) in patients at higher risk of influenza complications has not been published yet.[42] In the phase 2 trial, the median time to alleviation of influenza symptoms was 23.4 to 28.2 hours sooner with baloxavir than placebo (P <.05).[40] In the phase 3 CAPSTONE-1 trial, the median time to alleviation of influenza symptoms was 53.7 hours for baloxavir compared with 80.2 hours with placebo (P <.001), a median difference of 26.5 hours. The time to alleviation of influenza symptoms was similar with baloxavir and oseltamivir. Relative to placebo, patients who started baloxavir within 24 hours of symptom onset had significantly more rapid alleviation of symptoms (median difference 32.8 hours; P <.001) than those who started it later (median difference 13.2 hours; P = .008).

Results from the CAPSTONE-1 trial suggest that baloxavir could reduce the potential for influenza transmission to close contacts. The reduction in infectious viral load 1 day after initiation was greater with baloxavir than with oseltamivir or placebo. For baloxavir, oseltamivir, and placebo, the median reduction in infectious viral load ($\log_{10}$ 50% tissue-culture infective dose) from baseline was 4.8, 2.8, and 1.3, respectively. The median duration of infectious virus detection was also shorter with baloxavir (24 hours) than with either oseltamivir (72 hours; P <.001) or placebo (96 hours; P <.001). Adverse effects were reported in 20.7%, 24.6%, and 24.8% of baloxavir, placebo, and oseltamivir patients, respectively.[40]

Dosing for oral baloxavir is based on weight (see TABLE 5).[41] Because a single oral dose is all that is needed for influenza treatment, baloxavir can be considered for patients in whom adherence could be a concern.

Baloxavir is available as 20-mg and 40-mg tablets and may be taken with or without food; however, coadministration of baloxavir and polyvalent cations (eg, calcium, iron, magnesium, selenium, zinc) should be avoided as they will chelate, reducing the systemic absorption and, therefore, the efficacy of baloxavir.[43] This would include antacids, laxatives, and vitamin/mineral supplements. The interaction was discovered during animal trials and is being extrapolated to humans.[43] Baloxavir solubility was found to be independent of pH.[44] Additionally, no clinically significant changes in pharmacokinetics were found when baloxavir was coadministered with CYP450 substrates or inhibitors.[45] Therefore, it can be anticipated that administration with proton pump inhibitors and histamine 2 receptor antagonists should not be a problem.

TABLE 5. BALOXAVIR DOSING[41]

Weight	Recommended Dose
40 kg to <80 kg	Single dose of 40 mg
≥80 kg	Single dose of 80 mg

Adverse effects associated with baloxavir were similar to placebo.[31,41] The adverse effects with baloxavir compared with placebo occurring in at least 1% of the study participants included diarrhea (3% vs 5%), bronchitis (2% vs 4%), nausea (1% vs 1%), nasopharyngitis (1% vs 1%), and headache (1% vs 2%).[41]

The influenza strains circulating from the current and past 2 influenza seasons show low reduced susceptibility to baloxavir. However, there has been resistance seen in Japan, so it will be important to continue monitoring baloxavir resistance.[46,47]

Adamantanes

Amantadine and rimantadine are in the adamantane class and prevent the release of viral RNA into the host cell by blocking the M2 ion channel protein, specifically in influenza A viruses. Therefore, these drugs do not have activity against influenza B viruses. Previous influenza seasons show high levels of resistance (>99%) to adamantanes among circulating A(H3N2) and A(H1N1)pdm09 viruses.[29] Consequently, amantadine and rimantadine are not recommended for treatment or prophylaxis of currently circulating influenza A viruses.[31]

Importance of Timing in Treatment

Early initiation of antiviral pharmacotherapy is imperative as available agents are most effective if started within 48 hours of the onset of symptoms. Furthermore, the sooner that antiviral drugs are initiated after the onset of symptoms, the more effective they are. Data suggest the ideal initiation period is within 12 hours of illness onset.[48] Starting antiviral therapy within 48 hours can reduce fever and influenza symptoms and shorten the duration of illness by approximately 1 day.[49,50]

Despite this, late initiation of an antiviral may still have some benefit. A randomized clinical trial in 1190 children with uncomplicated influenza stratified patients according to how soon

oseltamivir was started after symptom onset.[51] The duration of symptoms and influenza virus shedding was modestly reduced even in patients who started treatment more than 48 hours after symptom onset. A post hoc analysis suggested that oseltamivir reduced the duration of symptoms by 1 day compared with placebo in patients who started treatment 72 hours after symptom onset. Even if the start of antiviral therapy is delayed, reduced viral shedding can be an important consideration because viral shedding may be prolonged in children, patients with severe influenza, and those who are immunosuppressed.[9,52]

Although a 1-day reduction in duration of influenza illness may seem minimal, it can have a significant effect on quality of life for the patient as well as on direct and indirect costs of treating influenza. Additionally, early antiviral treatment may diminish the risk of complications, such as otitis media in children, pneumonia requiring antibiotics in adults, and hospitalization.[49] For high-risk patients who could develop influenza complications, early antiviral treatment can mean a milder illness rather than a more severe illness that would require hospitalization or lead to death.[49]

Making treatment decisions for patients with severe influenza is challenging because clinical trials of antiviral agents have been conducted primarily in healthy outpatients with uncomplicated influenza.[31] Results of observational studies in hospitalized patients with influenza suggest that starting a neuraminidase inhibitor within 48 hours of symptom onset reduces mortality and length of stay. Further, starting oseltamivir as late as 4 or 5 days after symptom onset may reduce the risk of severe complications. Based on these findings, the CDC recommends that patients with severe, complicated, or progressive illness and patients hospitalized with influenza receive oseltamivir as soon as possible, including patients who have had symptoms for longer than 48 hours.[31]

Additional Therapies

Adjunct agents that can be used for influenza symptom management include acetaminophen and nonsteroidal anti-inflammatory drugs for fever and/or pain, first-generation antihistamines for rhinorrhea, and medicated lozenges for cough and/or sore throat.[32] These agents may be used concomitantly with antiviral drugs.

Nonpharmacologic therapies that can be used for influenza symptom management include adequate sleep and reduced level of activity for malaise as well as maintenance of adequate fluid intake.[32] Limiting contact with others by staying home from work and/or school, washing hands, and using tissues to cover a cough or sneeze will prevent the spread of infection.

Special Populations

The American Academy of Pediatrics (AAP) considers oseltamivir the drug of choice for treatment of influenza in children.[44] Although there are concerns related to the inhalation technique required for zanamivir, it can be considered an equally acceptable alternative when patients do not have chronic lung disease.[53] IV peramivir is listed as a third option in the AAP policy statement.

Oseltamivir is the preferred treatment for pregnant women.[31] The results of multiple recent studies have reported safe use of neuraminidase inhibitors during pregnancy.[45,54] Oseltamivir is preferred over inhaled zanamivir due to concerns about lower lung volumes resulting in reduced drug distribution as well as concerns about bronchospasm.[9] The safety of inhaled zanamivir has been evaluated in small studies of pregnant women and showed no harm to the developing fetus; this has resulted in some experts recommending it for prevention of influenza in pregnant women.[9] Peramivir safety and efficacy in pregnant women are limited, and therefore it is not recommended.[9] The CDC does not recommend use of baloxavir for the treatment of pregnant or breastfeeding women.[31] Data related to baloxavir safety and efficacy in pregnant or lactating women are not available.

The CDC and IDSA guidelines do not have specific recommendations related to an influenza antiviral drug of choice for older adult patients.[9,31] These patients are considered high risk and therefore should be treated with antiviral therapy as soon as possible after symptom onset with an appropriate dose based off renal function.

Although there is not a recommendation for a specific influenza antiviral agent to be used for immunocompromised patients, they are considered high risk. Therefore, immunocompromised patients should be treated with antiviral therapy as soon as possible after symptom onset with an appropriate dose based off age and renal function. In addition, clinicians can consider a longer duration of antiviral treatment as viral replication is often prolonged.[9]

Management of Complications

When patients present with influenza- and bacterial infection-associated complications, both influenza antiviral treatment and empiric- or pathogen-specific antibiotic therapy should be initiated.[9] Additionally, antibiotic therapy should be initiated for patients who deteriorate after initial improvement with antiviral therapy and for those whose symptoms fail to improve after 3 to 5 days of antiviral therapy.[9]

ROLE OF THE PHARMACIST AS PATIENT EDUCATOR AND ADVOCATE

As some of the most accessible health care providers, pharmacists have a critical role in promptly identifying patients who are exhibiting influenza-like illness symptoms by recognizing its common presentation. When patients present to the nonprescription medication aisle requesting recommendations for self-care of their symptoms, pharmacists can assess symptom characteristics and onset to determine if antiviral drugs are appropriate. This is especially important for high-risk patient populations in whom concerns for complications are enhanced. Pharmacists can often infer that patients have a chronic medical condition (eg, asthma,

CASE 1

At the community pharmacy where you work, an oseltamivir prescription was received and prepared this morning. It is for a 2-year-old boy with uncontrolled asthma. It is now late in the evening and the prescription has not been dispensed.
QUESTION: What is the most appropriate action to take about this prescription?

ANSWER: Given that this patient has a high risk of influenza complications because of his age and medical condition, the patient's parents should be contacted as quickly as possible to ask why the prescription has not been picked up. They may not be aware that antiviral drugs for influenza are most effective when given early and should be started within 48 hours of symptom onset.

CASE 2

You are counseling an older adult patient with COPD about an antibiotic prescription to treat pneumonia. He mentions that he won't get an annual flu shot anymore because he thinks the flu shot gave him the flu this year. His rationale is that he got the flu within a week after getting a flu shot this winter. To add insult to injury, he points out that the flu was followed by bacterial secondary pneumonia.
QUESTION: What is the most appropriate response to this statement?

ANSWER: Explain that:
- A flu shot cannot cause the flu.
- A flu shot takes up to 2 weeks to protect against the flu.

A more likely explanation for why he got the flu when he did is that he was exposed to influenza before the vaccine had a chance to boost his immunity. In fact, he should definitely get the flu shot next year because his age and COPD increase the risk of flu complications, such as bacterial secondary pneumonia. Further, he should get a flu shot at the beginning of the season next year before the virus is circulating in the community. This strategy is his best chance of avoiding another case of secondary pneumonia due to the flu.

CASE 3

A 66-year-old woman with type 2 diabetes and a recent ischemic stroke requires treatment for influenza. Concerns have been raised about medication adherence because she has cognitive impairment.
QUESTION: What are appropriate treatment options for influenza in patients who have difficulty with medication adherence?

ANSWER: Two antiviral drugs may be appropriate for the treatment of uncomplicated influenza in adults who have difficulty with medication adherence:
- Single-dose peramivir 600 mg IV over a minimum of 15 minutes
- Single-dose baloxavir taken orally without regard to meals at a weight-based dose of 40 mg for weight of 40 to <80 kg and 80 mg for weight of ≥80 kg

diabetes, drug-induced immunosuppression) that increases the risk of influenza complications by checking their medication profile for drugs that treat these conditions (eg, bronchodilators, hypoglycemic agents, disease-modifying drugs for arthritis or multiple sclerosis). Some high-risk patients (eg, elderly patients, young children, extremely obese patients, American Indian/Alaska Native) are identified easily through simple screening questions and observation.

During the patient encounter, pharmacists can either offer point-of-care influenza testing and early antiviral treatment, if appropriate, or medical referral when patients exhibit influenza-like illness symptoms. A study by Klepser et al demonstrates that pharmacists can provide timely treatment for patients with influenza using a physician–pharmacist collaborative practice model.[55] In addition, a few states have developed statewide collaborative drug therapy agreements to allow pharmacists to prescribe influenza antiviral medications.[56-58] Pharmacists can also prompt patients to discuss antiviral therapy with their primary care or a convenient care provider.

Pharmacists should stay current regarding CDC recommendations for influenza vaccines and other measures for infection control to prevent or minimize the transmission of influenza to other individuals. In accordance with state law, pharmacists can offer and administer influenza vaccines to all patients 6 months and older.

Pharmacists need to stay current with CDC and IDSA guidelines for initiating antiviral therapy for the safe and effective treatment of the influenza virus. Treatment with neuraminidase inhibitor antiviral medications has been shown to have clinical and public health benefits in reducing illness and severe outcomes of influenza based on evidence from randomized controlled trials, meta-analyses of randomized controlled trials, and observational studies during past influenza seasons. Unfortunately, evidence suggests that influenza drugs are underutilized. A study published in 2015 by Havers et al reported that just 15% of outpatients who were at high risk for complications of influenza and presented to care fewer than 2 days from influenza-like illness symptoms were prescribed an antiviral medication.[59] This information can be used to educate patients and other providers.

Additionally, pharmacists should be prepared to answer questions and counsel patients about antiviral therapy. Patient counseling for antiviral therapy should include the importance of early initiation of the therapy (ie, within 48 hours of symptom onset). In addition, pharmacists should review with patients proper use, inhalation technique (for zanamivir), and potential adverse effects and drug interactions to safely and effectively treat influenza illness and prevent complications. For example, patients taking oseltamivir should be advised that taking it with food reduces nausea.[34] For baloxavir, patients should be warned to avoid coadministration of polyvalent cations, such as antacids, laxatives, and vitamin/mineral supplements that contain polyvalent cations.[41] For additional practical tips when assisting patients, refer to the CASES.

CONCLUSION

It is crucial that pharmacists are able to identify patients presenting with influenza symptoms who may benefit from treatment with antiviral medications. The risks versus benefits as well as the advantages and disadvantages of the various influenza treatment options (neuraminidase inhibitors, endonuclease inhibitor, and adamantanes) should be compared and taken into consideration. When possible, pharmacists should ensure patients initiate influenza antiviral therapy as soon as possible or at least within 48 hours of symptom onset. Furthermore, it is important that recommendations for influenza treatment are based on clinical practice guidelines published by the CDC and IDSA. Ultimately, pharmacists can play a vital role in the benefit of treating influenza as both patient educators and advocates.

ADDITIONAL RESOURCES	
Centers for Disease Control and Prevention: Influenza (flu)	cdc.gov/flu/index.htm
CDC Weekly US Influenza Surveillance Report	cdc.gov/flu/weekly/index.htm
CDC Influenza Antiviral Medications: Summary for Clinicians	cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#modalIdString_CDCTable_0

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ON-DEMAND CE-ACCREDITED WEBINAR

THIS ACTIVITY IS SUPPORTED BY AN EDUCATIONAL GRANT FROM SANOFI PASTEUR US.

The Pharmacist's Role in Counseling Patients About Influenza Vaccinations

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TARGET AUDIENCE: Retail, specialty, health-system, and managed care pharmacists
TYPE OF ACTIVITY: Application
RELEASE DATE: August 9, 2018
EXPIRATION DATE: August 9, 2019
ESTIMATED TIME TO COMPLETE ACTIVITY: 1 hour
FEE: Free

Activity Overview

Adults 65 years and older compose about 80% of seasonal influenza deaths and 60% of influenza-related hospitalizations. Despite the great efforts in vaccinating patients for vaccine-preventable deaths, there are still significant gaps in vaccinations. It is crucial for pharmacists to select the most effective and appropriate vaccine option for each patient to provide optimal protection from influenza. Pharmacists need to become more aware of updates to guidelines, the associated costs and risks of not being vaccinated, how to address misconceptions surrounding the influenza vaccine, and the importance of proactively increasing vaccination rates to prevent influenza and its associated complications.

Educational Objectives

At the completion of this activity, the participant will be able to:

- Explain the health risks and complications associated with forgoing the influenza vaccination
- Differentiate high-dose and adjuvanted formulations of the influenza vaccine
- Evaluate the cost-effectiveness of influenza vaccines
- Identify counseling techniques for health-system and community pharmacists to debunk vaccine myths, encourage vaccines, and work towards achieving Healthy People 2020

LINK: www.pharmacytimes.org/go/flu-vaccines

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INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.
Go to **www.pharmacytimes.org/go/flu** to complete the online interactive posttest and activity evaluation form to receive credit.
Click "Proceed," then complete the online pretest.
Once completed, click "Next" until reaching the online interactive posttest.
After successfully completing the online decision simulation and activity evaluation, your credit will be uploaded into CPE Monitor.
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SYSTEM REQUIREMENTS
Computer or smartphone with Internet-access Web browser (IE7.0+ or Webkit-/Mozilla-compatible) with JavaScript enabled.

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