Influenza Antiviral Medications: Summary for Clinicians

The information on this page should be considered current for the 2023-2024 influenza season for clinical practice regarding the use of influenza antiviral medications. Clinicians may also wish to consult the IDSA antiviral treatment and antiviral chemoprophylaxis recommendations, and the ATS-IDSA Adult CAP Guidelines.

Priority Groups for Antiviral Treatment of Influenza

Antiviral treatment is recommended **as soon as possible** for any patient with suspected or confirmed influenza who:

- is hospitalized;
- has severe, complicated, or progressive illness; or
- is at higher risk for influenza complications.

Decisions about starting antiviral treatment for patients with suspected influenza should not wait for laboratory confirmation of influenza virus infection. Empiric antiviral treatment should be started as soon as possible in the above priority groups.

Clinicians can consider early empiric antiviral treatment of non-high-risk outpatients with suspected influenza [e.g., influenza-like illness (fever with either cough or sore throat)] based upon clinical judgement, if treatment can be initiated within 48 hours of illness onset.

Antiviral Drug Options

- For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.
- For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, or exacerbation of underlying chronic medical conditions), initiation of antiviral treatment with oral oseltamivir is recommended as soon as possible.
- For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment, depending upon approved age groups and contraindications. In one randomized controlled trial, baloxavir had greater efficacy than oseltamivir in adolescents and adults with influenza B virus infection (Ison, 2020).

Co-circulation of Influenza Viruses and SARS-CoV-2

During periods of community co-circulation of influenza viruses and SARS-CoV-2, empiric antiviral treatment of influenza is recommended as soon as possible for the following priority groups: a) hospitalized patients with respiratory illness; b) outpatients with severe, complicated, or progressive respiratory illness; and c) outpatients at higher risk for influenza complications who present with any acute respiratory illness symptoms (with or without fever).

- Influenza and COVID-19 have overlapping signs and symptoms. Testing can help distinguish between influenza virus infection and SARS-CoV-2 infection. However, clinicians should not wait for the results of influenza testing (view Table 3), SARS-CoV-2 testing, or multiplex molecular assays that detect influenza A and B viruses and SARS-CoV-2 (view Table 4) to initiate empiric antiviral treatment for influenza in the above priority groups.
- Co-infection with influenza A or B viruses and SARS-CoV-2 can occur and should be considered, particularly in hospitalized patients with severe respiratory disease.

- Clinicians should be aware that a positive SARS-CoV-2 test result does not preclude influenza virus infection. For hospitalized patients with suspected influenza who are started on empiric antiviral treatment with oseltamivir, use of influenza molecular assays (view Table 3) or multiplex assays that detect both influenza viruses and SARS-CoV-2 (view Table 4) can inform clinical management.
- Clinicians should be aware that a positive influenza test result does not preclude SARS-CoV-2 infection. For hospitalized patients with a positive influenza test result, antiviral treatment of influenza with oseltamivir sh be started as soon as possible, and clinicians should also follow guidelines for diagnosis and treatment of community-acquired pneumonia (view community acquired pneumonia treatment guidance for adults: Metlay, 2019) and other respiratory infections, including SARS-CoV-2 infection (view NIH COVID-19 treatment guidelines and IDSA COVID-19 treatment guidelines) if clinically indicated, while awaiting SARS-CoV-2 testing results. Oseltamivir does not have in-vitro activity against SARS-CoV-2 (Choy, 2020).

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- Clinicians can utilize telemedicine in place of office visits for patients with acute respiratory illness. It may be useful for providers to implement phone triage lines to enable high-risk patients to discuss symptoms over the phone. Please see the Algorithm to Assist in Medical Office Telephone Evaluation of Patients with Possible Influenza.
- Patients at higher risk for influenza complications should be advised to call their provider as soon as possible if they have acute respiratory illness symptoms (with or without fever) for consideration of infection with influenza A or B viruses (and early antiviral treatment), SARS-CoV-2, and other respiratory pathogens.
- Clinicians can consider starting early (≤48 hours after illness onset) empiric antiviral treatment of non-high-risk outpatients with suspected influenza [e.g., influenza-like illness (fever with either cough or sore throat)], based upon clinical judgement, including without an office visit. SARS-CoV-2 and other etiologies of influenza-like illness should also be considered.
- National Institutes of Health (NIH) COVID-19 Treatment Guidelines: Influenza and COVID-19 are available .
- Clinical algorithms for the testing and treatment of influenza when SARS-CoV-2 and influenza viruses are circulating are also available.

Overview of Influenza Antiviral Medications

Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza.

- Influenza antiviral prescription drugs can be used to **treat** influenza, and some can be used to **prevent** influenza.
- Six licensed prescription influenza antiviral drugs are approved in the United States.
  - Four influenza antiviral medications approved by the U.S. Food and Drug Administration (FDA) are recommended for use in the United States.
    - Three drugs are chemically related antiviral medications known as neuraminidase inhibitors that block the viral neuraminidase enzyme and have activity against both influenza A and B viruses: oral **oseltamivir phosphate** (available as a generic version or under the trade name Tamiflu®), inhaled **zanamivir** (trade name Relenza®), and intravenous **peramivir** (trade name Rapivab®).
    - The fourth drug is oral **baloxavir marboxil** (trade name Xofluza®), which is active against both influenza A and B viruses but has a different mechanism of action than neuraminidase inhibitors. Baloxavir is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication.
    - More information regarding the four recommended antiviral medications is available: Table 1.
- Amantadine and rimantadine are antiviral drugs in a class of medications known as adamantanes, which target the M2 ion channel protein of influenza A viruses. Therefore, these medications are active against influenza A viruses, but not influenza B viruses. As in recent past seasons, there continues to be high levels of resistance (>99%) to adamantanes among circulating influenza A(H3N2) and influenza A(H1N1)pdm09 ("2009 H1N1") viruses. Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A viruses.
- Antiviral resistance and reduced susceptibility to the neuraminidase inhibitors and to baloxavir among circulating influenza viruses is currently very low, but this can change.

- For weekly surveillance data on susceptibility of circulating influenza viruses to antivirals in the U.S. this season, see the FluView Weekly U.S. Influenza Surveillance Report.

- Influenza viruses with reduced susceptibility or resistance to antivirals can occur sporadically or emerge during or after antiviral treatment in some patients (e.g., immunocompromised). Oseltamivir resistance in influenza A(H3N2) and A(H1N1)pdm09 viruses can develop during treatment, particularly in young children (Roosenhoff, 2019 ; Lina, 2018 ;), and immunocompromised persons (Memoli, 2014) . Following treatment with baloxavir, emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir has been observed in clinical trials in immunocompetent children and adults, with higher detection among baloxavir-treated pediatric patients aged <12 years compared with adults (Hayden, 2018 ; Omoto, 2018 ; Hirostu, 2019 ; Uehara, 2019 ; Takashita, 2019).
  - Human-to-human transmission of influenza A(H1N1)pdm09 viruses with an H275Y mutation in viral neuraminidase conferring resistance to oseltamivir has been reported among severely immunocompromised patients in hospital units, (Gooskens, 2009 ; Chen, 2011 ;) and in the community (Hibino, 2017 ; Le, 2008; Hurt, 2011 ; Hurt, 2012 ; Takashita, 2013) , but currently appears to be uncommon.
  - Limited human-to-human transmission of influenza A(H3N2) virus with reduced susceptibility to baloxavir has been reported sporadically in Japanese children (Takashita, 2019 ; Takashita 2019 ; Imai, 2019), but currently appears to be uncommon.
- Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of some complications from influenza (e.g., otitis media in young children, pneumonia, and respiratory failure).
  - Early treatment of hospitalized adult influenza patients with oseltamivir has been reported to reduce death in some observational studies.
  - In hospitalized children, early antiviral treatment with oseltamivir has been reported to shorten the duration of hospitalization in observational studies.
  - Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset in clinical trials and observational studies.

Table 1: Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza

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Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended for Use in	Adverse Events
Oral Oseltamivir	Influenza A and B	Treatment	Any age[1]	N/A	**Adverse events:** nausea, vomiting, headache. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemo-prophylaxis	3 months and older[1]	N/A	

Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended for Use in	Adverse Events
Inhaled Zanamivir	Influenza A and B	Treatment	7 yrs and older[3]	People with underlying respiratory disease (e.g., asthma, COPD)[3]	**Adverse events:** risk of bronchospasm, especiall the setting of underlying airways disease; sinusitis, and dizziness. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemo-prophylaxis	5 yrs and older[3]	People with underlying respiratory disease (e.g., asthma, COPD)[3]	
Intravenous Peramivir	Influenza A and B[4]	Treatment	6 months and older[4]	N/A	**Adverse events:** diarrhea. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemo-prophylaxis[5]	Not recommended	N/A	
Oral Baloxavir	Influenza A and B[6]	Treatment	5 yrs and older[6]	N/A	**Adverse events:** none more common than placebo in clinical trials
		Chemo-prophylaxis[6]	Approved for post-exposure prophylaxis in persons 5 yrs and older[6]		

Abbreviations: N/A = not applicable, COPD = chronic obstructive pulmonary disease.

1. Oral oseltamivir phosphate is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people 14 days and older, and for chemoprophylaxis in people 1 year and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants less than 14 days old, and for chemoprophylaxis in infants 3 months to 1 year, is recommended by the CDC and the American Academy of Pediatrics. If a child is younger than 3 months old, use of oseltamivir for chemoprophylaxis is not recommended unless the situation is judged critical due to limited data in this age group.
2. Self-injury or delirium; mainly reported among Japanese pediatric patients.
3. Inhaled zanamivir is contraindicated in patients with underlying airways disease such as asthma or chronic obstructive pulmonary disease, and those with a history of allergy to lactose or milk protein.
4. Intravenous peramivir is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people 6 months and older. Peramivir efficacy is based on clinical trials versus placebo in which the predominant influenza virus type was influenza A; in one trial, a very limited number of subjects infected with influenza B virus were enrolled.
5. There are no data available for use of peramivir for chemoprophylaxis of influenza.
6. Oral baloxavir marboxil is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people aged ≥5 years who are otherwise healthy, or in people aged ≥12 years who are high risk of developing influenza-related complications. Baloxavir efficacy for initial FDA approval in October 2018 was based on clinical trials in previously healthy outpatients 12 to 64 years old (Hayden, 2018). Single-dose baloxavir treatment was superior to placebo and had similar clinical efficacyin time to alleviation of symptoms to a 5-day treatment course of oseltamivir.In October 2019, FDA approved an indication for baloxavir treatment of acute uncomplicated influenza within 2 days of illness onset in people 12 years and older at high risk of developing influenza-related complications, based upon the findings of a clinical trial (Ison, 2020). In this clinical trial of early initiation of antiviral treatment for uncomplicated influenza in high[1]risk patients, baloxavir was superior to placebo and had similar overall efficacy to oseltamivir in the time to alleviation of symptoms. For patients with influenza B virus

infection, baloxavir significantly reduced the median time to improvement of symptoms compared with oseltamivir by more than 24 hours. However, there are no available data for baloxavir treatment of influenza in pregnant people, immunocompromised people, or in people with severe influenza who are not hospitalized.For patients with influenza B virus infection, baloxavir significantly reduced the median time to improvement of symptoms compared with oseltamivir by more than 24 hours. However, there are no available data for baloxavir treatment of influe
pregnant people, immunocompromised people, or in people with severe influenza who are not hospitalized.

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In August 2022, FDA expanded approval of baloxavir for treatment of acute uncomplicated influenza within 2 days o illness onset in children aged 5 years to <11 years who are otherwise healthy. package insert xofluza [963 KB, 22 pages] . This was based upon the secondary clinical outcomes of a randomized clinical trial of baloxavir versus oseltamivir for treatment of uncomplicated influenza in children aged 1 year to <12 years (Baker, 2021).

In this study, baloxavir post-exposure prophylaxis (PEP) of influenza in household members (19% were younger than 12 years; 73% received baloxavir within 24 hours of onset of symptoms in the index household case who received antiviral treatment) significantly reduced the risk of laboratory-confirmed by 86% among those who received baloxavir PEP than among those who received placebo (1.9% [7 of 374] vs. 13.6% [51 of 375]; adjusted risk ratio, 0.14; 95% confidence interval [CI], 0.06 to 0.30; P<0.001). In August 2022, FDA expanded approval of baloxavir for post-exposure prophylaxis of influenza in persons aged 5 years and older within 48 hours of contact with an individual with influenza. package insert xofluza [963 KB, 22 pages] .

A randomized clinical trial reported that combination neuraminidase inhibitor (primarily oseltamivir) and baloxavir for treatment of hospitalized influenza patients aged ≥12 years did not result in superior clinical benefit (time to clinical improvement) compared with neuraminidase inhibitor and placebo (Kumar, 2022).

In November 2020, FDA expanded approval of baloxavir to include post-exposure prophylaxis of influenza for persons aged ≥12 years within 48 hours of contact with an individual with influenza, based on the findings of a clinical trial among household contacts of index patient with influenza (Ikematsu, 2020).

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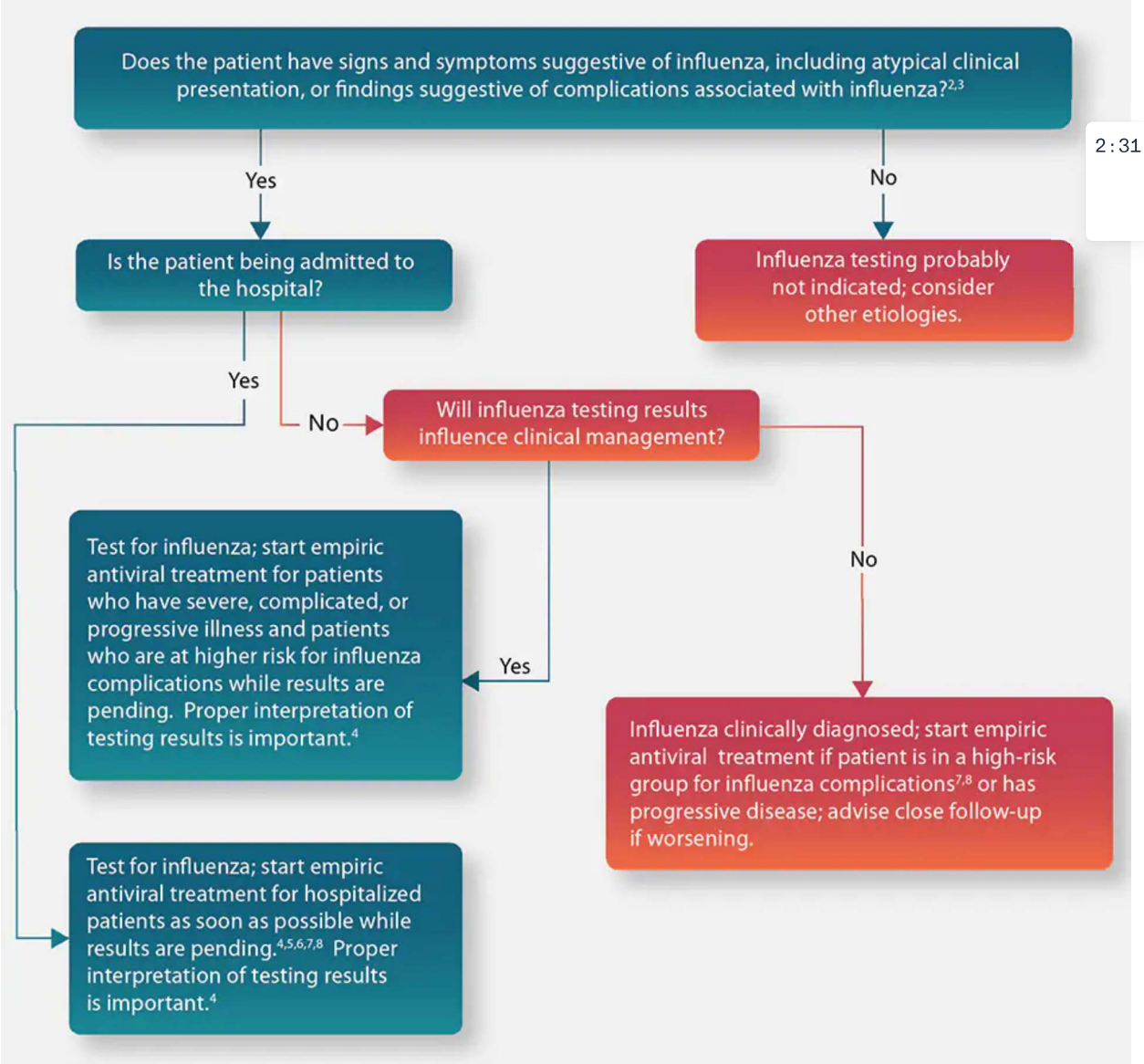
Summary of Influenza Antiviral Treatment Recommendations

- **Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who:**
  - **is hospitalized;***
  - **has severe, complicated, or progressive illness;* or**
  - **is at higher risk for influenza complications.**

***Note:** Oral oseltamivir is the recommended antiviral for patients with severe, complicated, or progressive illness who are not hospitalized, and for hospitalized influenza patients.

- Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk for influenza complications, who is diagnosed with confirmed or suspected influenza, on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.

Figure: Guide for considering influenza testing and treatment when influenza viruses are circulating in the community (regardless of influenza vaccination history)[1]



Complete footnotes for this algorithm are available.

- Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients at increased risk of severe disease.
- When indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might have some benefits in patients with severe, complicated or progressive illness, and in hospitalized patients when started after 48 hours of illness onset.
  - There are no data available from randomized clinical trials of oseltamivir or other neuraminidase inhibitors versus placebo or standard of care for treatment of hospitalized patients with influenza.
    - One randomized clinical trial reported that combination neuraminidase inhibitor (primarily oseltamivir) and baloxavir treatment of hospitalized influenza patients aged ≥12 years did not result in significantly superior clinical benefit (time to clinical improvement) compared with neuraminidase inhibitor and placebo, indicating that adding baloxavir did not result in additional clinical benefit, but significantly reduced nasopharyngeal influenza viral RNA levels (Kumar, 2022).
  - Observational studies in hospitalized patients with influenza have reported that clinical benefit is greatest when oseltamivir is started within 48 hours of illness onset (Hsu, 2012 ; Louie, 2013 ; Muthuri, 2013 ; Muthuri, 2014). However, some studies suggest that antiviral treatment might still be beneficial in hospitalized patients when started up to 4 or 5 days after illness onset (Louie, 2012 ; Yu, 2011). Antiviral treatment of pregnant people (in any trimester) with influenza A(H1N1)pdm09 virus infection has been shown to be most beneficial in preventing respiratory failure and death when started within less than 3

days of illness onset, but still provided benefit when started 3–4 days after onset compared with 5 or more days (Siston, 2010).

- Observational studies in hospitalized patients with influenza have reported greater clinical benefit when oseltamivir or other neuraminidase inhibitor treatment are started at or promptly after admission compared with later treatment initiation or no antiviral treatment. One observational study reported that initiating neuraminidase inhibitor treatment within 6 hours after hospital admission was associated with shorter duration of hospitalization versus starting antiviral treatment later (Katzen, 2018). Another observatic study reported that neuraminidase inhibitor treatment initiated at the time of hospitalization was associated with a significant reduction in hospital length of stay in patients with clinically suspected or laboratory-confirmed influenza A(H1N1)pdm09 virus infection compared with later initiation or no NAI treatment (Venkatesan, 2019).
- Observational studies in hospitalized adult patients with influenza have reported that starting oseltamivir treatment within 48 hours of hospital admission can reduce 30-day readmissions and mortality compared with no treatment or later initiation of treatment. One observational study reported that hospitalized adult influenza patients who were started on oseltamivir treatment within 48 hours of admission had significantly lower 30-day readmission or 30-day readmission and mortality compared with those not treated or started on oseltamivir treatment >48 hours after admission (Sharma 2021). Another observational study in hospitalized adults with influenza reported that starting oseltamivir treatment <48 hours of hospital admission (median time from symptom onset to oseltamivir initiation: 3 days) significantly reduced 30-day mortality and 30-day mortality or ICU admission >48 hours after admission, compared to untreated patients (Groeneveld 2020).

- **Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza** (see resources regarding Clinical Description and Lab Diagnosis of Influenza for more information on influenza diagnostic testing).
  - Clinical benefit is greatest when antiviral treatment is started as close to illness onset as possible.
- While influenza vaccination is the best way to prevent influenza illness, a history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms compatible with influenza.
- Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at increased risk of severe disease with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset. Multiple randomized controlled clinical trials (RCTs) and meta-analyses of RCTs have demonstrated efficacy of early initiation of treatment (started within 48 hours of illness onset) with neuraminidase inhibitors in reducing duration of fever and illness symptoms compared with placebo in otherwise healthy children and adults with uncomplicated influenza (Hayden, 1997 ; Monto, 1999 ; Monto, 1999 ; Nicholson, 2000 ; Hedrick, 2000 ; Treanor, 2000 ; Whitley, 2001 ; Heinonen, 2010 ; Fry, 2014 ; Whitley, 2015 ; Kohno, 2010 ; Hsu, 2012 ; Jefferson, 2014 ; Whitley, 2015 ;, Dobson, 2015 ; Malosh, 2017).
  - One randomized clinical trial in children with uncomplicated influenza demonstrated a modest reduction in duration of symptoms and influenza virus shedding in patients initiating treatment after 48 hours; post hoc analysis suggested that oseltamivir treatment initiated 72 hours after illness onset reduced symptoms by one day compared with placebo (Fry, 2014).
- **For outpatients with acute uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment.**
  - The recommended treatment course for uncomplicated influenza is two doses per day of oral oseltamivir or inhaled zanamivir for 5 days, or one dose of intravenous peramivir or oral baloxavir for 1 day.
  - Only one randomized clinical trial has compared baloxavir to oseltamivir for treatment of influenza B. This study found that baloxavir treatment was superior to oseltamivir among outpatients with influenza B virus infection (Ison, 2020).
  - CDC does not recommend use of baloxavir for treatment of influenza in pregnant people or breastfeeding mothers. There are no available efficacy or safety data for baloxavir in pregnant people, and there are no available data on the presence of baloxavir in human milk, the effects on the breastfed infant, or the effects on milk production.
  - CDC does not recommend use of baloxavir for monotherapy of influenza in severely immunosuppressed persons. There are no available efficacy, safety, or resistance data for baloxavir monotherapy of influenza in

severely immunosuppressed patients and emergence of resistance during treatment is a concern because of prolonged influenza viral replication in these patients.

    - There are no available data on the use of baloxavir for treatment of influenza more than 2 days after illness onset in outpatients.

- **Oral oseltamivir is preferred for treatment of pregnant people** (Rasmussen ,; 2011). Pregnant people ar recommended to receive the same antiviral dosing as non-pregnant people. Multiple recent studies have repo safe use of neuraminidase inhibitors during pregnancy (Dunstan, 2014 ; Xie, 2013 ; Saito, 2013 ; Wollenhaupt, 2014 ; Beau, 2014 ; Svensson, 2011 ; Greer, 2010 ; Graner, 2017); Ehrenstien, 2018 ; Chambers, 2019 ; Bennekom, 2019 ; ACOG Committee, 2018). See Recommendations for Obstetric Health Care Providers Related to Use of Antiviral Medications in the Treatment and Prevention of Influenza for additional information. Baloxavir is not recommended for the treatment of influenza in pregnant people, as there are no available efficacy or safety data for baloxavir in this population (Chow, 2021).
- **For patients with severe or complicated illness with suspected or confirmed influenza (e.g., pneumonia, or exacerbation of underlying chronic medical condition) who are not hospitalized, antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.** There are insufficient data for inhaled zanamivir and intravenous peramivir in patients with severe influenza disease. There are no available data from clinical trials on use of baloxavir treatment in nonhospitalized patients with severe influenza disease.

People at Higher risk for Influenza Complications Recommended for Antiviral Treatment

- Adults 65 years and older
- Children younger than 2 years old[1]
- Asthma
- Neurologic and neurodevelopment conditions
- Blood disorders (such as sickle cell disease)
- Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
- Endocrine disorders (such as diabetes mellitus)
- Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
- Kidney diseases
- Liver disorders
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- People who are obese with a body mass index [BMI] of 40 or higher
- People younger than 19 years old on long-term aspirin- or salicylate-containing medications.
- People with a weakened immune system due to disease (such as people with HIV or AIDS, or some cancers such as leukemia) or medications (such as those receiving chemotherapy or radiation treatment for cancer, or persons with chronic conditions requiring chronic corticosteroids or other drugs that suppress the immune system)
- People who have had a stroke
- Pregnant people and people up to 2 weeks after the end of pregnancy
- People who live in nursing homes and other long-term care facilities

- [1]Although all children younger than 5 years old are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 years old, with the highest hospitalization and death rates among infants younger than 6 months old. Because many children with mild febrile respiratory illness might have other viral infections (e.g., respiratory syncytial virus, rhinovirus, parainfluenza virus, or human metapneumovirus), knowledge of other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions.

- People from certain racial and ethnic minority groups are at increased risk for hospitalization with influenza, including non-Hispanic Black persons, Hispanic or Latino persons, and American Indian or Alaska Native persons

Treatment Considerations for Patients Hospitalized with Suspected or Confirmed Influenza

Treatment of patients with severe influenza (e.g., those requiring hospitalization) presents multiple challenges. The effect of specific antiviral strategies in serious or life-threatening influenza is not established from clinical trials conducted to support licensure of oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir, as those studies were conducted primarily among previously healthy outpatients with uncomplicated illness. No randomized, placebo-controlled clinical trials have been conducted of monotherapy with neuraminidase inhibitors for treatment of influenza in hospitalized patients. A secondary analysis of a multi-center unblinded clinical trial of oseltamivir treatment started within 24 hours of admission versus standard of care in adults hospitalized for lower respiratory tract infection reported that patients with laboratory-confirmed influenza had a significantly lower risk of clinical failure (composite outcome: failure to improve with 7 days, transfer to ICU care 24 hours after admission, or rehospitalization or death within 30 days) (Wiemken, 2021). Several observational studies in hospitalized influenza patients have shown clinical benefit of neuraminidase inhibitor antiviral treatment compared with no treatment, particularly when started within two days of influenza illness, or as soon as possible after hospital admission, including reducing the duration of hospitalization, and reducing the risk of invasive mechanical ventilation or risk of death (Hiba, 2011 ; Coffin, 2011 ; Viasus, 2011 ; Hsu, 2012 ; Louie, 2013 ; Muthuri, 2013 ; Muthuri, 2014 ; Miyakawa, 2019 ; Lytras, 2019 ; Campbell, 2021 ; Chen, 2020 ; Chen, 2020 ; Venkatesan, 2020 ; Katzen, 2019 ; Reacher, 2019). In addition, some observational studies have reported that oral oseltamivir treatment started 4 and 5 days after illness onset in patients hospitalized with suspected or confirmed influenza was associated with lower risk for severe outcomes (EH Lee, 2010 ; N Lee, 2008 ; N Lee, 2010 ; Louie, 2012 ; McGeer, 2007 ; Siston, 2010), although one report found this benefit only in hospitalized adult patients in the ICU (Muthuri, 2014). A small number of observational studies and one meta-analysis of observational studies of hospitalized influenza patients reported that neuraminidase inhibitor treatment did not have survival benefit (Choi, 2017 ; Wolkewitz, 2016 ; Heneghan, 2016).

One randomized clinical trial reported that combination neuraminidase inhibitor (primarily oseltamivir) and baloxavir treatment of hospitalized influenza patients aged ≥12 years did not result in superior clinical benefit (time to clinical improvement) compared to treatment with neuraminidase inhibitor and placebo, indicating that adding baloxavir did not result in additional clinical benefit, but significantly reduced nasopharyngeal influenza viral RNA levels (Kumar, 2022).

The following recommendations do not necessarily represent FDA-approved uses of antiviral products but are based on published observational studies and expert opinion and are subject to change as the developmental status of investigational products and the epidemiologic and virologic features of influenza change over time.

- **For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.** Antiviral treatment might be effective in reducing morbidity and mortality in hospitalized influenza patients, especially adults, even if treatment is started more than 48 hours after onset of illness.
- Inhaled zanamivir and oral baloxavir are not recommended because of the lack of data showing clinical benefit in hospitalized influenza patients. There are also insufficient data for treatment of hospitalized influenza patients with intravenous peramivir.
- For patients with lower respiratory tract disease, lower respiratory tract specimens, such as bronchoalveolar lavage fluid or endotracheal aspirates, are preferred; an oropharyngeal (throat) swab may be collected if lower respiratory specimens are not available. Testing of lower respiratory tract specimens may detect influenza viruses when testing of upper respiratory tract specimens is negative. Multiple respiratory tract specimens collected on different days should be tested if influenza virus infection is suspected but a definitive diagnosis has not been made.
- The optimal duration and dosing of antiviral treatment are uncertain for severe or complicated influenza. Treatment regimens might need to be altered to fit the clinical circumstances. For example, clinical judgment should be the guide regarding the need to extend daily treatment regimens longer than 5 days for patients whose

illness is prolonged. Critically ill patients with respiratory failure can have prolonged influenza viral replication in the lower respiratory tract and might benefit from longer duration of treatment.

- Clinical judgment and virologic testing of lower respiratory tract specimens by real-time reverse transcription-polymerase chain reaction (RT-PCR) should guide decisions to consider treatment regimens longer than 5 days for hospitalized influenza patients with severe and prolonged illness.
- Longer treatment regimens might be necessary in immunosuppressed people who may have prolonged influenza viral replication. Such patients are at risk of emergence of influenza viruses with reduced susceptibility or antiviral resistance during or after antiviral treatment.
- A higher dose of oral or enterically-administered oseltamivir has been recommended by some experts (e.g., 150 mg twice daily in adults with normal renal function) for treatment of influenza in immunocompromised patients and in severely ill hospitalized patients. However, oral or enterically administered oseltamivir has been reported to be adequately absorbed in critically ill adults, with standard doses producing therapeutic blood levels (Ariano, 2010), and available data suggest that higher dosing may not provide additional clinical benefit (Abdel-Ghafar, 2008 ; Ariano, 2010 ; Kumar, 2010 ; Lee, 2013 ; South East Asia Infectious Disease Clinical Research Network, 2013). Studies indicate that the exposure to oseltamivir carboxylate (the active metabolite of oseltamivir) is similar between obese and non-obese subjects for both 75 mg and 150 mg doses given twice daily (Ariano, 2010 ; Jittamala, 2014 ; Pai, 2011 ; Thorne-Humphrey, 2011).

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- Limited data suggest that oseltamivir administered orally or by oro/naso gastric tube is well absorbed in critically ill influenza patients, including those receiving continuous renal replacement therapy, and/or on extracorporeal membrane oxygenation (Ariano, 2010 ; Eyler, 2012a ; Eyler, 2012b ; Giraud, 2011 ; Kromdijk, 2013 ; Lemaitre, 2012 ; Mulla, 2013 ; Taylor, 2008).
- For patients who cannot tolerate or absorb oral or enterically-administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of intravenous peramivir should be considered (Lee, 2017 ; deJong, 2014 ; Ison, 2014 ; Ison, 2013).
  - In a randomized trial of treatment of influenza in hospitalized patients >6 years old, a significant clinical benefit was not demonstrated for intravenous peramivir at a dosage of 600 mg once daily (10 mg/kg once daily in children) for five days plus standard of care compared with placebo plus standard of care; however, peramivir was generally safe and well tolerated (de Jong, 2014)
- It is possible that some influenza viruses may become less susceptible or resistant to oseltamivir and peramivir during antiviral treatment with one of these drugs and remain susceptible to zanamivir; this has been reported most often for influenza A(H1N1)pdm09 viruses (Graitcer, 2011; Lackenby, 2011; Memoli, 2010; Nguyen, 2010; Nguyen, 2012) Influenza A(H1N1)pdm09 viruses have also emerged that are resistant to all neuraminidase inhibitors, including zanamivir, in highly immunosuppressed patients on prolonged neuraminidase inhibitor treatment (Tamura, 2015 ; L'Huillier, 2015). Resistance and reduced susceptibility of influenza viruses to antiviral drugs can also occur spontaneously, with no known exposure to antiviral medications (Hurt, 2011 ; Takashita, 2013 ; Takashita, 2014).
- If a hospitalized patient treated with oseltamivir or peramivir manifests progressive lower respiratory symptoms, resistant virus should be considered. However, clinicians should note that failure to improve or clinical deterioration during oseltamivir or peramivir treatment is more likely to be related to the natural history of acute lung injury and inflammatory damage or onset of other complications (e.g., renal failure, septic shock, ventilator-associated pneumonia) than to emergence of oseltamivir or peramivir resistance. Severely immunosuppressed people (e.g., hematopoietic stem cell transplant recipients) are at highest risk for emergence of oseltamivir- and peramivir-resistant influenza virus infection during or following oseltamivir and/or peramivir treatment (Hurt, 2012 ; Memoli, 2010). Molecular analyses can detect genetic changes in influenza viruses associated with resistance and reduced susceptibility to oseltamivir and peramivir. The CDC Influenza Division is available for consultation regarding antiviral susceptibility testing as needed. Information about neuraminidase inhibitor susceptibility testing and interpretation of results of neuraminidase inhibition assays is available on the WHO website .
- Intravenous zanamivir is an investigational parenterally administered neuraminidase inhibitor product that has been available in the past through enrollment in a clinical trial or under an emergency investigational new drug (EIND) request to the manufacturer. However, since the 2017-18 season, intravenous zanamivir is no longer available in the United States.
- Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia (e.g., *S. pneumoniae*, *S. pyogenes*, and *S. aureus*, including MRSA) also is critical for severely ill patients

(Bautista, 2010 ; Finelli, 2008 ; Hageman, 2006 ; Harper, 2009; Mandell, 2007; Mauad, 2010 ; Shieh, 2010).

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Table 2. Recommended Dosage and Duration of Influenza Antiviral Medications for Treatment or Chemoprophylaxis

Antiviral Agent
Oral Oseltamivir

Use
Treatment (5 days)[1]

Children
If younger than 1 yr old[2]: 3 mg/kg/dose twice daily[3,4] **If 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **twice** a day >15 to 23 kg, the dose is 45 mg **twice** a day >23 to 40 kg, the dose is 60 mg **twice** a day >40 kg, the dose is 75 mg **twice** a day

Adults
75 mg **twice** daily

Antiviral Agent

Use
Chemoprophylaxis (7 days)[5]

Children
If child is younger than 3 months old, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical due to limited data in this age group. **If child is 3 months or older and younger than 1 yr old**[2] **3 mg/ kg/dose once daily**[3] **If 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **once** a day >15 to 23 kg, the dose is 45 mg **once** a day >23 to 40 kg, the dose is 60 mg **once** a day >40 kg, the dose is 75 mg **once** a day

Adults
75 mg **once** daily

Antiviral Agent
Inhaled Zanamivir[6]

Use

Treatment (5 days)

Children
10 mg (two 5-mg inhalations) **twice** daily
(FDA approved and recommended for use in children 7 yrs or older)

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Adults
10 mg (two 5-mg inhalations) **twice** daily

Antiviral Agent

Use
Chemoprophylaxis (7 days)[5]

Children
10 mg (two 5-mg inhalations) **once** daily
(FDA approved for and recommended for use in children 5 yrs or older)

Adults
10 mg (two 5-mg inhalations) **once** daily

Antiviral Agent
Intravenous Peramivir[7]

Use
Treatment (1 day)[1]

Children
(6 months to 12 yrs of age) One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15 minutes **(FDA approved and recommended for use in children 6 months or older)**

Adults
(13 yrs and older) One 600 mg dose, via intravenous infusion for a minimum of 15 minutes

Antiviral Agent

Use
Chemoprophylaxis[8]

Children
Not recommended

Adults
N/A

Duration of Treatment or Chemoprophylaxis

- **Treatment:** Recommended duration for antiviral treatment is 5 days for oral oseltamivir or inhaled zanamivir. For the treatment of uncomplicated influenza with intravenous peramivir or oral baloxavir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment. Treatment should be started as soon as possible for the greatest clinical benefit.
- **Chemoprophylaxis:** Recommended duration is 7 days (after last known exposure). For control of outbreaks in institutional settings (e.g., long-term care facilities for older adults and children) and hospitals, CDC recommends antiviral chemoprophylaxis with oral oseltamivir or inhaled zanamivir for a minimum of 2 weeks and continuing up to 1 week after the last known case was identified. Antiviral chemoprophylaxis is recommended for all residents, including those who have received influenza vaccination. Baloxavir is approved for post-exposure prophylaxis (single-dose) of influenza in persons aged 5 years and older within 48 hours of contact with an individual with influenza.

Chemoprophylaxis

- Annual influenza vaccination [773 KB, 28 pages] is the best way to prevent influenza because vaccination can be given well before influenza virus exposures occur and can provide safe and effective immunity throughout the influenza season.
- Neuraminidase inhibitor antiviral medications are approximately **70%** to **90%** effective in preventing influenza against susceptible influenza viruses and are useful adjuncts to influenza vaccination.
- CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis except as one of multiple interventions to control institutional influenza outbreaks. Routine use of post-exposure chemoprophylaxis is not recommended; one reason for this is to avoid sub-therapeutic treatment dosing if infection is already established, although the likelihood of emergence of antiviral resistant viruses is unknown.
    - Clinicians may wish to also consult the antiviral chemoprophylaxis recommendations from the Infectious Diseases Society of America (Uyeki, 2019).
- In general, CDC does not recommend seasonal or pre-exposure antiviral chemoprophylaxis, but **antiviral medications can be considered for chemoprophylaxis to prevent influenza in certain situations, such as the following examples:**
    - Prevention of influenza in people at high risk of influenza complications during the first two weeks following vaccination after exposure to a person with influenza.
    - Prevention for people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to a person with influenza.
    - Prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as people receiving immunosuppressive medications, after exposure to a person with influenza.
    - Patients receiving antiviral chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness that might indicate influenza.
- **An emphasis on close monitoring and early initiation of antiviral treatment if fever and/or respiratory symptoms develop is an alternative to chemoprophylaxis after a suspected exposure for some people.**

- To be effective as chemoprophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza and continued for 7 days after the last known exposure. For people taking antiviral chemoprophylaxis after inactivated influenza vaccination, the recommended duration is until immunity after vaccination develops (antibody development after vaccination takes about two weeks in adults and can take longer in children depending on age and vaccination history).
- **Antiviral chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the first exposure to a person with influenza.**
- **Patients receiving antiviral chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness that might indicate influenza.**

Dosing in Adult Patients with Renal Impairment

Dose adjustment of oseltamivir is recommended for patients with creatinine clearance between 10 and 60 mL/min and patients with end-stage renal disease (ESRD) undergoing hemodialysis or continuous peritoneal dialysis receiving oseltamivir for the treatment or chemoprophylaxis of influenza. Oseltamivir is not recommended for patients with ESRD not undergoing dialysis. The recommended doses are detailed in Table 3; duration of treatment and chemoprophylaxis is the same as recommended for patients with normal renal function. The dose of intravenous peramivir should be reduced for patients with baseline creatinine clearance below 50 mL/min (see Table 3).

No dose adjustment is recommended for inhaled zanamivir for a 5-day course of treatment for patients with renal impairment. Pharmacokinetic analysis did not identify a clinically meaningful effect of renal function on the pharmacokinetics of baloxavir in patients with creatinine clearance 50 mL/min and above. The effects of severe renal impairment on the pharmacokinetics of baloxavir marboxil or its active metabolite, baloxavir, have not been evaluated.

Table 3. Recommended Oseltamivir and Peramivir Dose Adjustments for Treatment or Chemoprophylaxis of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis*

Creatinine Clearance	Recommended Treatment Regimen	Recommended Chemoprophylaxis Regimen
Oral Oseltamivir[1]		
Creatinine clearance 61 to 90 mL/min	75 mg twice a day	75 mg once daily

Creatinine clearance 31 to 60 mL/min

30 mg twice a day

30 mg once daily

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Creatinine clearance 11 to 30 mL/min

30 mg once daily

30 mg every other day

ESRD Patients on Hemodialysis Creatinine clearance ≤10 mL/min

30 mg after every hemodialysis cycle. Treatment duration not to exceed 5 days[2]

30 mg after alternate hemodialysis cycles[3]

ESRD Patients on Continuous Ambulatory Peritoneal Dialysis[4] Creatinine clearance ≤10 mL/min

A single 30 mg dose administered immediately after a dialysis exchange

30 mg once weekly immediately after dialysis exchange

Intravenous Peramivir (single dose)[5]

Creatinine clearance ≥50 mL/min

600 mg

N/A

Creatinine clearance 30 to 49 mL/min

200 mg

N/A

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Creatinine clearance 10 to 29 mL/min

100 mg

N/A

ESRD Patients on Hemodialysis

Dose administered after dialysis at a dose adjusted based on creatinine clearance

* From package inserts for oseltamivir and peramivir; see FDA Influenza (Flu) Antiviral Drugs and Related Information .

Abbreviations: N/A = approved, not recommended

1. Renal dosing of oseltamivir is not available in the package insert for pediatric patients. However, these tables may be useful for children who qualify for adult doses based on weight >40 kg.
2. Assuming 3 hemodialysis sessions are performed in the 5- day period. Treatment can be initiated immediately if influenza symptoms develop during the 48 hours between hemodialysis sessions; however, the post-hemodialysis dose should still be administered independently of time of administration of the initial dose.
3. An initial dose can be administered prior to the start of dialysis.
4. Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.
5. Renal dosing from peramivir package insert is available for pediatric patients: Creatinine clearance ≥50 mL/min: 12 mg/kg (up to maximum dose of 600 mg); Creatinine clearance 30 to 49 mL/min: 4 mg/kg; Creatinine clearance 10 to 29 mL/min: 2 mg/kg.

Adverse Events

- When considering use of influenza antiviral medications, clinicians must consider the patient's age, weight and renal function; presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.
- RCTs and meta-analyses of RCTs have indicated that gastrointestinal symptoms such as nausea and vomiting are increased with oral oseltamivir compared with placebo; these adverse events may be less likely when oseltamivir is taken with food (Aoki, 2003).
- For more information on safety, effectiveness and dosing for oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir, visit Antiviral Drugs or consult the package inserts.

Drug Interactions

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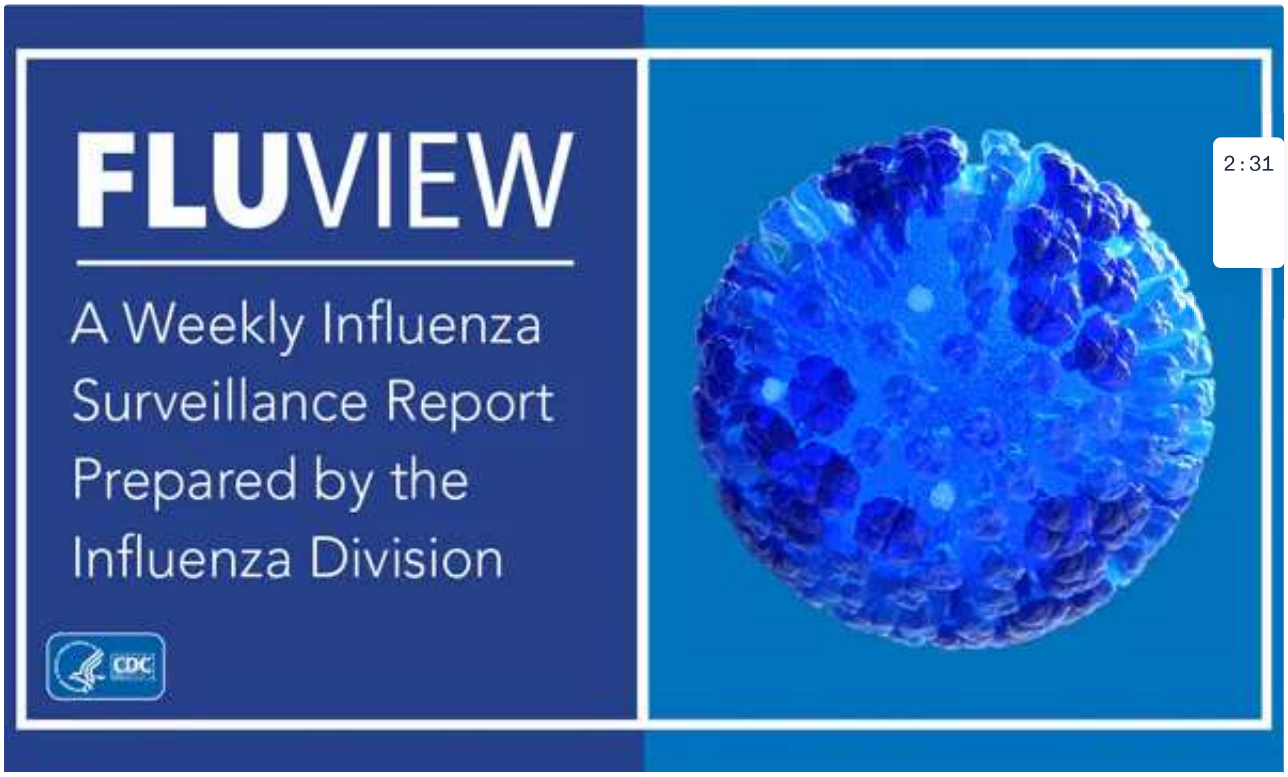
- Co-administration of baloxavir with polyvalent cation-containing products may decrease plasma concentration baloxavir which may reduce efficacy. Avoid co-administration of baloxavir with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).
- Concurrent administration of antiviral drugs with intranasal live attenuated influenza vaccine (LAIV) may inhibit viral replication of LAIV and thereby decrease the effectiveness of LAIV vaccination. LAIV should not be given if oseltamivir or zanamivir was administered within 48 hours of planned vaccination, or if peramivir was administered within 5 days of planned vaccination, or if baloxavir was administered within 17 days of planned vaccination. If LAIV is given, and antiviral medications are subsequently administered up to two weeks after vaccination, the effectiveness of LAIV might be reduced, and persons who receive these antiviral medications within two weeks after receiving LAIV should be revaccinated with another appropriate influenza vaccine (e.g., IIV or RIV4).

For more information, visit the Seasonal Influenza (Flu) site, email CDC-INFO, or call CDC at 800-CDC-INFO (English and Spanish) or 888-232-6348 (TTY).

Resources

Diagnostic Testing for Influenza

More information for clinicians on influenza diagnostic testing is available.



Information on Influenza Activity

Clinicians should contact their local or state health department for information about current local influenza activity. CDC's FluView report gives Information regarding national influenza activity weekly during influenza season.

References

A more complete list of influenza antiviral references is available.

Last Reviewed: November 27, 2023

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