Review

CDC and PHE recommendations for the antiviral treatment and prophylaxis of influenza

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SUMMARY

Influenza is a major cause of severe respiratory infections with excessive morbidity and mortality globally. Annual epidemics or pandemics still exert a major health and socioeconomic burden. Vaccination remains the principal means for preventing influenza-related morbidity and mortality. However, antiviral agents present with major beneficial effects since they could improve viral clearance, shorten illness duration and hospitalizations, diminish complications, reduce death risks and limit disease transmission. Decisions about starting antiviral treatment should not wait for test results or laboratory confirmation of influenza. When there is clinical suspicion of influenza and antiviral treatment is indicated, antiviral treatment should be started within 48 hours after the symptom onset. Oral oseltamivir for 5 days represent the optimal therapeutic regimen for both prophylaxis and treatment of influenza infection. Inhaled zanamivir is the first line of treatment for influenza infection (complicated or uncomplicated) in immunocompromised individuals or in cases of confirmed H1N1 infections with suspected resistance to oseltamivir. This short review summarizes the current Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) and the Public Health England (PHE) recommendations for the antiviral treatment and prophylaxis of influenza infection.
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INTRODUCTION

Influenza is a major cause of severe respiratory infections with excessive morbidity and mortality globally. Annual epidemics or pandemics still exert a major health and socioeconomic burden[1]. Rapidly emerging evidence from large multicenter randomized controlled trials (RCTs) suggests that antiviral agents present with major beneficial effects since they could improve viral

clearance, shorten illness duration and hospitalizations, diminish complications, reduce death risks and limit disease transmission[1,2]. Despite the above promising data, it is worth noting that antiviral agents for influenza are an adjunct to vaccine and not a substitute. Vaccination remains the principal means for preventing influenza-related morbidity and mortality[3]. However, a history of influenza **immunization does not exclude influenza** as a possible diagnosis. While influenza is unpredictable, laboratory data suggest that influenza A (H3N2) viruses are predominating during the 2016-17 season. Influenza A (H3N2)–predominant seasons often are associated with more severe illness, especially in young children and older adults[1]. While serious influenza complications can occur in people of any age, certain people are at **greater risk** for complications (Table 1).

Currently, there are three FDA-approved antiviral drugs recommended by CDC (https://www.cdc.gov/flu/antivirals/whatyoushould.htm) this season to treat influenza[1-5]. These drugs belong to the subclass of neuraminidase inhibitors and are the following:

TABLE 1. Risk factors for acute complicated influenza infection

Chronic Lung Diseases	Asthma COPD Cystic Fibrosis Pulmonary Fibrosis Bronchiectasis
Cardiovascular Disorders	Congenital Heart Disease Coronary Artery Disease
Hematological Disorders	Sickle cell disease
Endocrine Disorders	Diabetes Mellitus
Kidney Disorders	Chronic Renal Failure
Liver Disorders	Hepatitis, Hepatic Failure, Liver Cirrhosis
Metabolic Disorders	Mitochondrial disorders
Age	<2 or >65 years
Immunosuppression	HIV, chemotherapy
Other conditions	Pregnancy (up to two weeks postpartum), alcoholism, drug abuse, obesity, people <19 years of age who are receiving long-term aspirin therapy, malignancies

1. Oseltamivir (trade name Tamiflu®), is available as a pill or liquid. Generic oseltamivir is available as a pill.
2. Zanamivir (trade name Relenza®), is a powder that is inhaled. (Relenza® is not recommended for people with breathing problems like asthma or COPD).
3. Peramivir (trade name Rapivab®). Food and Drug Administration approved it to treat influenza infection in adults as an IV formulation.

PHARMACOKINETICS, PHARMACODYNAMICS AND TOXICITY

1. **Oseltamivir:** Oseltamivir is an inhibitor of the influenza neuramidase enzyme and has been approved for the treatment of uncomplicated acute illness due to influenza A and B infection in patients aged ≥1 year who have been symptomatic for no more than two days. It can also be for the chemoprophylaxis of influenza in adolescents 13 years and older. Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. It is systemically administered as prodrug (phosphate) and is hydrolysed hepatically to the active metabolite, the free carboxylate of oseltamivir. Oseltamivir carboxylate is extensively eliminated by renal excretion and reaches a peak effect (as indicated by reduction in viral titers) within 24 hours following administration. Coadministration with food has no significant effect in oseltamivir peak plasma levels while it is, yet, not known whether oseltamivir is distributed inti human breast milk; however, preclinical studies have shown that oseltamivir carboxylate is distributed into the milk of lactating rats. The most frequent side-effects are nausea, vomiting, that are mild to moderate and usually occur within the first 2 days of treatment. Scarce data supports an increase in headaches and psychiatric events. Further studies are warranted to support this notion[4,5].
2. **Zanamivir:** Zanamivir is manufactured by GlaxoSmithKline (Relenza --- inhaled powder). Zanamivir is approved for treatment of persons aged ≥7 years and approved for chemoprophylaxis of persons aged ≥5 years. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Zanamivir is available

as a powder for inhalation (licensed) or in aqueous solution (unlicensed). Aqueous zanamivir may be administered through a nebulizer or intravenously. It is the only unlicensed treatment recommended by Public Health England (PHE) (version 7.0, October 2016) in certain circumstances for first and second line therapy based on the significant experience of its use during the 2010/11 influenza season[2].

3. **Peramivir (IV)**: Peramivir is a neuraminidase inhibitor which has been licensed in the USA, in a preparation for intravenous use. It is licensed for the treatment of acute uncomplicated influenza in adults aged 18 years and over. Peramivir is administered as a single dose within 2 days of onset of acute influenza symptoms. Evidence of efficacy of the 600mg dose is limited to mainly influenza A infection but there is no evidence for the drug's routine use in treating serious influenza requiring hospitalization. There is no evidence for improved outcomes in combination therapy with oseltamivir, though there are recent case reports and retrospective cohort series of survival when used as salvage therapy[4,5,8].

EFFICACY

Clinical trials have demonstrated that 75 mg bid of oseltamivir administered to otherwise healthy individuals have reduced the illness duration up to 1.5 days, if started within 36 hours from the onset of symptoms. Moreover, a large meta-analysis of 10 RCTs has shown that oseltamivir reduced lower respiratory tract infections, hospitalizations and use of antibiotics in both healthy and at-risk individuals. Oseltamivir has also exhibited favorable effects in a clinical trial enrolling patients with chronic lung and heart diseases by significantly reducing the incidence of complications and use of antibiotics[6]. Zanamivir has also demonstrated similar therapeutic efficacy. Meta-analyses of large RCTs showed that zanamivir reduced duration of influenza symptoms by 0.6 to 0.7 days. On the other hand the benefit of zanamivir was similar to "relief medications", i.e. acetaminophen[4,5]. Zanamivir is contraindicated in patients with asthma and COPD due to severe bronchospasm in a substantial proportion of patients with underlying chronic lung disease. For both oseltamivir and zanamivir, studies showed no radiological improvement (x-ray) in signs of pneumonia[4,5].

With respect to peramivir, data derived from double-blinded placebo-controlled revealed a more pronounced drop in virus titers in patients commenced with oral peramivir 24 hours after onset of symptoms and continued for 5 days compared to placebo. However, this effect was dose-dependent and was only observed in high doses. Thus, alternative parenteral formulations were tested, i.e. intravenous; however, several large multicenter RCTs failed to show superiority against oseltamivir both in treatment and prophylaxis arms. Studies from Japan support the use of IV peramivir in children <18-years old, especially where the use of inhalation drugs is not feasible[4,5].

THERAPEUTIC ALGORITHM (Figure 1)

Decisions about starting antiviral treatment should not wait for test results or laboratory confirmation of influenza. When there is clinical suspicion of influenza and antiviral treatment is indicated, antiviral treatment should be started as soon as possible (within 48 hours after the symptom onset), along with use of appropriate infection control measures. Rapid testing for respiratory viruses including influenza virus is recommended for all patients fulfilling the clinical criteria for complicated infection[1].

First line treatment: Based on CDC guidelines, oseltamivir still lies at the core of influenza prophylaxis and treatment (complicated or uncomplicated) (Table 2)[1,2] in elderly high-risk groups without severe immunosuppression[6,7]. With regards to otherwise healthy individuals which present with clinical suspicion of influenza infection it is upon physician's discretion to administer antiviral agent. It should be underlined that most people who are otherwise healthy and get the flu do not need to be treated with antiviral drugs. To treat influenza, oral oseltamivir is usually prescribed for 5 days, although hospitalized patients may receive treatment for longer. Intention-to-treat analysis has revealed that patients treated with oseltamivir return to normal activities almost 1 day sooner; however, there is no robust data supporting that oseltamivir affects disease severity and mortality while there is scarce data on reduction of influenza complications[6,7].

Second line treatment: In the case scenario of poor clinical response to first line treatment then doctors based on their clinical judgment should: a) switch to zanamivir, b) test for antiviral resistance (generally is low but still can occur). Inhaled zanamivir can also be used as first line treatment in the following cases:

1) In severely immunocompromised individuals with complicated H1N1 infection and possible oseltamivir resistance.

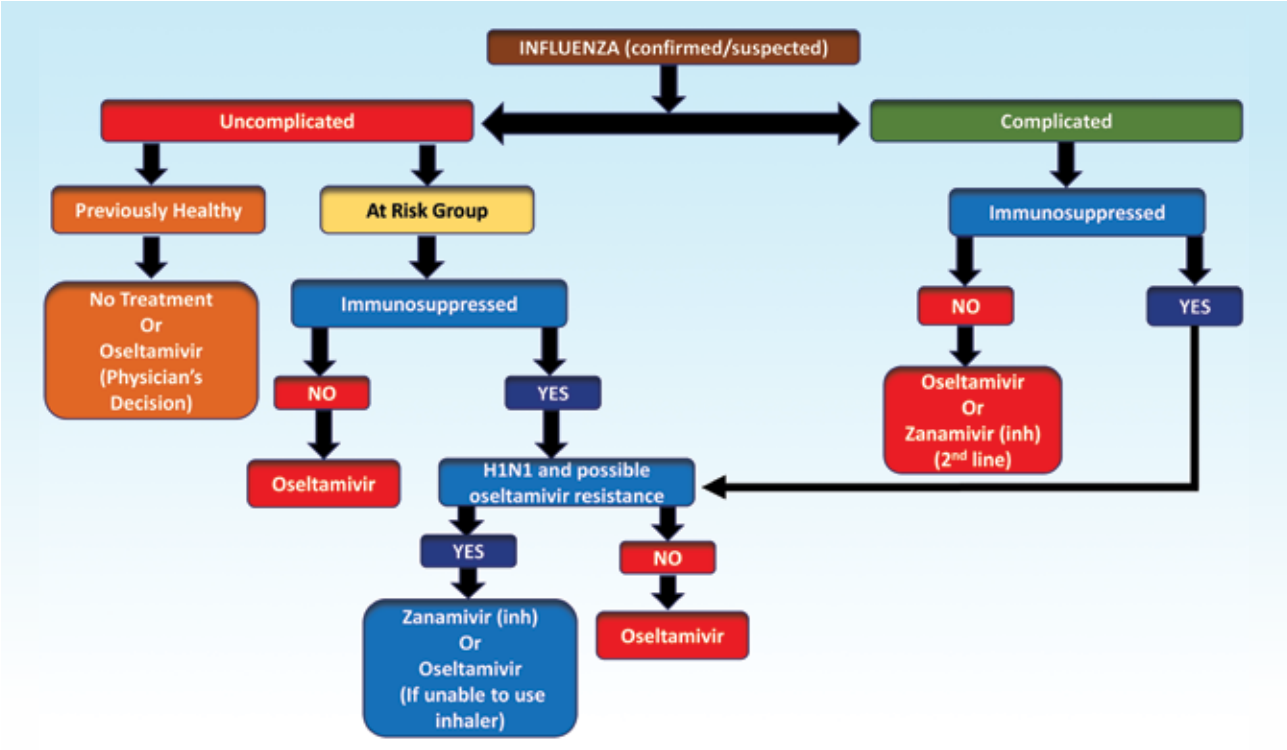

FIGURE 1. Diagram showing the strategy for prescribing antiviral drugs for suspected or confirmed influenza (modified from ref. 2).

TABLE 2. Definitions regarding influenza according to Public Health England (modified from reference 2)

1. **Uncomplicated influenza:** Influenza presenting with fever, coryza, generalized symptoms (*headache, malaise, myalgia, arthralgia*) and sometimes gastrointestinal symptoms, but without any features of complicated influenza.
2. **Complicated influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (*hypoxemia, dyspnea, lung infiltrate*), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.
3. **Severe immunosuppression:** Examples of severe immunosuppression
   a. Severe primary immunodeficiency.
   b. Current or recent (*within six months*) chemotherapy or radiotherapy for malignancy.
   c. Solid organ transplant recipients on immunosuppressive therapy.
   d. Bone marrow transplant recipients currently receiving immunosuppressive treatment, or within 12 months of receiving immunosuppression.
   e. Patients with current graft-versus-host disease.
   f. Patients currently receiving high dose systemic corticosteroids (*equivalent to ≥40 mg prednisolone per day for >1 week in an adult, or ≥2mg/kg/day for ≥1 week in a child*), and for at least three months after treatment has stopped.
   g. HIV infected patients with severe immunosuppression (*CD4<200/µl or <15% of total lymphocytes in an adult or child over five*).
   h. Patients currently or recently (*within six months*) on other types of highly immunosuppressive therapy.

2) If there is evidence of gastrointestinal dysfunction, which could cause decreased absorption of enterically-administered medications, use zanamivir. Examples include known gastroparesis, clinical evidence of malabsorption, uncontrollable vomiting, and gastrointestinal bleeding. Patients unable to use a zanamivir Diskhaler® should be considered for nebulized aqueous zanamivir.
3) Patients who failed to respond to nebulized or inhaled zanamivir or those with severe multiorgan involvement

may benefit from IV zanamivir; however, efficacy data is still scarce and controversial.

Importantly, it should be underlined that inhaled zanamivir is an absolute contraindication for high risk individuals with bronchial hyper-reactivity due to excessive bronchospasm that has been observed in a significant proportion of patients.

Intravenous peramivir is administered in a single infusion over 15-30 minutes. Peramivir is approved for treatment in adults, zanamivir for treatment of children 7 years or older, and oseltamivir for treatment even in infants. Antiviral dosage information for different age groups is shown in table 3. Antiviral resistance among circulating influenza viruses to any of the neuraminidase inhibitor antiviral drugs is currently low, but rare, sporadic cases of antiviral resistance can occur[1,3-5].

Special Populations

Children can take two of the approved antiviral drugs—oseltamivir and Zanamivir. Oseltamivir is recommended by the CDC and American Academy of Pediatrics (AAP) for the treatment of influenza in persons aged 2 weeks and older, and for the prevention of influenza in persons aged 3 months and older[7,8]. Zanamivir is recommended for the treatment of influenza in persons aged 7 years and older, and for the prevention of influenza in persons aged 5 years and older[9].

Pregnant women

Antivirals have been recommended for pregnant women due to the adverse clinical outcomes that have been observed for influenza infection in this group. Oseltamivir remains the first line option for the vast majority of pregnant women with influenza infection, including endemic seasons for influenza A (H1N1). For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (i.e. rapid diagnostics) and antiviral treatment should be discussed with an infection specialist. There are no data suggesting tolerability differs between pregnant and non-pregnant adults. Recent studies suggest there is no evidence of harm in pregnant women treated with oseltamivir or zanamivir[10,11].

TAKE HOME MESSAGES

1. Vaccination remains the principal means for preventing influenza-related morbidity and mortality. However, a history of influenza **immunization does not exclude influenza** as a possible diagnosis.
2. Decisions about starting antiviral treatment should not wait for test results or laboratory confirmation of influenza. When there is clinical suspicion of influenza and antiviral treatment is indicated, antiviral treatment should be started within 48 hours after the symptom

TABLE 3. Recommended dosage and schedule of influenza antiviral medications for treatment and chemoprophylaxis (modified from reference 1).

ANTIVIRAL AGENT	1 – 6 yrs.	7 – 9 yrs.	10 – 12 yrs.	>13 yrs.
Zanamivir (Relenza)				
Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
Chemoprophylaxis, influenza A and B	NA for ages 1 – 4	Ages 5 – 9 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir (Tamiflu)				
Treatment, influenza A and B	Dose varies by child's weight	Dose varies by child's weight	Dose varies by child's weight >40 kg = adult dose	75 mg twice daily
Chemoprophylaxis, influenza A and B	Dose varies by child's weight	Dose varies by child's weight	Dose varies by child's weight >40 kg = adult dose	75 mg once daily

onset, along with use of appropriate infection control measures.
3. Rapid testing for respiratory viruses including influenza virus is recommended for all patients fulfilling the clinical criteria for complicated infection.
4. Most people who are otherwise healthy and get the flu do not need to be treated with antiviral drugs
5. Oral oseltamivir for 5 days represent the optimal therapeutic regimen for both prophylaxis and treatment of influenza infection
6. Inhaled zanamivir is the first line of treatment for influenza infection (complicated or uncomplicated) in immunocompromised individuals or in cases of confirmed H1N1 infections with suspected resistance to oseltamivir
7. Inhaled zanamivir is contraindicated in patients with bronchial asthma and COPD
8. Oral oseltamivir is preferred for treatment of pregnant women because it has the most studies available to suggest that it is safe and beneficial
9. Oseltamivir is recommended for the treatment of influenza in children 2 weeks and older and for prevention in children 3 months and older. Zanamivir is recommended for the treatment of influenza in children 7 years and older and for prophylaxis in children 5 years and older.

No conflict of interest to declare

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