Pharmacological treatment and prophylaxis of influenza

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This document has been written in response to a rapidly evolving situation and is under continuous review based on feedback from clinicians; adult & paediatric.

The guidance may change as more epidemiological and virological data becomes available, so please look at the website regularly.

Context

This guidance summarises the current HPA recommendations for the antiviral treatment and prophylaxis of influenza. The summary draws on guidance already issued by the Health Protection Agency [1,2], the National Institute for Health and Clinical Excellence [3,4], the Department of Health [5,6] and the World Health Organization [7,8]. In areas where guidance or evidence from adequate randomized controlled trials is absent, the therapeutic recommendations rely on expert opinion and current consensus. The document provides typical scenarios (see annex III) that may be encountered in clinical practice to illustrate the specific recommendations for the administration of antiviral drugs, including the emergence of antiviral resistance. It also contains flow charts to assist in performing risk assessment and clinical decision making.

Complementary updated guidance on the surveillance and laboratory diagnosis of influenza as well as guidance for the management of critically-ill adult and paediatric patients has been published concurrently on the HPA website under seasonal influenza / information for health professionals (see link).

This advisory will be reviewed in the event of emergence of a novel influenza strain.

Summary of Main considerations

1. Antiviral therapy may be beneficial in human influenza and has been associated with prevention of disease or complications among patients exposed to the virus, shortened duration of illness among acutely-ill patients and reduction of morbidity and mortality among patients with severe infection [6].

2. Influenza vaccination and infection control practices are of utmost importance in preventing infection and are universally preferred over the administration of chemoprophylaxis.
3. Antiviral use in the community should be in accordance with NICE guidance (as amended by regulations to include pregnant women in the at-risk groups) and the recent guidance from the Chief Medical Officer for England. In the hospital setting, antivirals should be used to treat any patient in whom influenza is suspected.
4. Antiviral treatment should be started as soon as possible. In the community, antivirals should usually be given within 48 hours of the onset of symptoms; in a hospitalised patient antivirals can be given beyond the 48 hour period.
5. The choice of antiviral drug therapy (which in turn influences route of administration) should be guided by host risk factors, clinical condition, previous exposure to antivirals as well as knowledge of which influenza strains are circulating, their antiviral resistance profile and current epidemiology (Figure 1). Relevant definitions appear in Annex I.
6. A high index of suspicion should be maintained for diagnosing antiviral resistant influenza, especially among severely immunosuppressed patients, patients with treatment failure, progressive infection despite adequate therapy or contacts of individuals known to be infected with resistant strains.
7. Patient vaccination status should be taken into account for decisions regarding administration of prophylaxis, bearing in mind vaccine effectiveness and the propensity for change of infecting strains.
8. Adequate dose, dosing interval and duration of antiviral therapy reduce the likelihood of emergence of resistance during therapy. In certain patient groups, the risk for emergence of resistance during therapy should be taken into account in the choice of therapeutic agent [2].
9. The properties of antiviral drugs are summarised in Annex II.

10. In certain clinical situations, sequential monitoring of virus shedding may aid in determining the duration of antiviral chemoprophylaxis or therapy.
11. Major advice for treatment and prophylaxis are summarised in the tables 1 and 2 and the flowcharts in Figures 1-3 below. For more information please refer to the scenario-based recommendations in Annex III.

Table 1. Summary of treatment advice for seasonal influenza 2010/11 (includes pandemic H1N1 (2009), H3N2 and influenza B)

Uncomplicated clinical presentation of influenza (adults and children[1])	
Otherwise healthy population	• Generally need not treat; clinical discretion to be exercised according to CMO's letter [9]. • Advise self-isolation and action to take if symptoms worsen
NICE defined at-risk population (excluding severely immuno-suppressed individuals) or people who are considered by their GP to be at serious risk of developing complications	• Oseltamivir[2] • Advise self-isolation
Severely immunosuppressed people[3]	• Zanamivir is preferred because of the evidence showing an increased possibility of oseltamivir resistance emerging in this patient group • Advise self-isolation • Consider antiviral resistance if no improvement noted
Anyone in whom oseltamivir resistant virus is confirmed or suspected[4] either clinically or epidemiologically	• Zanamivir • Advise self-isolation • Antiviral resistance testing
Complicated or progressive clinical presentation of influenza	
Any person (excluding severely immunosuppressed individuals)	• Oseltamivir (if unable to take orally can be given by naso-gastric tube). Doses of up to 150mg bd and duration up to 10 days have been administered compassionately to critically-ill patients • Infection control measures • Consider antiviral resistance if no improvement noted within 5 days of therapy • If gastric absorption is problematic and an IV preparation is appropriate then zanamivir aqueous solution or IV oseltamivir (unlicensed) may be available on a named patient basis for compassionate use in serious influenza illness
Severely immunosuppressed patients[3]	• Zanamivir is preferred because of the evidence showing an increased possibility of oseltamivir resistance emerging in this patient group • Infection control measures • If gastric absorption is problematic and an IV preparation is appropriate then zanamivir aqueous solution (unlicensed) may be available on a named patient basis for compassionate use in serious influenza
A patient in whom oseltamivir resistant virus is confirmed or suspected[4] either clinically or epidemiologically	• Zanamivir • Infection control measures • If gastric absorption is problematic and an IV preparation is appropriate then zanamivir aqueous solution (unlicensed) may be available on a named patient basis for compassionate use in serious influenza illness

[1] Includes children under 1 – see table 3 or BNF for dosages. The MHRA safety data for antivirals in this age group is at http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087737
[2] Although either drug is considered clinically adequate, oseltamivir is preferred because of its wider availability through community pharmacy outlets.
[3] See annex I for definition of severe immunosuppression.
[4] See section 6 under 'summary of main considerations'.

Table 2. Summary of advice for post-exposure prophylaxis against seasonal influenza 2010/11 (includes H1N1 (2009), H3N2 and B)

Otherwise healthy population	• NO prophylaxis necessary
NICE defined at-risk population (excluding severely immuno-suppressed individuals)	• Consider prophylaxis – use oseltamivir if therapy can be started within 48 hours of last contact • If prophylaxis indicated and exposure to confirmed or possible oseltamivir resistant virus is suspected use zanamivir if therapy can be started within 36-48 hours of last contact
Severely immunosuppressed people[1]	• Consider prophylaxis with zanamivir if treatment can be started within 36-48 hours of last contact.

[1] See annex I for definition of severe immunosuppression.

References

1. Health Protection Agency. *HPA Review: the clinical effectiveness of neuraminidase inhibitors, including evidence from the 2009 influenza A/H1N1 pandemic.* September 2010. Available (For HPA personnel) at: http://hpanet/webc/HPAnetFile/HPAnet_C/1287144689883. Available on request for non-HPA personnel: email: pandemicflu@hpa.org.uk
2. Health Protection Agency. Inpatient clinical management issues relating to oseltamivir-resistant pandemic (H1N1) 2009 influenza virus http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152289698
3. TA168 Amantadine, oseltamivir and zanamivir for the treatment of influenza: review of NICE technology appraisal guidance 58. February 2009 Available at: http://guidance.nice.org.uk/TA168
4. TA158 Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza; review of NICE technology appraisal guidance 67. September 2008 Available at: http://guidance.nice.org.uk/TA158
5. Department of Health. *Pandemic H1N1 (2009) influenza: clinical management guidelines for adults and children.* October 2009 Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107769
6. 2010/11 Seasonal Influenza: Prescription of antivirals. GRN 15338 (add link)
7. World Health Organization. *Clinical management of human infection with H1N1 (2009): revised guidance.* November 2009 http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/
8. World Health Organization. *WHO guidelines for pharmacological management of pandemic influenza (H1N1) 2009 and other influenza viruses*. February 2010. Available at http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/
9. Department of Health. 2010/11 seasonal influenza: prescription of antivirals.

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_123094.pdf

10. Department of Health. 2010/11 seasonal influenza: update on supply and availability of antivirals for children under 1 year of age. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_123319.pdf
11. Department of Health. Immunisation against infectious disease – 'The Green Book'. Pp. 42-44. Updated 17 September, 2008. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_063623.pdf

12. United Kingdom Clinical Pharmacy Association. Antiviral management of influenza A (H1N1) in critical care. January 2011. Version 4.0.

Annex I – Definitions

1. Uncomplicated influenza – an influenza-like illness manifesting as fever (in the majority of patients), upper respiratory tract symptoms (cough, sore throat, rhinorrhea), generalized symptoms (headache, malaise, myalgia, arthralgia) and sometimes GI symptoms.
2. Complicated influenza – an influenza-like illness requiring hospital admission **and/or** presenting with symptoms and signs of lower respiratory tract infection (hypoxemia, dyspnoea, lung infiltrate), central nervous system involvement (altered consciousness, encephalitis) **and/or** a significant exacerbation of an underlying medical condition (such as cardiac, hepatic, pulmonary or renal insufficiency or diabetes mellitus).
3. Progressive influenza – progression from uncomplicated influenza to complicated influenza.
4. Risk factors for complicated or progressive influenza – host factors associated with a significantly increased risk for complicated or progressive disease, including pregnancy (especially in 3rd trimester and up to 2 weeks post-partum), children <2 years, adults >65 years, chronic cardiac, pulmonary, renal or hepatic insufficiency, diabetes mellitus, debilitating neurological conditions and primary or secondary immunosuppression.
5. Prophylaxis – low-dose antiviral therapy administered for the prevention of influenza. Prophylaxis is usually given post-exposure and should always be continued for 10 days. Full-dose (ie treatment dose) antiviral prophylactic therapy may be administered to certain immunocompromised individuals due to increased likelihood of emergence of resistance during therapy.
6. Standard therapy – antiviral therapy administered for suspected or proven clinical influenza.
7. Severe immunosuppression – please refer to the Green Book for further detail [11]:
    1. Severe primary immunodeficiency
    2. Current or recent (<6 months) immunosuppressive chemotherapy or radiotherapy for malignancy.
    3. Solid organ transplant recipients on immunosuppressive therapy.
    4. Bone-marrow transplant recipients currently or recently (<12 months) receiving immunosuppressive therapy or with a history of GVHD.
    5. Patients receiving high-dose systemic corticosteroids (>40mg/d in adults).
    6. Patients currently or recently (<6 months) on other types of immunosuppressive therapy.
    7. HIV-infected patients with severe immunosuppression.

Annex II.

Table 3. The properties of the major antiviral drugs

Drug	Mechanism of action	Typical adult dosage[1]		Side effects	Resistance profile	Remarks
		therapy	*prophylaxis*			
Oseltamivir (oral)	Neuraminidase inhibition	75 mg bd for 5 days[1,2]	75 mg Daily for 10 days	GI disturbances. Rarely hepatitis, arrhythmia and Stevens-Johnson	Uncommon H275Y mutation in H1N1 strains; More rare mutations in other subtypes	Dose reduction in renal failure[3] Pregnancy category C[4]
Zanamivir (inhaled)	Neuraminidase inhibition	10 mg inh.bd for 5 days[5]	10mg daily for 10 days	Rarely bronchospasm or angioedema	Rare altered susceptibility via I223R detected in ~10 cases of H1N1 (2009) worldwide.	Pregnancy category C
Peramivir (Unlicensed)	Neuraminidase inhibition	600 mg i.v. qd for 5-10 days	N/A	GI disturbances, psychiatric abnormalities, neutropenia	Rare. H275Y mutation reduces efficacy.	Dose reduction in renal failure. Unlicensed drug
Amantadine (NOT currently advised for treatment of influenza in the UK)	M2 channel inhibitor	100 mg daily for 5days	100 mg daily (duration variable)	Confusion, insomnia, exacerbation of underlying neurological conditions	Common. H1N1 (2009) 100% resistant Varying rates in H3N2 / influenza B	Dose reduction in renal failure. Pregnancy category C[4]

[1] Paediatric therapeutic dosages: oseltamivir – 2mg/kg bd for children 0-1 month, 2.5mg/kg bd for children 1-3 months, 3mg/kg for children 3-12 months. For 1-13 years the recommended oseltamivir dose is 30 mg, 45 mg, 60 mg or 75 mg bd for children weighing <15 kg, 15-23 kg, >23-40 kg or >40 kg, respectively. For those over 13 years the dose is the same as adults. For infants and young children, oseltamivir oral suspension is preferred [10]. Zanamivir dosage (≥ 5 years) same as for adults.

[2] Doses of up to 150mg bd and duration up to 10 days have been administered compassionately to critically-ill patients; i.v. oseltamivir also available for compassionate use from Roche. Please note that i.v. oseltamivir is indicated for poor GI absorption and is not the drug of choice when oseltamivir resistance is suspected.

[3] Inhaled zanamivir should be considered in patients with severe renal failure.

[4] Some authorities prefer inhaled zanamivir for pregnant women because of reduced systemic exposure. However, this is a purely clinical consideration and oseltamivir is not contra-indicated in pregnancy. There is no evidence that one drug is better or safer than the other.

[5] An unlicensed i.v. formulation is available from the manufacturer (GSK) on a named-patient, compassionate use, basis, for use in patients with severe illness. Refer to 'Antiviral management of influenza A (H1N1) in critical care' [12].

Annex III

Recommendations for Treatment and Prophylaxis of Influenza

Algorithms for therapeutic considerations are provided in figures 1-3 page 12-14.

Clinical illness (see also Figure 2)

Scenario 1 – Treatment of uncomplicated influenza in otherwise healthy individuals.

1. Otherwise healthy individuals in the community with suspected or proven uncomplicated influenza do not generally need antiviral therapy.
2. Clinical discretion should be exercised in accordance with the recent letter issued by the CMO [9].
3. Pregnant women are considered to be at-risk (see scenario 2) and should be offered treatment.
4. Patients should be informed of the signs and symptoms of complicated influenza and instructed to seek medical attention if these occur.
5. Patients should be advised to self-isolate until symptom free.

Scenario 2 – Treatment of uncomplicated influenza among high-risk individuals.

1. Those with suspected or proven influenza who are high-risk individuals, including pregnant women, or those who are considered by their GP to be at serious risk of developing should be offered antiviral therapy if treatment can be started within 48 hours (36 hours for Zanamivir treatment in children) of the onset of symptoms.
2. Treatment should commence as early as possible.
3. Therapy should be given empirically and not deferred until laboratory test results are known.
4. Unless other clinical/virological considerations prevail (see points below), oseltamivir is preferred because of its wider availability in community pharmacies.
5. With the exception of severely immunosuppressed patients, (see definitions) the drug of choice for high-risk patients is oseltamivir at standard dosage and duration.
6. There is no evidence to support the preferential use of inhaled zanamivir instead of oseltamivir in pregnant women and both oseltamivir and zanamivir may be administered to pregnant women
7. Consideration should be given to using inhaled zanamivir at a standard dose for 10 days for severely immunosuppressed patients.
8. If oseltamivir resistance is known or suspected on clinical or epidemiological grounds, inhaled zanamivir should be administered.
9. There is insufficient evidence to recommend dual neuraminidase inhibitor therapy.
10. Patients should be informed regarding symptoms and signs of complicated influenza and instructed to seek medical attention in such an occurrence.
11. Patients should be advised to self-isolate until symptom free.

Scenario 3 – Treatment of complicated or progressive clinical illness.

1. All patients with complicated or progressive influenza, including children at all ages, should be treated with antiviral drugs, regardless of risk factors and immune status.
2. Treatment should commence as early as possible.
3. Therapy should be given empirically and not deferred until laboratory test results are known.
4. The drug of choice is oseltamivir at standard dosage and duration.
5. Higher doses may be considered for critically-ill patients.
6. Longer treatment duration should be considered for critically ill patients.
7. Antiviral susceptibility should be tested in patients failing to improve after 5 days of therapy, especially if severely immunocompromised.
8. In critically-ill patients oseltamivir may be administered by nasogastric tube. Should significantly reduced drug absorption be suspected, intravenous zanamivir (or oseltamivir if zanamivir is unavailable) may be appropriate on compassionate use basis.
9. In patients with impending respiratory failure where resistance may be suspected, intravenous zanamivir is preferred over inhaled zanamivir. [See earlier note: zanamivir aqueous solution (unlicensed) may be available on a named patient basis for compassionate use in serious influenza].
10. Zanamivir is the drug of choice in severely immunosuppressed patients. Consideration should be given to the possibility of prolonged viral shedding in this group, which may be assessed through sequential sampling of the respiratory tract, and the duration of therapy reviewed accordingly.
11. If oseltamivir resistance is known or suspected on clinical or epidemiological grounds, inhaled zanamivir should be administered at standard dose for 5-10 days.
12. In all cases, strict infection control measures should be instituted. Viral shedding may persist beyond symptom resolution.
13. If Shedding of resistant virus is confirmed, avoidance of transmission to other vulnerable patients is important. It may be relevant to closely monitor viral shedding to ensure adequate infection control.
14. Peramivir (unlicensed) or parenteral oseltamivir (unlicensed) may be considered on compassionate use as an alternative to zanamivir if the latter drug is unavailable.
15. Experimental therapeutic agents such as, intravenous immunoglobulins (IVIG) or novel antiviral agents (e.g. laninamivir) should be considered for last-line compassionate use in unique cases.

Scenario 4 –New detection of antiviral resistance in patients with uncomplicated influenza already treated with oseltamivir.

1. Oseltamivir therapy should be stopped. Any further therapeutic decisions should be guided by the patient's condition.
2. Patients who are well or recovering need not receive alternative antiviral therapy.
3. Patients who are symptomatic should be switched to inhaled zanamivir at a standard dose for 5-10 days.
4. Patients with complicated or progressive clinical illness should be treated as above.

5. Consideration of infection control matters in hospitalised patients may require monitoring of viral shedding.
6. In all cases, strict infection control measures should be instituted.

Scenario 5 – Treatment of severely immunosuppressed children

1. Oseltamivir is the antiviral drug of choice for children. This includes those admitted to critical care and those with primary or secondary immunodeficiency, unless local virological and epidemiological data suggest otherwise.
2. While zamamivir is licensed for children aged 5yrs and older, few children can quickly learn to inhale powder effectively particularly if severely immunosuppressed and acutely unwell with influenza like illness.
3. Zanamivir powder for inhalation (or exceptionally nebulised zanamivir solution, excluding ventilated patients) should only be used where giving oseltamivir by the oro-gastric route is not possible OR there is strong evidence of malabsorption. Intravenous zanamivir should only be considered for use in patients with severe respiratory failure (ventilated) AND when the oro-gastric route is not suitable. At present intravenous zanamivir is only available from GSK on a named patient basis and requires courier delivery.
4. Severely immunosuppressed children who do not improve on oral oseltamivir after 48 hours should be given inhaled zanamivir for 10 days if they are capable of inhaling it. All such children should already be on broad spectrum antibiotics.

Prophylaxis

Scenario 6 – Possible exposure of otherwise healthy individuals to patients with influenza

1. Onward transmission of influenza should be minimised by institution of general hygiene measures.
2. Chemoprophylaxis is not recommended for otherwise healthy individuals in the setting of potential exposure to infected patients or following exposure.
3. Patients should be informed regarding severe symptoms and signs of influenza and instructed to seek medical attention if disease worsens
4. Prophylaxis may be considered by health protection professionals in institutional, healthcare or other special settings where continuous or repeated exposure is evident.

Scenario 7 – Possible exposure of individuals with risk factors for influenza to patients with influenza.

1. Onward transmission of influenza should be minimized by institution of strict infection control measures.
2. Chemoprophylaxis with an antiviral should be offered to individuals with risk factors for influenza who have been exposed to a patient with influenza if, antivirals can be started within 48 hours of last contact for oseltamivir or 36 hours for zanamivir. Close patient monitoring and prompt diagnosis and treatment of influenza are an alternative.
3. The drug of choice is oseltamivir at standard dosage for prophylaxis for 10 days.
4. If oseltamivir resistance is known or suspected among contacts on clinical or epidemiological grounds, inhaled zanamivir prophylaxis should be administered for 10 days.

5. There is no evidence to support the use of inhaled zanamivir instead of oseltamivir in pregnant women in terms of safety or efficacy and both zanamivir and oseltamivir may be administered to pregnant women.

Scenario 8 – Possible exposure of severely immunosuppressed individuals to patients with influenza.

1. Onward transmission of influenza should be minimized by institution of strict infection control measures.
2. Chemoprophylaxis should be offered to severely immunosuppressed patients who have been exposed to infected patients as in Scenario 7.
3. In light of the high risk for the development of oseltamivir resistance among H1N1 (2009) strains, full-dose inhaled zanamivir should be offered as chemoprophylaxis in severely immunosuppressed individuals, regardless of the source's antiviral susceptibility.

Figure 1 . Risk assessment - likelihood of oseltamivir resistance

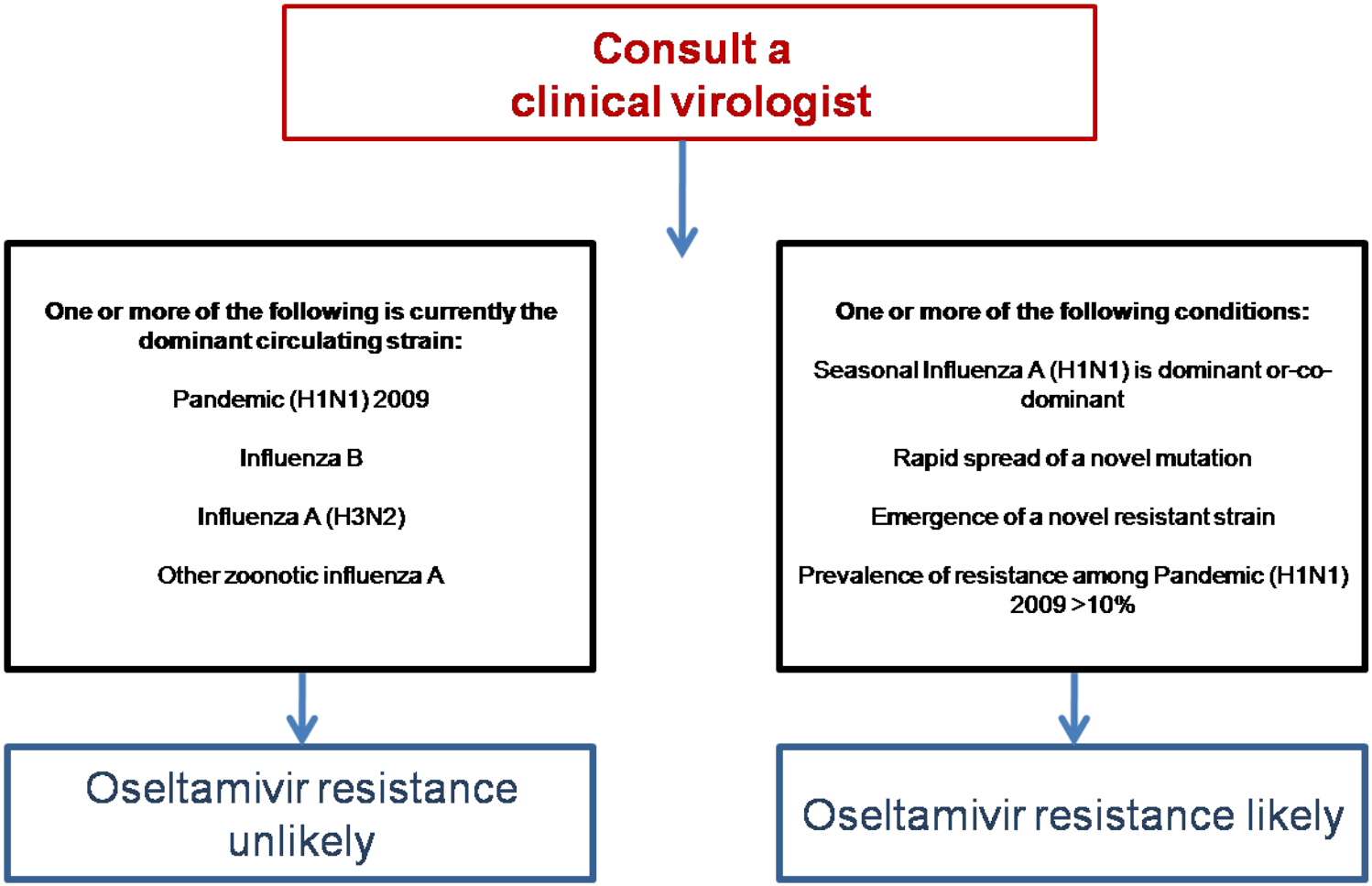

Figure 2 Choice of antiviral therapy for influenza-like illness

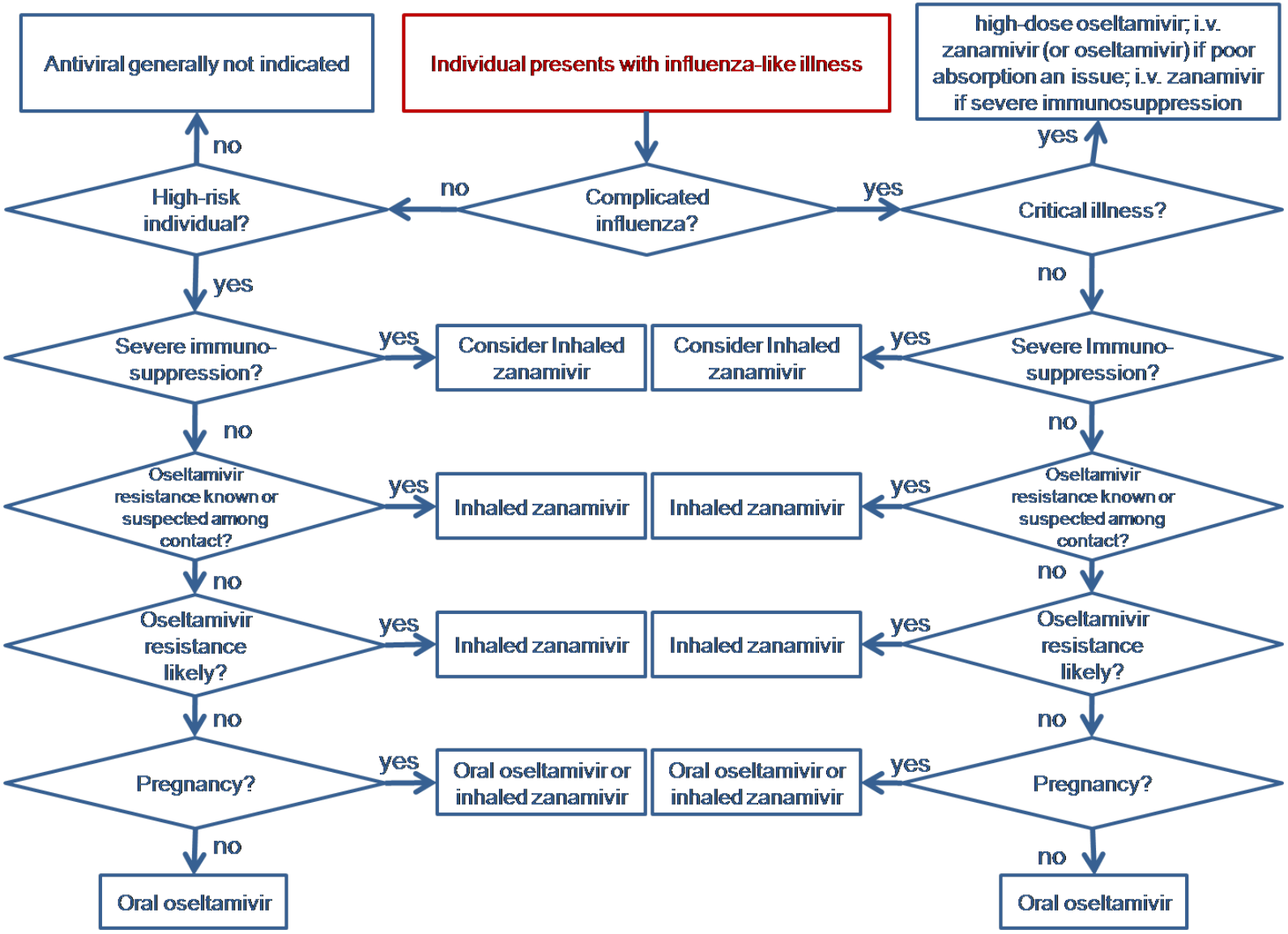

Figure 3 Choice of antiviral prophylaxis following exposure