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# Influenza A<sup>☆</sup>

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<b>Introduction</b>	1
<b>Definition</b>	1
<b>Classification</b>	1
<b>Consequences</b>	2
<b>Associated Disorders</b>	2
<b>Etiology</b>	2
<b>Epidemiology</b>	2
<b>Pathophysiology</b>	2
<b>Signs and Symptoms</b>	2
<b>Standard Therapies</b>	3
<b>Experimental Therapies</b>	4
<b>Animal Models</b>	5
<b>Journal Citations</b>	5

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## Introduction

The influenza viruses, which contain segmented, single-stranded RNA, are classified into three types, A, B, and C (Dolin, 2005; Murray et al., 2002; Treanor, 2005). The virus is enveloped with a nucleocapsid containing 8 (types A and B) or 7 (type C) segments. Type A subtypes vary in type of hemagglutinin (H1, H2, or H3 subtype), the protein that is important for host cell attachment. Antibodies directed at the hemagglutinin provide human immunity to infection. In addition, the virus possesses either N1 or N2 neuraminidase (N subtype), which also assists viral entry into the host cell and elicits the production of neutralizing antibodies (De Jong et al., 2003). Influenza is a highly communicable disease transmitted by aerosolized droplet-nuclei produced by coughing and/or sneezing, and by direct contact. All age groups are susceptible to this infection, although the very young, elderly, individuals with chronic medical complications, such as those with compromised pulmonary and cardiovascular conditions, kidney impairment, diabetes or immunosuppressive disorders, and pregnant women in the second and third trimester are at increased risk.

Although the reservoir is primarily human, influenza A viruses have been documented in pigs, horses, seals, ducks, chickens, and whales. Certain subtypes of influenza A are species specific, although all subtypes have been documented in birds. Prominent human subtypes include H1N1, H3N2, H2N2, and H1N2. The influenza A virus has 18 distinct H and 11 distinct N subtypes, although H1, H2, and H3 and N1 and N2 are prominently associated with disease outbreaks in humans (see: <http://www.cdc.gov/flu/about/viruses/types.htm>) [Accessed 03/27/2014]. Subtypes of influenza A viruses that are prominent in one species may on occasion infect and cause disease in another. In 1998, for example, the H3N2 subtype crossed from humans to pigs, causing serious disease in the swine population. In addition, influenza A viruses from birds can be transmitted to humans directly or indirectly by an intermediate host. In this way the eight genetic elements of influenza A virus may reassort to form a new subtype (H\*N\*) against which humans are not immune (Schweiger et al., 2002; Zhang et al., 2013). In this situation a worldwide pandemic can occur. Documented instances of avian influenza viruses infecting humans are numerous. The H5N1 designate emerged in southern China in 1997 continues to cause human infections, but causes the highest incidence of infectivity in domestic poultry and wild birds (Webster et al., 2013; Zhu et al., 2013). Infection with a novel H7N9 subtype has received recent attention and in addition to infecting domestic and wild birds has also been shown to infect ferrets and pigs (Gao et al., 2013; Uyeki and Cox, 2013; Zhu et al., 2013).

## Definition

Influenza A is a single-stranded enveloped RNA virus that causes an acute and highly contagious upper respiratory disease (Murray et al., 2013). Additional information can be found at: <http://www3.accessmedicine.com/content.aspx?aID=17572#17572>.

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## Classification

The influenza A virus is a member of the family of viruses termed Orthomyxoviridae. Influenza A has a negative-sense RNA genome that consists of eight separate segments, a nucleocapsid that is helical, and a viral specific RNA polymerase. Influenza viruses exit cells by budding from the host cell plasma membrane (enveloped), and possess two major proteins, neuraminidase [N] and hemagglutinin activity [H], that emanate from the lipid envelope. The virus has an irregular but spherical shape and measures 80–120 nm in diameter.

## Consequences

Influenza illness is uncomplicated in an otherwise healthy and nonelderly adult. Most fatalities (0.1–1.0%) occur due to secondary bacterial infection of the respiratory tree. Although the most common cause of bacterial pneumonia is due to pneumococci, the most serious is due to staphylococcal infection. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* are other infrequent causes of pneumonia. The mortality rate is higher among the elderly, pregnant women, and those with other medical complications.

## Associated Disorders

Influenza A infection is often confused with the common cold (<http://www.niaid.nih.gov/topics/commoncold/Pages/default.aspx>), which may have similar signs and symptoms (<http://www.niaid.nih.gov/topics/commoncold/Pages/symptoms.aspx>). Influenza A infection resembles numerous other mild febrile diseases but stands out due to cough, muscle aches, malaise, and 'sudden onset.' Other differential diseases include infections caused by RSV (respiratory syncytial virus), adenoviruses, rhinoviruses, parainfluenza viruses, measles virus, severe acute respiratory syndrome (SARS) coronavirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* (TWAR agent), *Bordetella pertussis*, *Salmonella typhi*, and *Streptococcus pyogenes*. Influenza may be difficult to diagnose in the absence of an epidemic.

## Etiology

The etiologic agent of influenza, or the flu, is the influenza virus. The three types of virus are classified as A, B, and C. All types contain a segmented, single-stranded RNA packaged into an enveloped nucleocapsid.

## Epidemiology

The influenza A virus is spread by droplet-nuclei from sneezing and coughing patients. The incidence parallels other upper respiratory infections that occur in northern frigid winter months (late autumn to early spring). Influenza A epidemics are cyclic and occur every 2–3 years. New epidemics occur because of antigenic drift or minor changes in the H and/or N antigens, thereby allowing the virus to avoid the immune system. The CDC collects and reports relevant surveillance data (<http://www.cdc.gov/flu/weekly/fluactivitysurv.htm>).

## Pathophysiology

Influenza A virus causes necrosis of the respiratory epithelium in the tracheobronchial tree and nasal turbinates. Desquamation of the ciliated epithelium, edema, hyperemia, increased secretions, and congestion may therefore result in a secondary bacterial infection. Laboratory findings include leukopenia and often proteinuria. The influenza A virus can be readily isolated from throat washings following the inoculation of cell cultures or embryonated hen's eggs. During the second week of infection complement-fixing and hemagglutination-inhibiting antibodies are present and can be readily detected. The definitive diagnosis of influenza relies on laboratory procedures, including virus isolation and serological tests. A rapid fluorescent antibody test against the virus is available for direct detection in clinical specimens taken from acutely ill febrile patients.

## Signs and Symptoms

Influenza A is a highly contagious disease marked by the acute onset of fever (102–104 °F), severe aches and pains, prostration, inflammation of the mucous membranes of the respiratory tract, and severe headache. In addition, the affected individual will

show signs of coryza, nonproductive cough, flushed face, and sore throat. In children, nausea, vomiting, and otitis media are often reported. Fever should subside in 3–4 days and recovery is usually complete in one week, although malaise and cough may continue for 2 weeks or more. The normal incubation period is 1–4 days, with an average of 2 days. Adults are contagious from the day prior to symptoms for up to 5 days after the onset of illness. Infants and children may shed virus up to 2 weeks. Immuno-compromised patients shed virus for weeks or months.

## Standard Therapies

The treatment for influenza A infections is aimed at the control of virus spread by immunization (Stohr, 2003; Weycker et al., 2005). Chemoprophylaxis for pregnant women and compromised patients can be accomplished with amantadine, rimantadine, zanamivir, or oseltamivir (Hayden, 2001; Schmidt, 2004). Antipyretics and analgesics are typically used for the symptomatic relief of fever and myalgia. At present there are four drugs for treatment: oseltamivir (Tamiflu), zanamivir (Relenza), rimantadine (Flumadine) and Amantadine (Symmetrel). Both rimantadine and amantadine are only active and useful for influenza A. However, the CDC has advised against the use of these drugs due to the development of resistance. The neuraminidase inhibitors (see above) oseltamivir and zanamivir are active against both type A and B influenza. Unfortunately, oseltamivir, zanamivir and amantadine need to be administered within 48 h of infection and resistance to both oseltamivir and amantadine have been documented (see: [http://wwwnc.cdc.gov/eid/article/16/1/09-1304\\_article.htm](http://wwwnc.cdc.gov/eid/article/16/1/09-1304_article.htm)). For antiviral agents for the treatment and chemoprophylaxis of influenza please refer to: [http://wwwnc.cdc.gov/eid/article/16/1/09-1304\\_article.htm](http://wwwnc.cdc.gov/eid/article/16/1/09-1304_article.htm), <http://www.med.sc.edu:85/lecture/chemo.htm>, <http://www.niaid.nih.gov/factsheets/cold.htm> and <http://www3.accessmedicine.com/content.aspx?aID=74879&searchStr=influenza+a+virus#74879> for more detailed information.

The text and Table 1 are taken from Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (MMWR 21 January 2011) and represent guidelines for 2013–2014 (See: <http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf> and <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#dosage>) [Accessed 03/27/2014]. See: <http://www.cdc.gov/flu/about/season/index.htm> and <http://familydoctor.org/517.xml> for additional information.

**Table 1** Recommended dosage and schedule of influenza antiviral medications<sup>a</sup> for treatment<sup>b</sup> and chemoprophylaxis<sup>c</sup>

Antiviral agent	Age group (years)					
	1–6	7–9	10–12	13–64	≥65	
Zanamivir	Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	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	10 mg (2 inhalations) once daily
Oseltamivir <sup>d</sup>	Treatment <sup>e</sup> , influenza A and B	Dose varies by child's weight <sup>e</sup>	Dose varies by child's weight <sup>e</sup>	Dose varies by child's weight <sup>e</sup> >40 kg = adult dose	75 mg twice daily	75 mg twice daily
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight <sup>f</sup>	Dose varies by child's weight <sup>f</sup>	Dose varies by child's weight <sup>f</sup> >40 kg = adult dose	75 mg once daily	75 mg once daily

Abbreviation: NA, not approved.

<sup>a</sup>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. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu – tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged ≥ 1 year. Oseltamivir is available for oral administration in 30, 45, and 75 mg capsules and liquid suspension. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children aged < 1 year. This information is based on data published by the Food and Drug Administration (FDA), available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm>.

<sup>b</sup>Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

<sup>c</sup>Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent known case was identified.

<sup>d</sup>See <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#dosage> for information about use of oseltamivir for infants aged < 1 year. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance < 30 ml min<sup>-1</sup>.

<sup>e</sup>The treatment dosing recommendation for oseltamivir for children aged ≥ 1 year who weigh ≤ 15 kg is 30 mg twice a day. For children who weigh > 15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh > 23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh > 40 kg, the dose is 75 mg twice a day.

<sup>f</sup>The chemoprophylaxis dosing recommendation for oseltamivir for children aged ≥ 1 year who weigh ≤ 15 kg is 30 mg once a day. For children who weigh > 15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh > 23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh > 40 kg, the dose is 75 mg once a day.

This information is based on data published by the Food and Drug Administration (FDA); see: <http://www.fda.gov> and <http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm295057.htm> and FDA approved drugs for influenza: <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm#ApprovedDrugs>.

<i>Agent name</i>	<i>Discussion</i>
Influenza vaccine	Three types of vaccines are FDA approved: Egg-derived, inactivated vaccine (traditional), live attenuated, nasally administered vaccine (FluMist), or a tissue culture-derived inactivated vaccine. The trivalent vaccines are typically comprised of two influenza A subtypes (H1N1 and H3N2), and one influenza B virus. The specific antigens in the influenza vaccine may vary from year to year. The 2004–05 vaccines, which were in limited supply (Cosgrove et al., 2005), were either trivalent inactivated or live attenuated vaccines. The principal virus strains were A/Fujian/411/2002 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens. The A/Wyoming/3/2003 and B/Jilin/20/2003 (or B/Jiangsu/10/2003) viruses were used to replace the A/Fujian/411/2002 and B/Shanghai/361/2002 viruses, respectively, by some manufacturers. The 2004–05 vaccine viruses were used because of their growth properties and representation of influenza viruses predicted to strike the United States. They were recommended and approved by the Advisory Committee on Immunization Practices (ACIP) (MMWR 28 May 2004; 53[RR06]:1–40). The terminology for influenza viruses is directly related to the type of virus, the origin or place it was first located, and the year of its discovery. The immunity invoked by influenza vaccine generally lasts 6–12 months
Amantadine	Amantadine is active against influenza A viruses but not influenza B. It was approved in 1966 for chemoprophylaxis and in 1976 for treatment and chemoprophylaxis of influenza type A virus in both adults and children $\geq 1$ year of age. Amantadine may cause central nervous system side effects (13%), including anxiety, nervousness, insomnia, light headedness, and concentration difficulty, and gastrointestinal side effects (1–3%), including nausea and anorexia, at dosages of 200 mg per day. Because its effects on pregnant women and their fetuses are unknown, it should be used during pregnancy only if the potential benefit justifies the risks. Drug resistance develops in approximately one-third of patients, with cross resistance to rimantadine. Maximum blood levels are attained within 4 h of administration of a single 100 mg dose. The peak excretion rate of amantadine is 5 mg h <sup>-1</sup> , and the mean half-life of the excretion rate is approximately 15 h. Clearance of amantadine is reduced 2–3-fold in adults with renal insufficiency. In otherwise healthy elderly adults ( $\geq 65$ years) the renal clearance is reduced and plasma levels therefore increased. The drug, like rimantadine, influences viral uptake by preventing membrane fusion and affects maturation of the hemagglutinin (H) to lower the infectivity of progeny virus. It is 70–90% effective in preventing illness in healthy adults and, if administered for prophylaxis within 2 days of illness, can reduce flu symptoms and shorten the duration of the illness by 1 or 2 days
Rimantadine	Rimantadine is effective against influenza A but not influenza B viruses. It was approved in 1993 for the treatment and chemoprophylaxis of influenza A infections in adults and prophylaxis in children. Some consider it appropriate for the treatment of disease in children. Rimantadine may cause central nervous system side effects (6%), including anxiety, nervousness, insomnia, light headedness and concentration difficulty, and gastrointestinal side effects (1–3%) such as nausea and anorexia, at dosages of 200 mg per day. Because its effects on pregnant women and their fetuses are unknown, it should be used during pregnancy only if the potential benefit justifies the risks. Drug resistance develops in approximately one-third of patients, with cross resistance to amantadine. Rimantadine is 70–90% effective in preventing illness in healthy adults and, if administered for prophylaxis within 2 days of illness, can reduce flu symptoms and shorten the duration of the illness by 1–2 days
Zanamivir	Zanamivir is a neuraminidase inhibitor that is active against both influenza A and B viruses. It was approved in 1999 for the treatment of uncomplicated influenza infections in patients aged $\geq 7$ years. Guidelines and recommendations for its use can be found at: <a href="http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm">http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm</a> . As its effects on pregnant women and their fetuses are unknown, it should be used during pregnancy only if the potential benefit justifies the risks. Resistance to zanamivir during treatment may occur, but does not happen frequently
Oseltamivir	Oseltamivir is a neuraminidase inhibitor that is active against both influenza A and B viruses. It was approved in 1999 for the treatment of uncomplicated influenza infections in patients aged $\geq 1$ year. In 2000 it was approved for the chemoprophylaxis of influenza infections in persons aged $\geq 13$ years. Guidelines and recommendations for its use can be found at: <a href="http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm">http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm</a> . As its effects on pregnant women and their fetuses are unknown, it should be used during pregnancy only if the potential benefit justifies the risks. Resistance to oseltamivir during treatment may occur, but does not happen frequently

## Experimental Therapies

Nasal spray.

<i>Agent name</i>	<i>Discussion</i>
Vaccine	Bacteria from fermented milk were incorporated into a nasal spray and used as a preventive treatment for influenza in mice (Hori et al., 2001). Killed <i>Lactobacillus casei</i> were used in an intranasal spray to stimulate the immune response in the respiratory tract. Treated mice had one-tenth the amount of virus in their nasal cavities after virus challenge, resulting in a four times greater survival rate

## Animal Models

The mouse model for influenza is used for the evaluation of vaccines and antiviral drugs (Sidwell and Smee, 2000). In addition, the ferret is a natural host for this virus, with the ensuing illness closely resembling the human condition (Maher and DeStefano, 2004).

## Journal Citations

- Stohr K (2003) Overview of the WHO Global Influenza Programme. *Developmental Biology* 115: 3–8.
- De Jong JC, Palache AM, Beyer WE, Rimmelzwaan GF, Boon AC, and Osterhaus AD (2003) Haemagglutination-inhibiting antibody to influenza virus. *Developmental Biology* 115: 63–73.
- Schmidt AC (2004) Antiviral therapy for influenza: A clinical and economic comparative review. *Drugs* 64(18): 2031–2046.
- Weycker D, Edelsberg J, Elizabeth-Halloran M, Longini IM Jr, Nizam A, Ciuryla V, and Oster G (2005) Population-wide benefits of routine vaccination of children against influenza. *Vaccine* 23(10): 1284–1293.
- Cosgrove SE, Fishman NO, Talbot TR, Woeltje KF, Schaffner W, Fraser VJ, McMillan JA, and Perl TM (2005) Strategies for use of a limited influenza vaccine supply. *JAMA* 293(2): 229–232.
- Hori T, Kyoshima J, Shida K, and Yasui H (2001) Effect of intranasal administration of *Lactobacillus casei* Shirota on influenza virus infection of upper respiratory tract in mice. *Clinical and Diagnostic Laboratory Immunology* 8: 593–597.
- Schweiger B, Zadow I, and Heckler R (2002) Antigenic drift and variability of influenza viruses. *Medical Microbiology and Immunology* 191: 133–138.
- Sidwell RW and Smee DF (2000) In vitro and in vivo assay systems for study of influenza virus inhibitors. *Antiviral Research* 48(1): 1–16.
- Maher JA and DeStefano J (2004) The ferret: An animal model to study influenza virus. *Lab Animal* 33(9): 50–53.
- Zhang L, Zhang Z, and Weng Z (2013) Rapid reassortment of internal genes in avian influenza A (H7N9) virus. *Clinical Infectious Diseases* 57: 1059.
- Gao R, Cao B, Hu Y, et al. (2013) Human infection with a novel avian-origin influenza A (H7N9) virus. *New England Journal of Medicine* 368: 1888.
- Uyeki TM and Cox NJ (2013) Global concerns regarding novel influenza A (H7N9) virus infections. *New England Journal of Medicine* 368: 1862.
- Webster RG, Malik Peiris JS, Webby RJ, and Guan Y (2013) H7N9 Influenza: What we learned from H5N1. *Microbe* 8(12): 499–505.
- Zhu H, Wang D, Kelvin DJ, et al. (2013) Infectivity, transmission, and pathology of human-isolated H7N9 influenza virus in ferrets and pigs. *Science* 341: 183–186.
- Book Citations

- Dolin R (2005) Influenza. Chapter 171, In: Kasper DL, Braunwald AS, Fauci AS, Hauser SL, Longo DL, Jameson JL, and Isselbacher KJ (eds.) *Harrison's principles of internal medicine*, 16th edn. Boston, MA: McGraw-Hill.
- Murray PR, Rosenthal KS, Kobayashi GS, and Pfaller MA (2002) Orthomyxoviruses. Chapter 56, In: *Medical microbiology*, pp. 535–542. St. Louis, MO: Mosby.
- Treanor JJ (2005) Influenza virus. Chapter 162, In: Mandell GL, Bennett JE, and Dolin R (eds.) *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, pp. 2060–2085. Philadelphia, PA: Churchill Livingstone.
- Hayden FG (2001) Antimicrobial agents: Antiviral agents (nonretroviral). In: Hardman JG, Limbird LE, and Gilman AG (eds.) *Goodman and Gilman's the pharmacological basis of therapeutics*, 10th edn., pp. 1313–1348. Boston, MA: McGraw-Hill.
- Murray PR, Rosenthal KS, and Pfaller MA (2013) Orthomyxoviruses. Chapter 57, In: *Medical microbiology*, 7th edn., pp. 524–532. St. Louis, MO: Elsevier.

## Relevant Websites

- Basic information on the diagnosis, clinical findings, complications, prevention and treatment of influenza, including vaccine safety recommendations, can be found at: <http://www3.accessmedicine.com/content.aspx?alD=17572#17572>
- Information for the 2013–2014 influenza season can be found at: <http://www.cdc.gov/flu/about/season/index.htm>.
- Information on the common cold and flu can be located at: <http://familydoctor.org/517.xml>.
- A chapter on antiviral chemotherapy can be found at: <http://www.med.sc.edu:85/lecture/chemo.htm>.
- Further information on the common cold and flu can be located at: <http://www.niaid.nih.gov/factsheets/cold.htm>.
- Detailed information on influenza viruses can be located at: <http://www3.accessmedicine.com/content.aspx?alD=74879&searchStr=influenza+a+virus#74879>.