Influenza

Angelena M. Labella, MD[a,*], Susan E. Merel, MD[b]

KEYWORDS

• Influenza • Pandemic influenza • Viral illnesses • Immunization • Treatment
• Transmission • Chemoprophylaxis

KEY POINTS

- Clinicians should suspect influenza when a patient presents with respiratory symptoms, fever, and systemic symptoms and when influenza virus is circulating in the community.
- Rapid influenza diagnostic tests (RIDTs) can be helpful in confirming the diagnosis, but these are most helpful within 24 hours of symptom onset and have a higher positive predictive value when the prevalence of influenza in the community is high. Reverse transcriptase polymerase chain reaction (RT-PCR) has high sensitivity and specificity but may not be practical in all clinic settings.
- Treatment of influenza is most efficacious within 48 hours of the onset of symptoms. Patients with conditions that predispose them to high-risk complications of influenza and hospitalized patients should be treated regardless of the timing of onset of symptoms. In most cases, oral oseltamivir is the treatment of choice.
- Influenza vaccination is currently recommended for everyone older than 6 months in the United States. Trivalent vaccines are available in several formulations, including a live attenuated nasal spray and an inactivated vaccine in intramuscular and intradermal formulations. The effectiveness of the vaccine in preventing influenza is between 50% and 80% depending on the population; it can be worse in a year in which there is a poor match between vaccine and circulating influenza strains.
- During the 2009 influenza A/H1N1 pandemic, pregnant women and patients with morbid obesity were at high risk for complications including death.
- Although still rare, clinicians should be aware of emerging influenza strains including variant (v) H3N2, which generally requires swine exposure.

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[a] Section of Hospital Medicine, Division of General Medicine, Department of Medicine, New York Presbyterian, Columbia University Medical Center, 177 Fort Washington Avenue, New York, NY 10032, USA; [b] Hospital Medicine Program, Division of General Internal Medicine, Department of Medicine, University of Washington Medical Center, 1959 Northeast Pacific Street, Box 356429, Seattle, WA 98195-6429, USA
* Corresponding author.
E-mail address: aml2250@columbia.edu

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BIOLOGY AND GENETICS OF INFLUENZA

What Are the Different Types of Influenza?

The influenza virus is made up of 8 distinct RNA segments (**Table 1**).[1] These segments each code for a different protein that is essential to the structure and function of the virus. There are 3 genera of influenza viruses: A, B, and C.[2] Influenza A alone has caused pandemic illness, while influenza B and C have caused illness of epidemic proportion only.[3] Influenza A is further subtyped by the glycoproteins on its cell surface: hemagglutinin and neuraminidase. Hemagglutinin, for which there are 16 different molecules, allows the virion (a particle of virus) to anchor to a cell surface, while neuraminidase, for which there are 9 molecules, allows for digestion of host secretions and, later, release of viral particles from the host cell.[4] The influenza virus is named after the types of hemagglutinin and neuraminidase molecules.

How Does the Influenza Virus Change or Mutate Over Time?

Because the influenza virion is made up of 8 independent RNA strands it is subject to genetic changes. The 2 types of genetic changes that have been best described are antigenic drift and antigenic shift or reassortment. Reassortment is when 2 viruses infect the same host cell and then exchange genes during replication (**Fig. 1**). This process results in a new virion that has gene segments from each of its parent virus. This change occurs from viruses specific to one species and can also result in a new virus of interspecies origin. The H1N1 virus that caused the 1918 pandemic was derived from genes (or RNA segments) from human influenza, swine influenza, and avian influenza.[5] The influenza virus can also undergo smaller changes. RNA segments or genes mutate such that the hemagglutinin and neuraminidase molecule do not change their type but only some of their structure. In other words, they are still called by the same number (eg, H1, H2) but may not be recognized by the host's immune system as the same virus. This process is called antigenic drift.

Why Are These Changes Important and How Do They Affect Immunity?

Any antigenic change in the influenza virus, be small changes in the composition of the hemagglutinin molecule or a larger change such as interspecies reassortment, will decrease the likelihood of the host having effective immunity. In addition, the diversity in RNA composition of influenza viruses from year to year makes vaccine development

Table 1
Eight RNA segments of the influenza genome and corresponding protein and function

RNA Segment	Protein	Function
PB2	Transcriptase	Cap binding
PB1	Transcriptase	Cap elongation
PA	Transcriptase	Protease activity
HA	Hemagglutinin	Anchoring to cell
NP	Nuclear protein	RNA binding and transport
NA	Neuraminidase	Release of virus
M1/M2	Matrix proteins	M1, major component of virion; M2, ion channel
NS1/NS2	Nonstructural protein	NS1, RNA transports, translation; NS2, unknown function

Data from Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. N Engl J Med 2009;361(3):225–9.

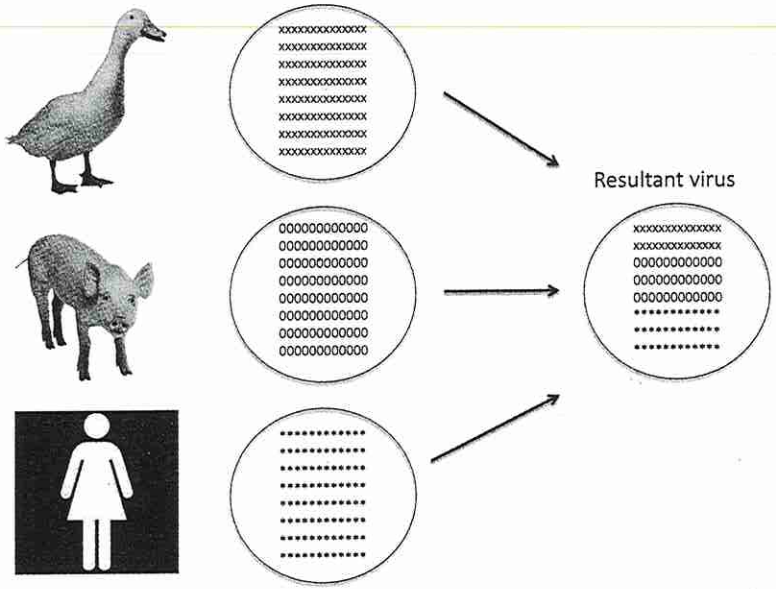

Fig. 1. Illustration of reassortment between 8 RNA segments from duck, pig, and human.

difficult because it becomes more difficult to predict which influenza virus will circulate.

HISTORY OF INFLUENZA

What Types of Influenza Have Affected the World in the Past Century?

The 1918 Influenza A/H1N1 pandemic killed approximately 40 million people worldwide.[6] During the 1918 influenza A/H1N1 pandemic, swine were also dying of a clinical syndrome that seemed akin to human influenza.[7] It was later shown that human anti-influenza antibodies neutralized swine respiratory antigens.[8] This and other experiments suggested that swine influenza had circulated in the human population and originated during the 1918 pandemic.[9] In 1947, the seasonal vaccine failed and it was found that the circulating H1N1 virus had several mutations on the hemagglutinin gene.[10] This incident provides a good example of how antigenic drift can cause public health problems that are similar to those of antigenic shift or reassortment.

In 1957, the H1N1 virus was not recovered from human sputa specimens, but instead, an H2N2 virus was recovered. This new influenza strain had 3 new RNA segments from an avian source along with segments from the 1918 H1N1 virus strain.[11] H1N1 reemerged in 1977 along with the more dominant subtype H3N2. At the same time, it was confirmed that influenza A/H1N1 was circulating in the swine population.[12] In the late 1980s, a new triple reassortment influenza A/H1N1 was circulating in the swine population. This strain had RNA segments from the original 1918 H1N1 strain and segments from the bird influenza.[13] Genetic analysis of strains from the 2009 influenza A/H1N1 pandemic strain showed that they were derived from a new reassortment of 6 gene segments from the known triple reassortment swine virus, and 2 gene segments (neuraminidase and matrix protein) from the 1918 influenza A (H1N1) swine virus lineage.[14]

What Other Variants or Strains of Influenza Are Circulating Now?

Outbreaks of swine-origin influenza in humans are rare; however, the incidence has increased over the past several years. When this occurs the virus is referred to as a variant (v). A hybrid virus of the pandemic 2009 H1N1 virus and the H3N2 virus has recently emerged and is referred to as (v)H3N2.[15] Almost all cases have been in young children who have been exposed to swine in either agriculture or fairs. This strain does not seem to transmit easily from human to human, although there have been documented cases with very close contact.[16,17] If clinicians suspect a case of vH3N2, they should contact their local public health department because a standard RIDT may not rule out the disease. The current vaccine does not protect against vH3N2. vH3N2 strains thus far have been sensitive to the neuraminidase inhibitors but resistant to amantadine and rimantadine.[17]

Since 2003, influenza A/H5N1 has killed over 100 million birds in Asia, Africa, and the Middle East.[18] In 2012, the World Health Organization (WHO) confirmed 610 human infected cases of this virus. Most of these cases had close contact with diseased birds, and 360 of the patients died of their disease.[19] The strain's virulence in humans seems to be partially related to its ability to alter the host's protein synthesis machinery allowing for unrestrained viral replication.[20] The H5N1 virus is, in most cases, neuraminidase inhibitor susceptible, although there have been documented cases of isolates with the N1 neuraminidase mutation.[21] One retrospective study of data mined from clinical records from 12 countries showed a crude survival of 43.5%. Survival was improved greatly with treatment even when started 6 to 8 days after the onset of symptoms.[22]

INFLUENZA A/H1N1 2009 PANDEMIC

What Should Be Known About the 2009 Influenza A/H1N1 Pandemic?

In late March 2009, a novel H1N1 strain was identified in Mexico and found to be of swine origin.[23] In June 2009, the WHO declared the start of this pandemic.[24] This novel strain, often referred to as H1N1pdm09, derives 6 genes from triple reassortment North American swine virus lineages and 2 genes from Eurasian swine virus lineages.[25] Most of the initial patients were between the ages of 13 and 47 years, and only a minority had coexisting conditions.[23] Adults older than 60 years had been disproportionately spared from this disease suggesting that they had cross-over immunity from antigenically similar influenza virus in the past.[26]

What Special Populations Were Disproportionately Affected During the 2009 Influenza A/H1N1 Pandemic?

Although most patients with confirmed H1N1pdm09 disease had an uncomplicated course, severe cases of acute respiratory distress and death were reported and the morbidly obese and pregnant patients seemed to be disproportionately affected.[27] Several observational studies have shown that pregnancy and specifically third trimester pregnancy was a risk factor for more severe H1N1 disease, intensive care unit (ICU) hospitalizations, and morbidity.[28,29] One study showed that pregnant women were 7 times more likely to be hospitalized and 2 times more likely to die than their nonpregnant counterparts.[30] Pregnant women with human immunodeficiency virus (HIV) infection were at an even higher risk of death. Another study showed that while pregnant women constitute only 1% to 2% of the population, this group made up 6% to 9% of patients in ICU.[13]

Morbid obesity was found to be an additional risk factor for severe influenza illness. Morbidly obese patients were found to have a higher likelihood of ICU admissions and death than patients without morbid obesity. The same association was not found with seasonal influenza.[31,32]

INFLUENZA B

How is Influenza B Different from Influenza A?

Influenza B virus is discussed much less than influenza A virus partly because it is the cause of only a minority of seasonal influenza cases each year.[33] The Center for Disease Control and Prevention's (CDC) Morbidity and Mortality Weekly Report (MMWR) showed that influenza B accounted for only 18% of cases from January 2011 to February 2012.[34] In general, the influenza B virus does not undergo the same antigenic changes that result in the pandemics that novel influenza A viruses have caused. In fact, all circulating influenza B viruses are genetically related to 2 distinct lineages.[35] In addition, seals are the only interspecies hosts resulting in less variation and interspecies transmission.[36]

Although it is generally accepted that influenza B causes a disease that is only of intermediate severity, there are certainly cases of fatal influenza B disease each year, especially in the pediatric population.[37] Like influenza A, influenza B is, in most cases, sensitive to the neuraminidase inhibitors. There have been cases of the HY123 mutation in influenza B isolates.[38] Influenza B is resistant to all adamantanes.[39]

MAKING THE DIAGNOSIS OF INFLUENZA

When Should Influenza Be Suspected?

In general, a clinician should suspect influenza when a patient presents with acute onset of fever, cough, and systemic symptoms such as weakness or myalgias between fall and spring. The probability of influenza in an individual patient varies with the prevalence of influenza in the community and with the vaccination status of the patient. It may be more difficult to use vaccination status as a predictor in a year when there is a mismatch between circulating and vaccine strains of influenza.[40] Attempts to develop clinical prediction rules based on symptoms and other aspects of the patient's clinical presentation have been hampered by virus evolution, the wide range of influenza prevalence in different settings, and the possibility of different clinical presentations in different populations such as children and the elderly.[41]

Nationally, influenza-like illness usually hits a peak in January, February, or March. Between 1982 and 2012, influenza activity (as defined by the percentage of respiratory specimens testing positive for influenza virus) has most often peaked in February, followed by January and March.[42] However, this pattern can vary from year to year. Influenza activity peaked twice during the 2009 H1N1 pandemic, once in the spring when the virus first emerged and again in the second week of October.[43] Detailed information about the number of influenza cases in a particular state or community is available from the CDC or from the local health department.

Fever and cough during a local epidemic may be the symptoms that are most predictive of influenza infection, with one study showing a positive predictive value of 79% ($P<.001$) for the diagnosis of seasonal influenza.[44] A systematic review in 2004 concluded that individual symptoms or signs are of limited value in diagnosing influenza. However, rigors, the combination of fever and presentation within 3 days of symptom onset, and sweating were most helpful in making the diagnosis of influenza, with a likelihood ratio of 7.2 for rigors. In the same study, lack of systemic symptoms, lack of cough, and the ability to perform activities of daily living decreased the likelihood of influenza.[45] Two subsequent systematic reviews concluded that independent predictors of influenza varied by patient age and that clinical findings identify patients

with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza.[46,47] **Box 1** provides guidelines from the Infectious Disease Society of America (IDSA) regarding when to suspect influenza.

It may be particularly difficult to make the clinical diagnosis of influenza with certainty in an elderly patient. A study of outpatients older than 60 years in the Netherlands showed a positive predictive value of only 30% for the acute onset of both fever and cough.[48] In a US population of elderly hospitalized patients, the combination of fever, cough, and illness duration of 7 days or less had a positive predictive value of only 53%.[49]

The H1N1 influenza pandemic of 2009 posed particular challenges for clinicians to diagnose disease based on the patients' clinical presentation. More adults infected with H1N1 pandemic influenza in 2009 presented with gastrointestinal symptoms including nausea, vomiting, and diarrhea than had previously been common with seasonal influenza; about 25% of adult patients hospitalized with influenza presented with diarrhea, abdominal pain, or vomiting.[50] Fever may also have been a less prominent part of the initial clinical presentation in hospitalized patients with H1N1pdm09 influenza; 42% of hospitalized patients in one study with laboratory-confirmed H1N1 influenza did not have fever before presentation.[50]

When Should the Test for Influenza Be Performed and What Test Should Be Used?

Diagnostic testing can be helpful in confirming a clinical diagnosis of influenza and should be used when the results will influence clinical decision making or infection control measures (**Box 2**). However, CDC guidelines emphasize that confirmation of diagnostic testing is not required when prescribing antiviral medications and that the decision to administer antivirals should be based on clinical presentation and epidemiologic factors.[51] The IDSA recommends using RT-PCR as the preferred confirmatory test because it is the most sensitive and specific of the options. Furthermore, results are often available within hours. Results of immunofluorescence tests may be available more quickly than results of RT-PCR, but immunofluorescence is less sensitive. Commercially available RIDTs provide results in less than 30 minutes but have decreased sensitivity (generally thought to be 40%–60% in adults, with a range of 10%–80%) compared with RT-PCR or viral culture.[51–54] Although RT-PCR may be the preferred test, it is not available everywhere in a timely manner, and the time it takes to get the results makes it less helpful in an ambulatory setting. Options for diagnostic testing are described further in **Table 2**. Common clinical scenarios and the suggested approach for testing and treatment are described in **Table 3**.

Box 1
When to consider the diagnosis of influenza in adults

When influenza viruses are circulating in the community, consider the diagnosis of influenza in the following patient populations:

- Immunocompetent or immunocompromized adults with fever and the acute onset of respiratory symptoms
- Persons with fever and an acute-onset exacerbation of underlying chronic lung disease
- Elderly adults with new or worsening respiratory symptoms (including exacerbation of congestive heart failure) or altered mental status, with or without fever
- Severely ill adults with fever or hypothermia without an alternate explanation
- Adults hospitalized without fever or respiratory symptoms who develop febrile respiratory illness after admission

During any time of year, consider the diagnosis of influenza in patients with acute febrile respiratory symptoms who are epidemiologically linked to an influenza outbreak.

Data from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32.

Box 2
When to perform a diagnostic test for influenza in adults

During influenza season, consider testing the following populations:

If the patient presents within 5 days of acute febrile respiratory symptoms:

- Outpatient immunocompetent persons of any age who are at high risk of developing complications of influenza

Regardless of when symptoms began:

- Outpatient immunocompromized persons presenting with febrile respiratory symptoms
- Hospitalized persons of any age with fever and respiratory symptoms, including those with a diagnosis of community-acquired pneumonia
- Elderly persons with suspected sepsis or fever of unknown origin
- Persons who develop febrile respiratory symptoms after hospital admission

At any time of the year, consider testing the following populations:

- Health care personnel, residents, or visitors in an institution experiencing an outbreak of influenza, presenting within 5 days of developing febrile respiratory symptoms
  - In investigating a suspected influenza outbreak in an institutional setting, consider testing when there are 2 or more persons with symptoms compatible with influenza, with the onset of symptoms within 2–3 days of each other, *if* the results of testing will change outbreak control strategies in the population *or* the setting includes persons at high risk of influenza complications.
- Persons otherwise linked to an influenza outbreak (eg, travelers who have returned from countries where influenza viruses may be circulating) presenting within 5 days of developing febrile respiratory symptoms

Data from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32; and Centers for Disease Control. Influenza testing algorithm. Available at: http://www.cdc.gov/flu/professionals/diagnosis/testing_algorithm.htm.

When Should Rapid Influenza Diagnostic Tests (RIDTs) Be Used Given the Test's Low Sensitivity?

Two cost-effectiveness analyses suggest that in patients presenting less than 48 hours after the onset of cough and fever in influenza season, empirical treatment is more cost-effective than approaches involving testing.[44,45] Authors of a systematic review of influenza diagnosis suggest that RIDTs do not add to the cost-effectiveness of treatment when the probability that the patient has influenza is greater than 25% to 30%.[47] In summary, when clinical suspicion for influenza is high and especially if the patient is quite ill, hospitalized, or at high risk for complications of influenza (eg, an immunocompromized or frail elderly patient) RIDTs should be avoided because

Table 2
Diagnostic tests for influenza

Method	Approximate Test Time	Sensitivity	Specificity
1. RT-PCR	Hours	High	Very high
2. Immunofluorescence (direct or indirect antibody staining)	Hours	Moderately high	High
3. Rapid influenza diagnostic tests	<30 min	Low to moderately high	High
4. Viral isolation (standard culture or shell vial culture)	Days	Moderately high	Highest

Listed in the order recommended by the IDSA.

Data from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32; and Centers for Disease Control. Influenza testing algorithm. http://www.cdc.gov/flu/professionals/diagnosis/testing_algorithm.htm. Accessed May 7, 2013.

of their lower sensitivity. In this situation, one should consider treating empirically and using RT-PCR if it is available and if it would change management (eg, if having strong evidence that the patient's symptoms are caused by influenza would help the patient avoid further testing or treatment of alternative causes, such as antibiotics). Laboratory confirmation of influenza with RT-PCR also may be helpful in making decisions about infection control or prophylaxis for contacts (eg, if the patient is a health care worker or a resident of a long-term care facility).

Whether there is high or low influenza activity in the community at the time of the patient's presentation is helpful in interpreting the results of RIDTs. False-positive and true-negative results are more likely to occur when influenza prevalence in the community is low, such as at the beginning and end of the influenza season. At these times, the negative predictive value of the rapid influenza test is relatively high and may be helpful in excluding influenza. Conversely, when the prevalence of influenza in the community is high, the positive predictive value of the RIDT is also high (although, as discussed above, using an RIDT may not be cost-effective in this setting[51]).

Of note, one study in a laboratory setting comparing 11 commercially available RIDTs, using 23 influenza viruses provided by the CDC, found that while most rapid diagnostic tests detected the viruses at the highest concentrations, many tests did not detect many of the viruses at lower concentrations.[55] These results support current recommendations to collect specimens as early as possible after symptom onset, ideally within 24 to 72 hours after illness onset, when viral concentrations may be higher.

TREATMENT OF INFLUENZA

What Antivirals Are Available and What Are the Advantages and Disadvantages of Each?

Neuraminidase inhibitors block the release of virions from an infected cell so that subsequent cells cannot be infected.[56] The 2 neuraminidase inhibitors that are approved by the Federal Drug Administration (FDA) are oral oseltamivir and inhaled zanamivir. Peramivir is only available for investigational use as are the intravenous formulations of oseltamivir and zanamivir. Oseltamivir is a prodrug that is converted to its active

Table 3
Common outpatient scenarios and suggested approach for diagnosis and treatment

Clinical Scenario	Suggested Approach and Rationale
40-year-old unvaccinated school teacher presenting in January 24 h after acute onset of fever and cough; quite debilitated and unable to perform ADLs	Empiric treatment; consider RT-PCR if available and if it would be helpful in recommending prophylaxis for close contacts
30-year-old man with well-controlled diabetes presenting in November with 4 d of subjective fever and cough	Reassurance and symptomatic treatment of presumed viral upper respiratory tract infection
85-year-old woman residing in a nursing home presenting in January with 48 h of cough and altered mental status without fever	Empiric treatment; consider hospitalization; consider RT-PCR and prophylactic antivirals for close contacts
50-year-old unvaccinated nurse presenting in early October with 5 d of upper respiratory tract symptoms and fever	Consider viral isolation to establish diagnosis if she has had possible exposure to influenza; antivirals unlikely to be helpful
42-year-old oncologist with no medical problems who works in a hospital and takes care of patients who have undergone bone marrow transplant who would like live attenuated intranasal influenza vaccine	Patient is a candidate for LAIV but should not treat patients for 2 wk after vaccine is given
22-year-old asymptomatic woman who lives with her boyfriend who was diagnosed this morning with influenza	Offer patient both influenza vaccine and chemoprophylaxis with oseltamivir
50-year-old man with kidney transplant 7 y previously, presenting with acute onset of nonproductive cough and malaise, which started yesterday. Poor PO intake. Chest radiograph shows normal result	RT-PCR and empirical treatment while waiting for results; consider hospitalization for hydration and close monitoring of renal function
25-year-old woman 1 wk postpartum with 48 h of fever and chills in February	Empiric treatment, RT-PCR and speak with infant's pediatrician

Abbreviations: ADLs, activities of daily living; LAIV, live attenuated intranasal influenza vaccine; PO, Oral.

form in the liver. This drug is generally well tolerated, with some patients experiencing mild nausea,[57] and it has a wide volume of distribution with a half-life of about 6 to 10 hours.[58] In critically ill patients, the solution formulation can be used and given via a nasogastric tube. Zanamivir has poor oral bioavailability and therefore is available as a powder for inhalation use. This drug is generally well tolerated, although bronchospasm can occur.[57] Zanamivir has been shown to reduce length of illness by 1 day when started within 48 hours of symptom onset.[59] Intravenous peramivir has been approved in South Korea and Japan. This formulation differs from other neuraminidase inhibitors in that it binds to multiple sites of the neuraminidase molecule instead of just one (**Tables 3** and **4**).[57]

Inhaled zanamivir was found to cause fatal ventilator failure in a 25-year-old pregnant woman who was found to have severe influenza A requiring ventilator assistance. The patient was given oral oseltamivir and nebulized zanamivir. Over the next several days, the patient was witnessed to have low expiratory tidal volumes, which resolved with a change in the ventilator system. Eventually the patient died of hypoxic respiratory failure thought to be secondary to expiratory filter obstruction by inhaled

Table 4
Treatment options for influenza

Characteristics	Oseltamivir	Zanamivir	Adamantanes
Susceptible influenza types	Most influenza A and B isolates[a]	Influenza A and B isolates	Some influenza A isolates
Available routes of administration	Oral	Inhaled	Oral
Common side effects	Mild nausea	Bronchospasms, headaches	Orthostatic hypotension
Recommended dose	75 mg twice daily × 5 d[b,c]	2 inhalations (10 mg) twice daily × 5 d	not recommended
Contraindications	Hypersensitivity to oseltamivir	Not recommended for patients with COPD and asthma and patients with an allergy to milk[d]	Hypersensitivity to adamantanes
Pregnancy class	C	C	C

[a] Some isolates of influenza and B are not sensitive to oseltamivir.
[b] Some experts agree that in critically ill patients, a dose of 150 mg twice daily should be used for an extended period of time.
[c] Should be renally dosed.
[d] Zanamivir has a lactose carrier.
From CDC - Seasonal influenza (flu) - antiviral medications: summary for clinicians. Available at: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed March 8, 2013.

zanamivir. It is presumed that the obstruction was caused by lactose powder that is part of the Relenza diskhaler product, which should not be reconstituted in liquid.[60]

Another group of anti-influenza drugs is the adamantanes, of which amantadine and rimantadine have been approved by the FDA. These drugs block viral uncoating within the host cell, which is necessary for replication. Influenza B is intrinsically resistant to adamantane therapy.[61] Unfortunately, the adamantanes are also associated with high-level resistance to some influenza A isolates, and studies have shown that adamantane-resistant influenza A is just as pathogenic as its wild-type counterpart.[62] Because of this, there is little role for these drugs in the treatment of influenza and the CDC recommends against their use.[63] **Table 4** provides a summary of treatment options.

Is There a Role for Ribavirin?

Several studies have focused on the role of ribavirin, both the intravenous and the inhaled formulation, and neither showed definitive benefit in clinical trials.[64] Although ribavirin does have *in vitro* activity against influenza, the risks of hemolytic anemia and teratogenicity need to be weighed against the potential benefits.[65]

Should All Patients with Confirmed or Suspected Influenza Be Treated?

Antiviral medications are the most effective when initiated within 48 hours of the onset of symptoms of illness.[59,66] Treatment of influenza not only decreases the duration of illness but also reduces nasal shedding of the virus.[67] Given this fact, all persons who present to care within 48 hours of onset of symptoms of influenza should be offered treatment regardless of comorbidities. The United States Advisory Committee on Immunization Practices (ACIP) and the CDC recommend that all patients who are at higher risk for complications should also receive treatment regardless of the timing of the onset of symptoms (**Box 3**). Patients without conditions that place them at a higher risk for complications should not be offered treatment if they present 48 hours after the onset of symptoms because the risk of potential resistance is higher than the benefit of therapy.[63]

Box 3
Adults at high risk for complications from influenza

- Adults older than 65 years
- Residents of long-term care institutions, of any age
- Adults who are immunosuppressed (either from immunodeficiencies such as HIV or on immunosuppressive therapy)
- Pregnant or postpartum women (within 2 weeks after delivery)
- People who are morbidly obese (body mass index >40)
- People receiving long-term aspirin therapy
- American Indians/Alaska Natives
- Adults of any age with the following conditions:
  - Chronic pulmonary disease (including asthma, chronic obstructive pulmonary disease, and cystic fibrosis)
  - Hemodynamically significant cardiac disease
  - Hemoglobinopathies including sickle cell disease
  - Chronic metabolic disease including diabetes
  - Any condition that may compromise the handling of respiratory secretions (eg, neuromuscular disease, dementia)
  - Cancer
  - Chronic renal disease

Data from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32; and Centers for Disease Control. Influenza antiviral medications: summary for clinicians. 2013;888. Available at: http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinicians.pdf. Accessed November 14, 2012.

Patients requiring hospitalization secondary to influenza should be treated regardless of the timing of the onset of illness. A recent meta-analysis showed that treatment with neuraminidase inhibitors nonsignificantly reduced mortality in hospitalized patients when compared with patients who did not receive therapy (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.51–1.01).[68] However, there was a significant reduction in mortality when early treatment (less than 48 hours from onset of symptoms) was compared with late treatment (greater than 48 hours from onset of symptoms) (OR, 0.38; 95% CI, 0.27–0.53). In a Canadian study of hospitalized patients with seasonal influenza, 71% received oseltamivir 48 hours after symptoms and there was a statistically significant reduction in death (OR, 0.21; $P = .03$) compared with patients who were untreated.[69] A retrospective study in Thailand showed that any treatment with oseltamivir (regardless of the time of initiation) was associated with increased survival when compared with untreated patients (OR, 0.11; 95% CI, 0.04–0.30).[68]

Some experts think that patients who are critically ill with influenza should be given oseltamivir, 150 mg twice daily, rather than the standard 75 mg twice a day dosage.[52] Higher doses with extended treatment lengths have been shown to decrease the

severity of illness in animal models with H5N1.[70] Although there are no randomized controlled trials showing superiority of the higher dose, pharmacokinetic studies have shown that pregnant women seem to metabolize and clear the active form of oseltamivir faster than their nonpregnant counterparts.[58] In contrast, similar studies do not show a need to increase the dose of oseltamivir for morbidly obese patients.[71] The ACIP and CDC recommend a treatment length of 5 days for all patients. Experts agree that this should be extended in the critically ill requiring hospitalization.[52]

During the 2009 influenza A pandemic, the CDC recommended that all pregnant women be treated with oseltamivir if they had suspected or confirmed influenza infection.[72] One study showed that women who were treated within 48 hours of the onset of symptoms were 4 times less likely to require ICU admission or to die. Although oseltamivir is a pregnancy category C drug, most experts think that the benefits to the mother's health outweigh the potential risks to the fetus. Providers should be aware that the postpartum period poses a risk of more severe disease.[72,73] It seems that immediately postpartum immunologic function is not normal and takes weeks to months to return to baseline.

Should the Elderly Population Be Treated Differently for Influenza?

All patients older than 65 years are considered to be at high risk for complications of influenza and should be treated with antivirals.[74] Pharmacokinetic studies of oseltamivir have shown a slightly increased exposure-to-dose ratio in elderly patients because of age-related decline in renal function, but dose adjustment is not thought to be necessarily based on age alone.[75] Safety and adverse effect profile of oseltamivir in the elderly is thought to be similar to that in younger adults. In one placebo-controlled study of frail elderly residents of nursing facilities with a mean age of about 80 years treated with oseltamivir for prophylaxis, rates of gastrointestinal symptoms such as nausea and vomiting were similar in the 2 groups, with headache being the only symptom that was more common in the treatment group than in the placebo group.[76] **Table 5** provides a list of patient examples of who to treat.

What Should Be Done if the Patient Does Not Respond to Oseltamivir?

During the 2009 H1N1 pandemic, approximately 1% to 1.5% of the strains were neuraminidase resistant, overwhelmingly because of an H275Y amino acid substitution of the neuraminidase gene.[77] Ultradeep sequencing of isolates from nasopharyngeal swabs of persons who were untreated from a household outbreak showed minor populations of viruses with the H275Y mutation. Transmission of this mutated virus was found, suggesting some fitness advantage of this strain over the wild type.[77] Resistance to neuraminidase inhibitors arises when the neuraminidase gene mutates such that the inhibitor can no longer recognize the receptor site. Mutations result in various degrees of resistance to the different available neuraminidase inhibitors. Thus far, most mutations of the influenza A/H1 strains that result in high-level resistance to oseltamivir still confer adequate susceptibility to zanamivir.[78] Neuraminidase inhibitor resistance should be considered when one is failing oseltamivir therapy and gastrointestinal absorption of that drug can be relied upon. Neuraminidase inhibitor resistance can be tested by plaque assay, neuraminidase inhibition assays, and neuraminidase gene sequencing.

When Should a Patient Be Treated for Concomitant Bacterial Pneumonia?

Bacterial pneumonia is a well-known complication of both seasonal and pandemic influenza. During the 2009 H1N1 pandemic, it was estimated that 29% of fatal cases were complicated by a secondary bacterial pneumonia.[79] Although bacterial pneumonia caused by *Staphylococcus aureus* is widely publicized, the most common causative pathogen is *Streptococcus pneumoniae*. In general, patients who can be treated as an outpatient with suspected secondary bacterial pneumonia should be treated with age-appropriate antibiotic coverage for community-acquired pneumonia. It is not necessary to treat *S aureus* infection in this situation. Patients who are critically ill or who have a strong history of *S aureus* infections or those with necrotizing pneumonia should be broadly covered with intravenous antibiotics including coverage for methicillin-resistant *S aureus* pneumonia.[80]

Table 5
Vaccine formulations and recommended populations

Type	Administration	Indications	Contraindications
"Regular" trivalent inactivated	Intramuscular	Children and adults older than 6 mo, including healthy adults, adults with chronic medical conditions and pregnant women	See below[a]
Intradermal trivalent inactivated	Intradermal	Adults aged 18 through 64 y	See below[a]
"High-dose" trivalent inactivated	Intramuscular	Adults older than 65 y	See below[a]
Live attenuated	Intranasal	Healthy, nonpregnant children and adults aged 2–49 y	Egg allergy of any severity; chronic illness including heart disease, kidney disease, and lung disease including asthma; caregivers for severely immunocompromized persons[a,b]

[a] Contraindications to all of the above vaccines include severe egg allergy, severe past reaction to influenza vaccine, current moderate to severe illness with fever, a history of Guillain-Barré syndrome within 6 weeks of receipt of the influenza vaccine in the past.[110]

[b] According to the CDC, persons in close contact with patients who are so immunocompromized that they require care in a protected environment such as a bone marrow transplant unit should not receive the LAIV. Close contacts of other immunocompromized patients such as health care personnel in neonatal intensive care units, oncology clinics, and HIV clinics may receive LAIV.

Data from Anon. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2012–13 influenza season. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6132a3.htm. Accessed December 30, 2012; and Anon. CDC - Seasonal influenza (flu) - vaccination: summary for clinicians. Available at: http://www.cdc.gov/flu/professionals/vaccination/vax-summary.htm. Accessed December 30, 2012.

TRANSMISSION AND PREVENTION OF INFLUENZA

How is Influenza Transmitted?

Influenza is transmitted between individuals through large-particle respiratory droplets; transmission is primarily related to close contact (probably within 1 m) with an infected person, but infection may also occur through surfaces contaminated with respiratory droplets. Adults are generally considered infectious from the day before symptom onset until 5 to 10 days after the first symptoms appear. There is a more

prolonged period of viral shedding in children and immunocompromized patients, and one study of an elderly cohort of patients hospitalized for pneumonia also showed prolonged influenza viral shedding in this population; severely immunocompromized patients may shed virus for weeks or months.[81,82]

What Types of Vaccines Are Available and What Are the Guidelines for Vaccination Against Influenza?

Since 2010, the ACIP has recommended annual influenza vaccines for everyone older than 6 months in the United States.[83] Previously, the CDC only recommended that higher risk populations and health care workers be vaccinated. This newer recommendation is meant to streamline the vaccination process and improve protection of the community against influenza. Also, vaccination of everyone may prevent complications among higher risk populations; for example, one large Medicare database study showed a correlation between increased rates of influenza vaccination in children and a decreased rate of hospitalizations for pneumonia and influenza in older adults, with no significant association with vaccination rates among the older patients themselves. Because vaccination is more efficacious in children than in the elderly, vaccinating children may actually be an important way to prevent complications among the elderly.[84]

There are 2 types of influenza vaccine: trivalent inactivated vaccine (TIV) (available in standard and high-dose formulations for intramuscular administration and in a standard formulation for intradermal administration) and the live attenuated intranasal influenza vaccine (LAIV), which is available as a nasal spray. Currently, both vaccines are trivalent, meaning that they contain influenza A H1N1, A H3N2, and influenza B viral antigens. A quadrivalent LAIV, which includes a second influenza B virus lineage, is expected to be available for the 2013–2014 influenza season. There are several important contraindications to receiving the LAIV including pregnancy, chronic illness, and egg allergy of any severity. Among healthy nonpregnant individuals aged 2 through 49 years, there is no official recommendation for either the LAIV or the TIV and either is reasonable.[83]

The High dose TIV (known as "Fluzone High Dose") was introduced in the 2009–2010 influenza season and is approved for use in people 65 years and older. Clinical trials have suggested that elderly patients do have higher antibody levels after immunization with the high-dose vaccine as opposed to the standard dose TIV; however, it is not clear whether this confers greater protection against influenza. The safety profile of the 2 vaccines is thought to be similar, although adverse events such as pain and swelling at the injection site and malaise were more frequent in patients receiving the high-dose TIV. A study to compare the effectiveness of low- and high-dose TIV in preventing illness in the elderly is expected to be completed in 2014–2015. The CDC and ACIP are not expressing a preference for the low- or high-dose vaccine in the elderly population at this time.[85] The "Fluzone Intradermal" vaccine was first made available in the 2011–2012 flu season and has been shown to provide an immune response similar to the standard intramuscular TIV. This vaccine requires 40% less antigen than the standard TIV, so more doses of vaccine can be made from the same amount of antigen and may be more acceptable to individuals with a needle phobia.[86]

All currently available influenza vaccines are prepared by inoculating virus into chicken eggs. People who report serious reactions to eggs, such as angioedema or respiratory distress, or who require emergency medical care after egg exposure are more likely to have a serious systemic reaction to the influenza vaccine and should be referred to an allergy specialist before administering influenza vaccine. According to the ACIP guidelines, people who developed hives after egg exposure without more severe symptoms can be vaccinated with TIV and observed for at least 30 minutes for signs of a reaction.[83]

Guidelines or expert recommendations are available regarding vaccination in special populations such as patients who have undergone solid organ transplant and other immunocompromized populations. Experts have reviewed available data on the safety and efficacy of vaccines before and after solid organ transplant, and vaccination with TIV 3 months or later after transplantation is strongly recommended in this population. The level of seroprotection is generally reduced in patients who underwent solid organ as compared with the general population, and this may vary depending on the transplant and immunosuppressive regimen, with patients who underwent lung transplant having lower response rates and recipients of kidney transplant generally having very good seroprotection rates.[87] There are theoretical concerns about T-cell responses to influenza vaccines causing early allograft rejection, and some case reports and small case series support this but elevated rates of rejection or allograft dysfunction in immunized patients have not been seen.[88] The optimal timing of the first yearly immunization after transplant is not known, but guidelines suggest immunizing 3 to 6 months after transplant. Close contacts of patients who have undergone transplant should also be immunized.[87] Experts also recommend immunization with TIV for patients with autoimmune diseases such as rheumatoid arthritis and lupus, and there is no evidence that the degree of disease activity at the time of vaccination affects the efficacy or safety of the vaccine.[89] However, patients taking rituximab for rheumatologic disease or hematologic malignancy have little or no protective response to influenza vaccine because of B-cell depletion.[90,91] A meta-analysis of studies of influenza vaccination in patients who are immunocompromized because of HIV infection, malignancy, respiratory disease with glucocorticoid use, autoimmune disease on immunosuppression, or solid organ or hematological transplant concluded that vaccination does decrease the risk of influenza-like illness in these populations. There is limited evidence supporting a transient increase in viremia and a decrease in the percentage of CD4+ cells in patients who test HIV positive after influenza vaccination, but no evidence of worsening of clinical HIV related to influenza vaccination.

Updated vaccine guidelines, including detailed dosing information and guidelines for vaccination in children and people with egg allergies, are issued yearly by the CDC through the ACIP and are published in MMWR; the guidelines for the 2012–2013 influenza season were published in August of 2012.[82]

How Effective Is Influenza Vaccination in Preventing Illness?

Influenza vaccine effectiveness varies with patient age and immune status as well as with the match between circulating and vaccine strains in a particular year. The effectiveness of influenza vaccine in preventing laboratory-confirmed symptomatic influenza is estimated at 50% to 80% depending on the population studied.[92,93] A randomized controlled trial of the efficacy of TIV in healthy adults aged 18 to 64 years during the 2006–2007 influenza season in the Czech republic and Finland found an efficacy of about 60%.[94] Vaccine effectiveness is probably reduced in patients with chronic illness and in the elderly, with one study conducted during a season of poor antigenic match and circulating strains finding a vaccine effectiveness of only 36% in patients with high-risk medical conditions such as chronic lung, heart, or kidney disease.[95]

Who Should Receive Chemoprophylaxis?

Chemoprophylaxis against influenza should not be used as a substitute for vaccination. Antivirals should be used judiciously to avoid contributing unnecessarily to the

development of resistance and to preserve available supplies. Chemoprophylaxis is only recommended in patients who present within 48 hours of exposure to an infected person, are at high risk of developing complications from influenza (see **Box 3**), and have not been vaccinated, have been vaccinated within the past 2 weeks, or are severely immunosuppressed and may not have responded appropriately to the vaccine. Vaccination should be administered along with chemoprophylaxis if the patient has no strong contraindications. Patients should be treated for a total of 7 days. Institutionalized patients can be treated for up to 2 weeks to control further outbreaks.[63] One study showed that daily oseltamivir, when given to patients who underwent either stem cell transplant or solid organ transplant in the past year, may reduce the incidence of PCR-confirmed influenza.[96]

What is the Role of Nonpharmacologic Methods in the Prevention of Transmission of Influenza?

Clinicians should implement proven strategies to prevent transmission of influenza and other respiratory viruses in the health care setting. The most effective single measure is vaccination of all health care workers. Effective strategies to improve vaccination rates among health care workers include mandating vaccines for all workers without contraindications, providing vaccine without cost, and improving access by making vaccines available at the site during work hours.[97] Mandatory vaccination of health care workers has been shown to dramatically increase the percentage of health care workers who are vaccinated, but these policies are controversial.[98] Health care workers who develop fever and respiratory symptoms should be excluded from work until at least 24 hours after they no longer have a fever; those wishing to return to work before respiratory symptoms have resolved should be evaluated by occupational health to determine whether they can safely be in contact with patients and at minimum should wear a mask until symptoms resolve. More stringent criteria should apply to workers caring for severely immunocompromized patients such as patients who underwent hematopoietic stem cell transplant, and organizations should develop guidelines according to CDC recommendations. Clinicians should advocate within their organizations for sick leave policies for health care workers that are flexible and allow providers with suspected or confirmed influenza to stay home as appropriate. Facemasks, droplet precautions, and hand hygiene are also important parts of the prevention strategy in the health care setting.[97] In the community, facemasks and hand hygiene may also be helpful in preventing transmission in households, although compliance is an issue. In a cluster randomized trial in Hong Kong, hand washing and facemasks seemed to prevent influenza transmission if started within 36 hours of symptom onset, with an adjusted odds ratio of 0.33, 95% CI 0.13–0.87.[99]

COMPLICATIONS OF INFLUENZA

What Are Some Infectious Complications of Influenza?

Myocarditis is a rare but potentially life-threatening complication of both influenza A and influenza B. A recent study showed that among patients with influenza-related myocarditis, most of these patients have fulminant disease. In addition, the number of patients with myocarditis seems to be increased during periods of pandemic influenza A.[100]

What Are Some Noninfectious Complications of Influenza?

Influenza has been associated with various neuropsychiatric adverse events (NPAE) including encephalitis, loss or depressed level of consciousness, delirium, convulsion, and hallucinations. For sometime, these symptoms were thought be caused by oseltamivir; however, newer studies have shown a more distinct association with inflammation caused by the virus and not the treatment.[101,102] In addition, treatment with oseltamivir seems to have decreased the incidence of NPAE. Interestingly, a large observational study showed that influenza infections are associated with transient Parkinson's symptoms but does not predispose one to Parkinson disease.[103]

There may be some association between thrombotic events and influenza infection, although data remains conflicting.[104] Several studies have shown that the influenza vaccine has decreased the incidence of deep venous thrombosis.[105]

FUTURE DIRECTIONS IN RESEARCH AND POLICY

Studies have suggested that patients are not well educated about the risks and benefits of influenza vaccination and antiviral treatment; in one study, 37% of patients in an internal medicine clinic thought that the influenza vaccine could cause influenza and 63% were unaware that antiviral medication is ineffective against bacteria.[106] There are likely important racial and economic disparities in vaccination and appropriate use of antiviral medication as well. Among Medicare beneficiaries, white patients are more likely to be vaccinated than African American or Hispanic patients; this should be a target for further research and public health efforts.[107]

In a recent article, Poland and Jacobson[108,109] argue that clinicians, scientist, and the public alike need to help to end the antivaccinationist's campaign. The investigators suggest that the funding of studies to address the concerns about vaccines, the improvement of vaccine monitoring programs, and the education of both clinicians and the public will help to accelerate this effort.

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