in the clinic

Influenza

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The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including PIER (Physicians' Information and Education Resource) and MKSAP (Medical Knowledge and Self-Assessment Program). Annals of Internal Medicine editors develop In the Clinic from these primary sources in collaboration with the ACP's Medical Education and Publishing Division and with the assistance of science writers and physician writers. Editorial consultants from PIER and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://pier.acponline.org and other resources referenced in each issue of In the Clinic.

CME Objective: To provide information on the prevention, diagnosis, and treatment of influenza

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Prevention

What are the different types of influenza and what do we know about their cause?
The 3 main types of influenza virus are A, B, and C. Influenza A is subtyped according to its main surface glycoprotein components, hemagglutinin and neuraminidase. There are at least 15 different kinds of hemagglutinin and 9 types of neuraminidase and a multitude of possible combinations. Since 1977, the circulating influenza A strains have been primarily of the H1N1 and H3N2 subtypes.

Influenza A viruses have great capacity for mutational change, and minor antigenic changes periodically occur in either the hemagglutinin or the neuraminidase component or both. This phenomenon, called "antigenic drift," introduces viruses that are different enough from preceding strains that previously acquired immunity is not fully effective. Thus "drift" contributes to the pattern of yearly seasonal epidemics, and is the basis for the yearly change in vaccine formulations.

More-dramatic antigenic change (a "shift") results in a virus of distinctly different antigenic character to which most or all of the population is susceptible. Generally, such shifts occur only every few decades, and are the basis for influenza pandemics. Influenza viruses also infect other species, including birds and pigs. Under circumstances not completely understood, these animal strains sometimes adapt to infect humans and spread from person to person. For example, despite the H1N1 designation, the currently circulating "novel" strain of H1N1 (also known as 2009 H1N1 or swine flu), which seems to have originated in swine, is entirely different from the H1N1 strains of recent years, and thus has triggered a pandemic (1).

Influenza B viruses also mutate periodically, but less dramatically; they drift but do not shift, and thus are associated with seasonal epidemics but not with pandemics. Influenza C viruses are of little clinical significance.

What is the difference between seasonal epidemics and pandemics of influenza?
Seasonal epidemics of influenza A and B cause substantial morbidity and mortality, disproportionately affecting elderly persons, very young persons, and those with certain underlying medical conditions. The average yearly toll in the United States is 51,000 deaths and more than 500,000 hospitalizations due to influenza infection and its complications (2).

Pandemic disease may differ from seasonal influenza in some features. Unlike yearly epidemics during the cold-weather months, pandemics may begin and persist during the warmer months. Although pandemic disease is widespread, it is generally less severe than seasonal disease. The 1918 pandemic was notable for rapid and devastating disease in young, healthy adults. Although the current pandemic seems to cause milder disease in general, both the frequency and severity of infection have been greatest in those younger than 24 years (3).
Which patients should clinicians immunize against influenza and when during the year is the optimal timing for vaccination?

Current guidelines for vaccination against seasonal influenza, updated yearly by the Centers for Disease Control and Prevention (CDC) focus on providing universal immunization for children aged 6 months to 18 years and for adults aged 50 years or older. The CDC also recommends vaccinating all persons with conditions that place them at high risk for complications of influenza and their close contacts, including out-of-home caregivers and health care workers. Immunization is also encouraged for anyone who wants to prevent becoming infected with influenza or spreading it to others, as long as supplies are adequate and the person has no contraindications (4).

These recommendations are based on public health considerations and the CDC’s assessment of risk and benefit, guided by existing data. Vaccine efficacy studies have examined populations of different ages and underlying health status and many end points, including serologic conversion, laboratory-confirmed influenza, influenza-like illness, and such complications as hospitalization and death. Efficacy varies with age, baseline health, and immune function and with the degree of match between vaccine strains and circulating strains. Recent systematic reviews found vaccine to be effective in reducing laboratory-confirmed influenza in healthy children older than 2 years and in healthy adults (5, 6).

Efficacy in elderly patients and in high-risk populations has been less clear. Few trials have focused on these populations, and selection bias may lead to healthier patients being more likely to be vaccinated. Several large cohort studies have shown a reduction in respiratory and cardiovascular complications as well as hospitalization and death in elderly persons living in the community and in other persons with chronic medical conditions (7–11).

A large study of community-dwelling elderly persons conducted during 10 influenza seasons (713 872 person-seasons) showed a 27% reduction in the risk for hospitalization for pneumonia and a 48% reduction in the risk for death among recipients of the influenza vaccine compared with those who had not been immunized against influenza (12).

In a cluster randomized, controlled trial during 2 influenza seasons in 44 nursing homes in the United Kingdom, vaccination was offered to staff in 22 facilities. In the 2003 to 2004 influenza season, acceptance by staff in these “intervention” homes was 48.2% compared with 5.9% in the 22 nursing homes in which vaccination was not offered; in the 2004 to 2005 season, the rates were 43.2% and 5.9%, respectively. During periods of influenza activity in 2003 to 2004, the decrease in mortality in intervention facilities was significant compared with control facilities (rate difference, −5.0 per 100 residents [95% CI, −7.0 to −2.0]). No differences were found in 2004 to 2005 when the national incidence of influenza was unusually low (13).

Pregnant women (and their infants) are at high risk for severe influenza and complications, and vaccination is recommended for women who are or will be pregnant during the influenza season. Live vaccine is contraindicated and inactivated vaccine is classed by the U.S. Food and Drug Administration as pregnancy category C, so data are limited. However, available evidence suggests that inactivated vaccine confers benefit to both mother and infant. Transplacental transfer of maternal antibody against influenza has been documented (14).

A prospective study of 340 pregnant women randomly assigned to influenza vaccine or pneumococcal vaccine (control) showed reduction in febrile respiratory illnesses among women vaccinated against influenza during pregnancy and among their infants, as well as a reduction in documented influenza in the infants, compared with women in the control group and their infants. Vaccine effectiveness against
Influenza, 2009

Vaccination Against Seasonal Influenza, 2009

- All children aged 6 mo to 18 y
- All persons aged ≥60 y
- Women who will be pregnant during influenza season
- Adults and children with chronic pulmonary (including asthma and any condition that causes difficulty handling respiratory secretions), cardiovascular (excluding hypertension), renal, hepatic, hematologic, or metabolic (including diabetes mellitus) disorders, or immunosuppression (including related to medications or HIV)
- Residents of long-term care facilities
- Persons aged 6 mo to 18 y receiving long-term aspirin therapy who are at risk for the Reye syndrome
- Contacts of high-risk persons, including health care workers involved in direct patient care, out-of-home caregivers, and household contacts.
- Household contacts and caregivers of children aged ≤5 y
- Any other person who wants to reduce their risk for influenza or for transmitting it to others

laboratory-confirmed influenza in the infants was 63% (CI, 5% to 85%). Reduction in febrile respiratory illness was 36% (CI, 4% to 57%) (15).

Recommendations for immunization of children have been expanded from those at highest risk (age >5 years) to all children aged 6 months to 18 years. Several studies show that vaccination of school-aged children results in fewer reports of flu-like symptoms by household members, suggesting the occurrence of “herd immunity” and potential benefit to the community at large (16, 17).

How does pandemic H1N1 affect vaccination policies?
The emergence of the pandemic H1N1 strain, which is not included in the present formulation of vaccine for seasonal influenza, has complicated influenza vaccination policies. Guidelines advise that the following groups receive highest priority for immunization: pregnant women, household contacts and caregivers for children younger than 6 months, health care and emergency medical services personnel, all persons aged 6 months to 24 years, and persons aged 25 to 64 years who have conditions that put them at high risk for complications (Box) (18). Indications may expand as vaccine becomes available. The current recommendations are based on the rationale that children and young adults live under close conditions that foster transmission of the disease and on observations that the disease is more severe in young persons.

What kinds of seasonal influenza vaccine are available in the United States?

Two types of vaccines against seasonal influenza are available in the United States: the trivalent inactivated vaccine (TIV), which is injected, and the live attenuated influenza vaccine (LAIV), which is a nasal spray. Both vaccines contain 3 strains of influenza: an H3N2 virus, an H1N1 (seasonal) virus, and an influenza B virus. In any given year, both kinds of vaccine contain antigenically equivalent strains. Vaccine composition is adjusted yearly. The CDC uses data on the global pattern of prevailing strains to select which viruses to include in vaccine produced for the U.S. population. The match between vaccine strains and strains that come to be prevalent is not always perfect. However, even when the match is not exact, the vaccine strain and the circulating strain are often sufficiently similar to provide some immunity (19–21).

In October 2009, vaccine against novel H1N1 became available in the same formulations as seasonal influenza vaccine, TIV (including a thimerosal-free version) and LAIV, and the same cautions apply. The novel H1N1 vaccine is produced by the same manufacturers that produce seasonal vaccine, using the same process by which vaccine is adapted to yearly strain changes.

How should clinicians determine whether to use TIV or LAIV?

Live attenuated influenza vaccine is approved only for healthy nonpregnant persons aged 2 to 49 years. The inactivated vaccine is approved for use in all persons older than 6 months. Both vaccines are produced in a process that uses chicken eggs, and allergy to eggs (or any other vaccine component) is a contraindication to either vaccine. Neither vaccine should be given to anyone with history of the Guillain-Barré syndrome unless the risk for influenza or complications is high, in which case TIV may be

Highest Priority Groups for H1N1 Vaccine

- Pregnant women
- Household contacts and caregivers for children aged <6 mo
- Health care and emergency medical services personnel
- All persons aged 6 mo to 24 y
- Persons aged 25 to 64 y at high risk for flu complications

preferable to LAIV. Neither vaccine should be given to persons with significant febrile illness; minor acute illness without significant fever is not a contraindication, although when significant nasal congestion is present and may impede delivery of LAIV, vaccine should be postponed or substituted with TIV. In addition, LAIV should not be given to anyone younger than 2 years or older than 49 years; to persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; to persons with other underlying medical conditions, such as diabetes mellitus, renal dysfunction, hemoglobinopathies, or immune deficiency; to children or adolescents receiving long-term aspirin therapy; to pregnant women; or to persons receiving antiviral drugs active against influenza. Because of the theoretical risk for spreading live (albeit attenuated) virus to severely immunocompromised patients (for example, stem cell transplant recipients in protective isolation), health care workers caring for these patients and other close contacts should be immunized with TIV. Acquisition of LAIV by immunocompetent or immunosuppressed children through viral shedding has been reported, but no serious illness is known to have been caused by unvaccinated persons through infection by LAIV due to accidental environmental exposure or shedding of LAIV by vaccinated contacts (4).

Not all TIV formulations are licensed for children. TIV is classified as pregnancy category C. However, data from the Vaccine Adverse Event Reporting System (VAERS) and other sources show no significant adverse events to pregnant women or to their fetuses attributable to influenza vaccine (4).

Among healthy nonpregnant persons aged 2 to 49 years, the CDC guideline states no preference for either LAIV or TIV (4). Few studies have been designed specifically to compare the 2 vaccines.

A randomized trial enrolled 1952 healthy adults during the 2007 to 2008 influenza season and assigned them to placebo or TIV or LAIV. Absolute efficacy was 68% [CI, 46% to 81%] for TIV and 36% [CI, 0% to 59%] for LAIV. Both vaccines prevented influenza, but LAIV was less effective than TIV (22).

LAIV may also offer a protective advantage by eliciting respiratory mucosal as well as systemic immunity. Some authors also cite more rapid acquisition of antibody with LAIV than with TIV (2, 23). Table 1 summarizes differences in indications for TIV and LAIV.

When during the year is the optimal timing of vaccination?

Ideally, persons living in the United States should receive vaccination in October and November, but vaccine should be offered throughout the

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Table 1. Comparison of Inactivated TIV with LAIV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIV</th>
<th>LAIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved age</td>
<td>≥6 mo</td>
<td>2 to 49 y</td>
</tr>
<tr>
<td>Indicated for persons with medical risk factors for influenza complications?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Indicated for close contacts of immunosuppressed persons not requiring a protected environment?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indicated for close contacts of immunosuppressed persons who require a protected environment (for example, stem cell transplant patients)?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Indicated for close contacts of persons at high risk for influenza complications but not immunosuppressed?</td>
<td>Yes (Pregnancy category C, but no VAERS or other data showing harm to mother or fetus)</td>
<td>Yes</td>
</tr>
<tr>
<td>Indicated for pregnant women?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

LAIV = live attenuated influenza vaccine; TIV = trivalent influenza vaccine; VAERS = Vaccine Adverse Event Reporting System.

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winter, because the influenza season often does not peak until February or March. If vaccine is available in September, clinicians should offer it to high-risk patients who present for routine appointments or at the time of hospital discharge to avoid delayed or missed opportunities. Note that 2 doses separated by at least 4 weeks are recommended for children who have not received at least 1 dose previously; the first dose should be given as early as possible to achieve full effect by the onset of influenza season. Nursing home residents should not be immunized before October, because antibody levels may not last through the influenza season. These recommendations reflect the consensus of experts, based on the usual chronology of influenza in the United States and the duration of vaccine-induced antibody.

**How does vaccine supply influence vaccination priorities and timing?**
If difficulties in vaccine production or distribution result in shortages or delays, priority should be given to vaccinating persons at high risk for severe disease or complications and their close contacts, including health care workers. Under such circumstances in the past, the CDC has provided triage guidelines on their Web site (www.cdc.gov/flu/professionals).

**What is the role of behavioral strategies to prevent influenza transmission?**
Few studies have evaluated the efficacy of “nonpharmaceutical interventions” for the prevention of influenza. Adults may be able to spread influenza from 1 day before symptoms develop to 5 days after. Children and persons with immune deficiencies can be infectious longer. Handwashing and respiratory etiquette are easy, cheap, common-sense measures shown in a systematic review to contain infection caused by respiratory viruses (24). Based primarily on what is known about the transmission of disease, experts also recommend that infected (or potentially infected) persons wear a surgical mask when in close contact with others, and that they be isolated when hospitalized or confine themselves to home until afebrile for 24 hours. The protective value of facemasks to uninfected persons in the community is unknown. Other “social distancing” strategies, such as closing schools and prohibiting large gatherings, have been studied primarily historically, and these observations seem to indicate that such measures can contribute to controlling or slowing spread of disease (25).

To investigate whether hand hygiene and use of facemasks prevents household transmission of influenza, 407 persons presenting to outpatient clinics in Hong Kong with influenza-like illness and positive rapid tests for influenza A or B were randomly assigned by household to lifestyle education, hand hygiene, or surgical facemasks plus hand hygiene. Hand hygiene and facemasks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset (26).

**What is the role of antiviral agents in preventing influenza, and are there special considerations during outbreaks of novel H1N1?**
Antiviral drugs can supplement or replace vaccine if there is a shortage or if vaccination is contraindicated, and can prevent the spread of disease during outbreaks in institutions and in households. Zanamivir, oseltamivir, amantadine, and rimantadine are proven efficacious when used for prophylaxis in community or family settings in which circulating virus was sensitive to the drug. This protection extends to high-risk patients.

A systematic review of 7 trials involving 7021 participants found that neuraminidase chemoprophylaxis for >4 weeks decreased the frequency of symptomatic influenza (RR, 0.26 [CI, 0.18 to 0.37]), but not asymptomatic influenza infection (RR, 1.03 [27]).
Prophylaxis for the duration of the influenza season has been effective in preventing laboratory-confirmed influenza and secondary complications in nursing home patients (28). Substantial evidence exists for the efficacy of prophylactic use of antiviral agents in controlling established outbreaks in nursing homes (29–32).

During an outbreak, unvaccinated staff members and residents should receive vaccine if it is available. Staff members vaccinated at the onset of the outbreak should receive chemoprophylaxis for 2 weeks. In nursing homes, the potential for high-intensity virus exposure and possible suboptimal immune response to vaccine by debilitated residents suggest that all residents, regardless of previous vaccination, should receive chemoprophylaxis in an outbreak. Antiviral medications should be continued in residents for at least 2 weeks and for 1 week longer than the duration of the outbreak.

In the community, short-term prophylaxis for 10 to 14 days is appropriate for persons (and their close contacts) who are at high risk and received TIV after the seasonal epidemic has begun, until vaccination becomes effective. Postexposure prophylaxis (for example, in a household setting) should be considered for unimmunized high-risk persons in conjunction with vaccination (TIV) if possible, and for healthy household contacts of those with recently diagnosed influenza.

Prophylaxis may be provided throughout the influenza outbreak to high-risk persons and their close contacts (including health care workers) when vaccine is unavailable or contraindicated, when a major antigenic difference exists between the epidemic strain and the vaccine strains, or when severe immunosuppression makes response to the vaccine unlikely. Should pandemic disease with the novel H1N1 continue, antiviral prophylaxis may play an important role in management, particularly if vaccine production does not meet demand.

The selection of an appropriate antiviral regimen has become increasingly complex. Various strains have developed resistance to some antiviral agents, and no clinically available tests exist to determine antiviral susceptibility patterns or even viral subtypes. Table 2 shows available agents and Table 3 summarizes currently prevailing sensitivity patterns, including those seen in the novel H1N1 strain. The CDC provides periodic updates to guide antiviral use (www.cdc.gov/flu/professionals/index.htm) as well as weekly surveillance reports that include the geographic distribution of prevailing strains (www.cdc.gov/flu/weekly). At present, zanamivir alone or a combination of oseltamivir and rimantadine are appropriate empirical regimens when the specific etiologic strain has not been identified.

What measures should clinicians take to prevent influenza among patients and staff in health care institutions?

All health care personnel should receive influenza vaccination unless vaccine is contraindicated or unavailable. In the latter case, clinicians should consider prophylaxis with antiviral medications for themselves and other health care workers. The use of standing orders, which allow trained health care professionals other than physicians to identify and vaccinate high-risk patients, improves rate of immunization of hospital patients at discharge and of nursing home residents, especially if structured in
an “opt-out” format (33). Likewise, providing cost-free vaccine at convenient times and places may improve vaccine coverage among hospital and nursing home staff. During outbreaks, infection control measures, such as limiting visitors, using droplet precautions, and cohorting infected patients, should also be implemented. 

### Table 2. Antiviral Drugs for Treatment and Prophylaxis of Influenza in Adults

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Benefits</th>
<th>Side Effects and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanamivir</td>
<td>Inhibition of the influenza neuraminidase enzyme</td>
<td>Treatment: 2 inhalations (10 mg) bid for 5 d. Prophylaxis: 2 inhalations (10 mg) qd. Duration of prophylaxis is based on situation.</td>
<td>Shortens duration of symptoms by 1 to 2 d, reduces complications by about 40%. Provides effective prophylaxis in family, community, and institutional settings.</td>
<td>Same as placebo in controlled trials. Postmarketing reports suggest rare bronchospasm. Active against both influenza A and B viruses. Approved only for persons without underlying pulmonary or cardiovascular disease. Pregnancy category C.</td>
</tr>
<tr>
<td>Osel tamivir</td>
<td>Inhibition of the influenza neuraminidase enzyme</td>
<td>Treatment: 75 mg PO bid for 5 d. On the first day, doses should be taken at least 2 h apart; subsequent doses should be spaced at 12-h intervals. Prophylaxis: 75 mg PO qd Duration of prophylaxis is based on situation.</td>
<td>Shortens duration of symptoms by 1 to 2 d; reduces complications by about 40%. Provides effective prophylaxis in family, community, and institutional settings when the circulating strain is sensitive.</td>
<td>Nausea (about 10% of first dose) and vomiting (about 6%). Postmarketing reports include some cases of confusion, self-injury. Dosage reduction for CrCl &lt;30. Significant resistance has emerged in recent seasonal H1N1 strains. Pregnancy category C.</td>
</tr>
<tr>
<td>Amantadine</td>
<td>M2 ion channel inhibitor</td>
<td>For treatment or prophylaxis: 200 mg/d as single or 2 divided doses. Treatment should continue for 5 d. Duration of prophylaxis is based on situation.</td>
<td>Shortens duration of symptoms by 1 to 2 d. Provides effective prophylaxis in family, community, and institutional settings when the circulating strain is sensitive.</td>
<td>Confusion, balance disturbance, insomnia, exacerbation of preexisting neurologic conditions. Not effective against influenza B or recently circulating strains of seasonal H3N2 or the novel strain of H1N1. Currently recommended for combination therapy with oseltamivir when the etiologic strain is not known and when rimantadine (preferred M2 inhibitor) is not available. Pregnancy category C.</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>M2 ion channel inhibitor</td>
<td>For treatment or prophylaxis: 200 mg/d as single or 2 divided doses. Treatment should continue for 5 d. Duration of prophylaxis is based on situation.</td>
<td>Shortens duration of symptoms by 1 to 2 d. Provides effective prophylaxis in family, community, and institutional settings when the circulating strain is sensitive. Better tolerated than amantadine.</td>
<td>Not effective against influenza B or recently circulating strains of seasonal H3N2 or the novel strain of H1N1. Currently recommended for combination therapy with oseltamivir when the etiologic strain is not known. Pregnancy category C.</td>
</tr>
</tbody>
</table>

### Table 3. Susceptibility of Prevailing Strains to Antiviral Agents

<table>
<thead>
<tr>
<th>Influenza Strains</th>
<th>Amantadine</th>
<th>Susceptible to Antiviral Agent?</th>
<th>Rimantadine</th>
<th>Osel tamivir</th>
<th>Zanamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal H1N1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Seasonal H3N2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Novel H1N1†</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*As of 12 August 2009. †Pandemic strain.

CrCl = creatinine clearance.


In the Clinic

What symptoms and signs should prompt clinicians to suspect influenza?

The symptoms of influenza frequently overlap those of other viral respiratory symptoms, but the presence of fever and cough help differentiate influenza from other viral infections, especially when influenza is known to be present in the community. Higher temperatures, acute symptom onset, and more severe symptoms also support the diagnosis of influenza (34). Symptoms may be more subtle in elderly persons. Table 4 summarizes the differential diagnosis for patients presenting with influenza-like symptoms.

In a retrospective pooled analysis of baseline clinical trial data from 3744 mainly unvaccinated adults and adolescents who had influenza-like symptoms, cough and fever were found to be the best multivariate predictors of influenza infection in the setting of an outbreak, with a positive predictive value of 79% and a sensitivity of 64% for laboratory-confirmed influenza (35).

A prospective study of 100 patients with influenza-like illness showed fever and cough to be highly predictive of laboratory-confirmed influenza (86.6% positive predictive value, 39% negative predictive value, 77.6% sensitivity, 55% specificity) (36).

Although weakness, myalgia, sore throat, nausea, rhinorrhea, and headache are common in influenza, they occur with similar frequencies in other viral illnesses. In most cases, gastrointestinal symptoms suggest another diagnosis, although early...
reports of novel H1N1 disease indicate that diarrhea is prominent.

In addition to fever, the physical examination may reveal nasal congestion and tracheal tenderness. The presence of rales or consolidation on chest examination may suggest viral pneumonia or other diagnoses or complications, such as bacterial pneumonia or heart failure.

**When should clinicians suspect H1N1, avian flu, or other influenza virus infections? Do clinical presentations differ?**

Other forms of influenza should be considered when a patient with typical influenza-like symptoms presents outside of the usual influenza season, particularly if they have traveled recently or have other history that suggests an unusual form of influenza (for example, close exposure to birds or pigs). Very severe disease, particularly in a young, previously healthy person may also suggest a nonseasonal strain.

Human infections due to various avian strains have been reported, and presentations range from very mild upper respiratory symptoms to overwhelming systemic disease with respiratory failure. Reported cases of H5N1 (avian influenza) from Asia in recent years have been characterized by rapid, fulminant disease and a mortality rate of 50% or more.

Disease due to the novel H1N1 pandemic strain has occurred throughout the northern hemisphere during the summer of 2009, but generally has been mild. Some cases of severe, rapidly progressive, often fatal cases have been reported in young adults with no underlying disease. These cases have been characterized by dyspnea, cyanosis, hemoptysis, chest pain, confusion, and hypotension. A published description of 18 hospitalized patients reported markedly elevated levels of serum lactate dehydrogenase in all; lymphopenia and elevated creatine kinase levels were also common (37). Factors that might predict such an explosive clinical course are as yet unidentified (38).

**When should clinicians obtain diagnostic testing, including rapid tests and tests for novel H1N1, to confirm influenza diagnosis?**

Testing should be performed early in a suspected outbreak to confirm the presence of influenza in the community and whenever necessary to confirm the diagnosis in atypical cases. It can also be done to investigate and monitor outbreaks in hospitals and nursing homes.

Although viral cultures on nasopharyngeal specimens are most sensitive and specific, results may take 3 to 10 days or longer, which limits clinical usefulness. Rapid tests for seasonal influenza are widely available and can be helpful for individual patients in whom the results will contribute to treatment decisions. Diagnostic testing does not need to be done in all patients who present with a typical clinical picture of influenza when the disease is prevalent in the community. In hospitalized patients, rapid confirmation of diagnosis aids in prompt institution of appropriate infection-control measures and of antiviral therapy as well as a reduction in the use of antibacterial antibiotics.

In a published hospital record review, rapid testing led to a reduction of antibacterial antibiotic use in patients who tested positive for influenza (86% vs. 99%; \(P = 0.002\)) and to greater use of antivirals in patients who tested positive (73% vs. 8%; \(P < 0.001\)) (39).

In the face of increasing resistance to antiviral medications, testing that can differentiate influenza A from B may help to determine an appropriate regimen for treatment or prophylaxis, but none of the commercially available rapid tests distinguish between different...
subtypes of influenza A (seasonal H1N1 or H3N2). No rapid tests are designed specifically to detect the novel H1N1. Preliminary studies show that some of the rapid tests designed to detect seasonal influenza A also detect novel H1N1, but the sensitivity varies from 40% to 69%, and a positive result does not differentiate between seasonal and pandemic strains (40).

In general, CLIA (Clinical Laboratory Improvement Act)-waived tests for physicians’ offices are more than 70% sensitive and more than 90% specific for the detection of seasonal influenza. Sensitivity is higher in children than in adults, higher with nasal samples than with throat samples, and higher during the first few days of illness. The positive predictive value is greatest during influenza season, and the negative predictive value is greatest outside of influenza season.

Commercial laboratories can confirm rapid tests if necessary during seasonal influenza. If novel H1N1 is suspected and if confirmation is required (for example, for community surveillance or in a very ill or immunocompromised patient), definitive testing may be obtained through public health authorities. In either of these cases, clinicians should initiate empirical management without awaiting results.

A list of commercially available tests and their performance characteristics can be found at www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm.

When should clinicians suspect bacterial complications in patients initially believed to have influenza? Clinicians should consider possible bacterial complications in patients who remain ill, worsen, or have acute onset of high fever and malaise after initial improvement. Fever in adults with uncomplicated influenza generally lasts about 3 days, by which time most will show signs of improvement. Although it may take 10 to 14 days for complete recovery, lack of improvement or worsening symptoms suggest either a complication or an alternative diagnosis.

Acute bronchitis is the most commonly recognized complication, but others include sinusitis, pneumonia, and noninfectious sequelae (41). Patients who remain febrile for more than 3 to 5 days, or who develop fever or new symptoms, require evaluation. Symptoms and clinical findings should guide blood tests, cultures, and imaging studies. Consultation with a specialist should be considered, especially if the patient is severely ill or immunosuppressed.

Occasionally, serious systemic bacterial infections, such as pneumonia, staphylococcal bacteremia, meningococcal disease, and inhalational anthrax, can present initially with influenza-like symptoms. The differential diagnosis should be broadened in patients whose condition deteriorates rapidly, and work-up and treatment should be adjusted accordingly. Again, consultation with a specialist might be appropriate in such cases.
Treatment

What is the role of hydration and antipyretics in treating patients with influenza?

Hydration is important to replace the large insensible water losses that occur with fever. In patients with infection due to the novel H1N1 strain, diarrhea may also necessitate fluid replacement. Antipyretics, such as acetaminophen or ibuprofen, can help to reduce fever and thus prevent further insensible loss. Reduction of fever can prevent other consequences of increased metabolic rate, such as tachycardia, and may relieve such symptoms as chills and myalgia. No convincing evidence exists that antipyretic therapy either prolongs or shortens the course of illness. Aspirin and aspirin-containing medicines should be avoided, particularly in adolescents and children, because of their association with the Reye syndrome.

When should clinicians prescribe antiviral agents for patients with influenza and which agents should they prescribe?

Clinicians should consider antiviral medication for people who present within 48 hours of symptom onset, for hospitalized patients, and for those at risk for severe disease. Pregnant women are particularly vulnerable, and especially in the context of the present pandemic, prompt antiviral therapy is recommended. The CDC provides periodic updates to guide antiviral treatment with either oseltamivir or zanamivir results in early resolution of symptoms and a more rapid return to normal activities (42–47).

The duration of treatment is 5 days. Table 2 summarizes dosages, benefits, and side effects.

A systematic review that examined trials of antiviral treatment for influenza concluded that amantadine and rimantadine use should be discouraged and that, because of their low effectiveness, neuraminidase inhibitors should be used only in serious epidemi or pandemic situations rather than for control of seasonal influenza (48, 49).

In a meta-analysis of 17 treatment trials and 7 prevention trials involving children younger than 12 years, healthy adults aged 12 to 65 years, and high-risk persons, zanamivir reduced the mean duration of symptoms by 1.0 day (CI, 0.5 to 1.5), 0.8 day (CI, 0.3 to 1.3), and 0.9 day (CI, 0.1 to 1.9), respectively. Oseltamivir reduced symptoms by 1.0 day (CI, 0.5 to 1.5), 0.8 day (CI, 0.3 to 1.3), and 0.9 day (CI, 0.1 to 1.9), respectively. Oseltamivir reduced symptoms in the same groups by 0.9 day (CI, 0.3 to 1.5), 0.9 day (0.3 to 1.4), and 0.4 day (CI, −0.7 to 1.4), respectively. The authors concluded that both drugs were effective for treating influenza, although the evidence was limited for certain populations (50).

A retrospective pooled analysis of data exclusively from 321 high-risk patients with a clinical diagnosis of influenza showed that 154 of those patients treated with inhaled zanamivir experienced a reduction in the length of illness by 2.5 days compared with those given placebo (P = 0.015). Treated

strains of H1N1 have become resistant to oseltamivir but remain sensitive to the adamantanes. Table 3 summarizes these resistance patterns. All these strains remain sensitive to zanamivir, which is the treatment of choice for persons who can tolerate aerosolization medication. In other cases, a combination of oseltamivir and rimantadine would be an appropriate empirical regimen. Rapid diagnostic testing (for example, to differentiate influenza A and B) and information from public health authorities about the identity of locally prevailing strains may help refine the selection.

Many studies showed that early treatment with either oseltamivir or zanamivir results in earlier resolution of symptoms and a more rapid return to normal activities (42–47).

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high-risk patients returned to normal activities 3.0 days earlier (P = 0.022) and had a 43% reduction in the number of complications requiring antibiotics (P = 0.045) (51).

Fewer studies have been done in hospitalized patients, but at least 1 has shown a reduction in mortality among hospitalized patients with laboratory-confirmed influenza who were treated with antiviral drugs (52). A retrospective cohort study showed decreased length of stay in hospitalized patients treated with oseltamivir (53).

Most studies on the use of antiviral agents are based on initiation of therapy within 48 hours. However, treatment is generally well-tolerated and, even if started late, may improve outcome in critically ill or high-risk patients. For this reason, some authorities endorse the use of antiviral therapy in hospitalized patients and other selected persons even after 48 hours of illness (54).

Although oseltamivir and zanamivir are pregnancy category C drugs, the CDC advises that pregnancy should not be considered a contraindication to treatment. If H1N1 is suspected, treatment should be given immediately because of the observed severity of disease in pregnant women. Under these circumstances, oseltamivir may be preferred to zanamivir because of its systemic absorption (55).

When should clinicians hospitalize patients with influenza?

Hospitalization should be considered for patients who are severely ill because of influenza or its complications. Such conditions as dehydration, inability to maintain adequate intake, respiratory distress, or hypoxemia should prompt admission. Likewise, an uncertain clinical course or frail baseline health might prompt admission for close observation.

When should clinicians consider consultation from an infectious disease specialist or public health authority?

Consultation should be considered for help with diagnosis or management as needed. Diagnostic consultation might be useful in seriously ill patients in whom the diagnosis of influenza is suspected but unproven, in patients with an atypical presentation, when a complication is suspected, or when the differential diagnosis is unusually broad (for example, an immunosuppressed patient with atypical pneumonia).

Consultation for management should be sought with infectious disease specialists for guidance in the use of antiviral agents and the need for antibacterial antibiotics, and with pulmonary or critical care specialists for maintaining oxygenation and obtaining specimens for testing.

Consultation with public health authorities should be sought if avian influenza or another unusual strain is suspected. Public health authorities can expedite laboratory identification of the strain and can guide decisions on antiviral therapy on the basis of available susceptibility data. Also, they are responsible for monitoring disease outbreaks, determining the source, evaluating possible human-to-human transmission, and instituting measures to limit the spread of disease.

Treatment... The mainstay of influenza treatment is supportive care with hydration and antipyretics. Initiate antiviral treatment in hospitalized patients and in those at risk for complications. Consider treatment of others who present early in the course of disease, because early treatment can reduce duration of illness. Hospitalization and subspecialty consultation should be considered for severe illness, uncertain diagnosis, or complications.

CLINICAL BOTTOM LINE

What measures do stakeholders use to measure the quality of care related to influenza?

Since October 2005, the Centers for Medicare & Medicaid Services (CMS) has required participating nursing homes to offer influenza vaccine to all residents (56). The CMS also includes influenza immunization of patients 50 years and older as a performance measure in its Physician Quality Reporting Initiative (PQRI) (57). The Joint Commission on the Accreditation of Health Care Organizations (JCAHO) requires documentation of efforts to vaccinate independent practitioners and staff against influenza (58).

What do professional organizations recommend for preventing and treating influenza?

The recommendations of most professional organizations agree with the CDC’s Advisory Committee on Immunization Practices (ACIP) consensus. ACIP includes representatives from the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Medical Association, the American College of Physicians, the American Osteopathic Society, the Infectious Diseases Society of America, the National Foundation for Infectious Disease, the Society for Healthcare Epidemiology of America, and numerous other organizations. The Infectious Diseases Society of America has also recently published a set of clinical guidelines for prevention, diagnosis, and treatment of seasonal influenza (54). The recommendations listed in this issue of *In the Clinic* reflect those guidelines.
THINGS YOU SHOULD KNOW ABOUT INFLUENZA

What is influenza?

- Influenza (flu) is an illness caused by infection with the influenza virus.
- Flu symptoms include fever, cough, body aches, tiredness, sore throat, and runny nose.
- Usually, flu is not serious and persons recover completely. However, older persons, very young children, and persons with long-term conditions can get very sick or even die of flu or its complications.

What is the difference between regular flu and novel H1N1 (swine) flu?

- Novel H1N1 (referred to as “swine flu” early on) is a new influenza virus causing illness in people.
- Novel H1N1 spreads from person to person worldwide, probably in much the same way that regular seasonal influenza viruses spread, but occurs outside the regular flu season.
- Although regular flu is most serious in older persons, novel H1N1 seems to affect younger persons more than older persons.
- Symptoms of novel H1N1 are similar to regular flu, but many patients also have diarrhea, which usually doesn’t occur in regular flu.

How can you keep from getting the flu or spreading it to other people?

- Get a flu shot every fall if you are aged 6 months to 18 years or 50 years or older; have diabetes, heart or lung disease, or other health problems; or live with or take care of an older person, someone with health problems, or children younger than 5 years.
- Wash your hands often with soap and water and try not to touch your eyes, nose, or mouth.
- Stay away from people who are sick.
- If you get sick, stay home from work or school.

How will I know if I have the flu or something else?

- Doctors usually can make the diagnosis without special tests, especially when symptoms occur during a local outbreak.
- Your doctor may need to do tests to rule out other illnesses.

Call your doctor if you have the flu and you:

- Have a high fever for more than 3 days
- Are short of breath
- Cannot eat or drink

What can I do for the fever, cough, and aches of the flu?

- Fluids and medicines to lower fever are helpful.
- Flu medicines do not cure the flu, but they may shorten the time you are sick. They are most effective when started within 1 to 2 days of the first symptoms.

For More Information

Web Sites with Good Information about Influenza

Centers for Disease Control and Prevention
www.cdc.gov/flu

American Lung Association
www.lungusa.org/site/pp.asp?c=dvLUK900E&b=35426

National Institute of Allergy and Infectious Diseases
www3.niaid.nih.gov/healthscience/healthtopics/Flu/aboutFlu/DefinitionsOverview.htm

American Thoracic Society
1. A 19-year-old male college student presents in late August with fever of 102°F, chills, body aches, nonproductive cough, loss of appetite, and diarrhea for 4 days. He lives in an apartment with 3 other young adults, 1 of which is currently ill with similar symptoms. He has no underlying medical conditions. Public health officials have identified pandemic H1N1 in the southeastern United States community that the patient lives in.

On physical examination, he seems ill. Temperature is 101.3°F and blood pressure is 120/75 mm Hg in lying position and 120/70 mm Hg in standing position. The physical examination is otherwise normal.

Which of the following is most appropriate for managing this patient?
A. Hospitalize the patient for observation because of residence in a community with pandemic H1N1 influenza
B. Make a presumptive diagnosis of H1N1 influenza and do not obtain laboratory tests. Prescribe antipyretics, oral fluids, and bed rest. Instruct patient to distance himself from others and remain at home until afebrile off antipyretics for 24 hours
C. Obtain nasal swabs to test for H1N1 testing
D. Prescribe oseltamivir

2. During February, a 37-year-old male respiratory therapist is seen in your office 1 day after developing fever, rigors, generalized muscle aches, and mild respiratory symptoms. He is otherwise in excellent health. The patient mentions that he had not received an influenza vaccination in the fall.

Physical examination is normal except for a temperature of 39.4°C (103.0°F) and coryza. Influenza A has been documented in your community, and you have seen several patients with similar symptoms this week.

Which of the following is most appropriate for preventing influenza in this patient?
A. Administer influenza vaccine and prescribe no new drugs
B. Obtain a nasopharyngeal culture for influenza and treat only if the result is positive
C. Administer influenza vaccine and prescribe oseltamivir for 2 weeks
D. Prescribe a fluoroquinolone antibiotic
E. Administer an intramuscular or intravenous dose of ceftriaxone and prescribe azithromycin

3. In January, a 56-year-old woman with chronic obstructive pulmonary disease and type 2 diabetes mellitus comes for a routine office visit. She is currently clinically stable and has no new or acute symptoms. An outbreak of influenza A is occurring in your community, but the patient failed to receive an influenza vaccination last fall.

Which of the following is most appropriate for preventing influenza in this patient?
A. Administer influenza vaccine and prescribe no new drugs
B. Obtain a nasopharyngeal culture for influenza and treat only if the result is positive
C. Administer influenza vaccine and prescribe oseltamivir for 2 weeks
D. Administer influenza vaccine and prescribe amantadine, rimantadine, or oseltamivir for 6 weeks
E. Tell the patient that it is too late for an influenza vaccination but prescribe amantadine, rimantadine, or oseltamivir for 2 weeks

4. A 45-year-old man with asthma is evaluated because of malaise, myalgias, coryza, and a cough. Both influenza A and B are occurring in the community, and the patient has not been immunized against influenza. Medications include an angiotensin–converting enzyme inhibitor, an inhaled bronchodilator, and low-dose aspirin. The patient has never traveled outside the United States.

On physical examination, he seems ill. Temperature is 38.3°C (101°F), pulse rate is 95/min, and respiration rate is 24 breaths/min. Blood pressure is normal, and the examination is otherwise unremarkable. Chest radiography is normal.

Which of the following antiviral agents is most appropriate for this patient?
A. Zanamivir
B. Amantadine
C. Oseltamivir
D. Rimantadine

5. The medical director of a primary care practice is developing vaccination policy for the practice in the setting of anticipating a supply of vaccine for H1N1 influenza.

Which of the following describes the groups that the Centers for Disease Control (CDC) identifies as highest priority for H1N1 vaccine?
A. Pregnant women, household contacts and caregivers for children younger than 6 months, health care and emergency medical services personnel, all persons aged 6 months to 24 years, and persons aged 25 to 64 years who have conditions that put them at high risk for complications
B. Patients aged 65 years or older, and all persons with chronic conditions, health care workers, and children younger than 12 months
C. Children younger than 12 months, college students living in dormitories, patients aged 65 years or older, and health care workers
D. Pregnant women and their household contacts, health care workers, all persons aged 6 years to 24 years, and persons aged 65 years or older regardless of the presence of chronic conditions