Influenza is a negative-sense stranded RNA virus. Of the various strains, influenza A is the main concern because it makes up the bulk of human infections. Its genome is simple, consisting of only 8 genes.

Influenza is an ancient disease, and its name comes from the Italian word for “influence.” Centuries ago, it was believed that this constellation of symptoms (fever, myalgia, coryza, prostration, diarrhea, cough, and sometimes pneumonia or death) was caused by the influence of supernatural powers on humankind. Today, the source of influenza is well known. Influenza is a negative-sense stranded RNA virus. In fact, influenza comes in 2 main families, influenza A and influenza B, neither of which should be confused with the similarly named parainfluenza virus or the totally unrelated bacterium *Haemophilus influenzae*. Because it was originally isolated from the respiratory tracts of flu patients, *H influenzae* was thought, for a time, to be the cause of the flu, which we now know to be incorrect. Today, when we talk about the flu virus, we are referring to the influenza virus, especially influenza A. Influenza B is also a problem for humans and has the potential to make patients very sick. For this reason, the trivalent seasonal influenza vaccine always contains 1 influenza B antigen. However, influenza A is the main concern because it consistently makes up the great bulk of human infections. **Influenza A:** Influenza A’s genome is simple, consisting of just 8 genes. Two of the most important genes are for hemagglutinin (knob-like protein on virus’s surface that allows it to bind to respiratory epithelial cells) and neuraminidase (protein that allows new virions to bud from infected human cells, thus perpetuating the infection). Without both hemagglutinin and neuraminidase, influenza A would be rendered essentially harmless to human populations. The nomenclature of influenza A (H1N1, H3N2, etc) is based on the different combinations of antigens found on a given strain. (Reviewer-).
Influenza's error-prone RNA genome means that minor changes in neuraminidase molecules are common, which can render our most valuable antiinfluenza drugs, the neuraminidase inhibitors, ineffective.

(Card 2 of 2) Influenza's error-prone RNA genome is both a boon and a burden. On the beneficial side, these viruses cannot permanently integrate their genes into human cells. In contrast, the DNA-based varicella-zoster virus or herpes simplex virus can become latent and cause clinical illness years later. However, with the influenza virus, once we are over a case of influenza, we are over it for good. In fact, we should be armed with B cell clones producing specific antiinfluenza antibodies that protect us significantly from subsequent infection with the same or even closely related strains. But there are downsides to fighting these negative-sense stranded RNA viruses. The high error rate inherent in passing RNA genomes from 1 generation to the next means that minor changes are common in the hemagglutinin (knob-like protein on virus's surface; allows it to bind to respiratory epithelial cells) and neuraminidase molecules (allows new virions to bud from infected human cells). These changes can result either in small changes to the genome (antigenic drift) or in bigger changes involving whole chunks of RNA from other species (antigenic shift). In the spring of 2009, the so-called swine flu detected in Mexico resulted from an antigenic shift. This flu strain was derived from a strain that usually infects pigs instead of humans, and it was comprised of a unique never-before-seen mix of genes from North American bird and swine viruses, a Eurasian pig flu strain, and a human flu strain. This meant that a significant proportion of the world's population, especially people aged <65 years, had never been infected by similar viruses, thus placing them at increased risk of infection. A small proportion of cases also had an increased risk of poor outcomes, even death. **Neuraminidase Inhibitors:** The neuraminidase protein is the target of our most valuable antiinfluenza medications, the neuraminidase inhibitors, including oseltamivir and zanamivir. Mutations in the neuraminidase gene can render these medications ineffective. Oseltamivir resistance, in particular, has been demonstrated to evolve rapidly among patients on antiviral therapy. This RNA virus has considerable genetic infidelity, which poses a major challenge for clinicians worldwide.

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Keywords: H1N1, Flu, Virology

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H1N1 Shocks World With Off-Season Transmission

2009 Novel H1N1 Influenza: General Epidemiology.
Paul Pottinger, MD

Paul Pottinger, MD - Special Presentation

The 2009 novel H1N1 flu strain was alarming because early reports of transmission in Mexico were well beyond the expected flu season peak and because a high number of children and young adults became severely ill.

Everyone who practices medicine in the northern hemisphere knows the hallmark of influenza transmission: its transmission occurs in a seasonal fashion. Each fall, we gear up for flu season, which typically peaks at slightly different times in different regions, but most often in February or March. It is not entirely clear why this has happened so predictably for so long. Common explanations include crowding of people during cold months and vulnerability of the respiratory epithelium due to dry air or coinfections with other respiratory pathogens. However, our colleagues who practice in equatorial and tropical regions of the world have had a different experience. In these regions, year-round transmission of influenza is the rule. In the United States, we finally had a taste of tropical flu transmission when, in April 2009, the world was stunned to read credible reports of influenza transmission in Mexico well beyond the expected peak of flu season. Two predominant strains of human influenza A had already circulated that season: human H3N2 and human H1N1. This new flu in Mexico underwent a variety of name changes during subsequent months, both in the lay press and in scientific journals. Today, its official name is the "novel swine-origin epidemic 2009 H1N1 influenza A strain." The novel H1N1 influenza strain was alarming, not only because of its unusual timing, but also because of an unusually high number of children and young adults who seemed to become severely ill, sometimes fatally ill. Epidemiologists were worried early in the epidemic that we were making a classic blunder by reporting case-fatality rates based only on fatal cases. Without a reliable reporting system that looked at both mild and severe cases, we worried that the infection might appear to be more dangerous than it was in actuality. Indeed, this does seem to be the case. Because the epidemic has reached U.S. soil, we can use our excellent domestic public health surveillance system in conjunction with foreign surveillance services to better understand the communicability and the spectrum of clinical illness caused by H1N1. In late October 2009, H1N1 illness was already widespread in 46 states. Only Connecticut, Hawaii, New Jersey, and South Carolina are reporting sporadic rather than widespread infection. (Reviewer-).

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Keywords: H1N1, Flu, Epidemiology

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The 2009 novel H1N1 influenza strain was alarming, not only because of its unusual timing (transmission began in off-peak season), but also because of an unusually high number of children and young adults who seemed to become severely ill. **2009 H1N1 Replaces Seasonal Strains:** As of late October 2009, the novel H1N1 influenza strain essentially has replaced seasonal flu infections. Most influenza isolates typed in the United States in the late summer and early fall of 2009 were H1N1. At that time, it remained unclear as to how long this would be true and whether expected seasonal strains (human H3N2 or human H1N1 from 2008) would rise to predominance in the coming February or March of 2010. My advice as of late October 2009 was that, if a patient had a clinical diagnosis of flu, he or she almost certainly had H1N1 flu. **2009 H1N1 Clinical Illness:** The clinical illness caused by the novel H1N1 influenza virus has been distributed across a broad spectrum similar to the regular seasonal flu. Fever and fatigue are the most common clinical findings, followed by various frequencies of myalgias, coryza, diarrhea, abdominal pain, and cough. Most patients infected with flu make a full, uneventful recovery, albeit with plenty of misery and missed work or missed school obligations. **2009 H1N1 & Poor Outcomes:** Although most patients infected with the H1N1 influenza virus will make a full recovery, some patients are at higher risk for poor outcomes. Some of these cases have not been previously considered to be in high-risk populations. A pair of papers from Mexico published in 2009 in *The New England Journal of Medicine* details the early experience with the epidemic in that country. One paper describes outcomes among >2000 patients with severe pneumonia reported to the Mexican Ministry of Health. The results of this study demonstrated that death rates were higher than in historical controls for patients aged 5 to 59 years. A second paper examined the experience of a single medical ICU in Mexico City. Eighteen cases of confirmed H1N1 pneumonia were described. Of those 18 patients, 13 were between the ages of 5 and 50 years. Most of the illnesses were severe; 10 patients required mechanical ventilation, and 7 of these died. **Reference 1:** Chowell, Bertozzi, et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. *N Engl J Med* 2009; 361 (August 13): 674-679. **Reference 2:** Perez-Padilla, de la Rosa-Zamboni, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 361 (August 13): 680-689. (Reviewer-).
Several possible risk factors associated with death due to the novel H1N1 influenza virus have been identified. These include pregnancy, obesity, synchronous presentation with *Staphylococcus aureus* pneumonia, and childhood.

As of late October 2009, young adults in the United States have borne a disproportionate and an unusually high burden of illness with the novel H1N1 influenza virus. The Centers for Disease Control and Prevention (CDC) estimates that there have been “many millions” of acute influenza cases. However, because we rarely test for and report cases anymore, this is indeed an estimate. The CDC has actually confirmed 22,080 cases of H1N1 flu among patients aged 5 to 24 years (case rate: 23 infections for every 100,000 people in that age range) and about 500 cases among patients aged >65 years (case rate: 1.3 per 100,000 population in that age range). This is a striking reversal of the usual epidemiology of flu. We strongly suspect that there have been >1000 deaths in the U.S. due to H1N1 as of late October 2009. Strictly speaking, the CDC has reported only 303 deaths, of which 82% have been among people aged <65 years, and 57% have been among patients aged 5 to 49 years. Pregnancy: Pregnancy is a risk factor associated with death due to influenza. At our Seattle medical center, a previously healthy woman in her third trimester of pregnancy was admitted with pneumonia, which rapidly progressed to acute respiratory distress syndrome, requiring prone ventilation with high positive end-expiratory pressures. The patient died shortly after an emergency C-section. The CDC’s *Morbidity and Mortality Weekly Report* in May 2009 detailed the cases of 3 pregnant women with H1N1, 1 of whom died (*MMWR* 2009: 58 [May 15]; 497-500). Similar cases have been reported in San Francisco. Obesity: A possible link between body weight and severe illness was also suggested by a subsequent *MMWR* issue describing 10 critically ill patients in Michigan, 9 of whom were obese (*MMWR* 2009: 58 [July 17]; 749-752). At the time of the report, 2 remained critically ill and 3 had died. Autopsies revealed bilateral severe hemorrhagic viral pneumonitis with interstitial inflammation and diffuse alveolar damage, as well as concurrent bilateral pulmonary emboli. Concurrent Pneumonia: The classical teaching has been that patients with influenza pneumonia may develop *Staphylococcus aureus* pneumonia as a sequel, usually when clinical improvement for flu is well under way. However, a disturbing trend observed with the novel H1N1 outbreak has been the synchronous presentation of influenza and *S aureus* pneumonia. These cases may be severe necrotizing coinfections requiring mechanical ventilation, and several cases have been fatal. Childhood: Children are heavily affected by this novel H1N1 virus, even more so than during typical epidemics. In the U.S., the CDC is investigating >80 suspected flu deaths among children. The death rate is approximately double the typical annual child death rate during most entire flu seasons. (Reviewer-).
With the outbreak of the novel H1N1 influenza virus, a very important prevention strategy is to practice diligent respiratory hygiene. Filter sneezes in disposable handkerchiefs or the crook of the elbow, then immediately clean hands with soap and water or an alcohol-based hand sanitizer. H1N1 flu is spread primarily via droplet nuclei. The central question is how health care workers should protect themselves against acquiring flu while on duty. **Droplet Controls:** The Infectious Disease Society of America, the Society of Hospital Epidemiologists of America, and the Association for Practitioners in Infection Control all agree: when caring for patients with suspected or proven flu (H1N1 or seasonal), protect yourself with diligent hand hygiene and wear gloves, a gown, eye protection, and a surgical mask. **N95 Masks:** One concern is that, in theory, influenza may also be transmitted by aerosolization, not just by droplet nuclei. Therefore, is an N95 mask superior to a regular surgical mask? N95 masks have been tested by the National Institute for Occupational Safety and Health, filter at least 95% of all particulate matter ≥0.3 µm in diameter, and are the same masks worn when caring for patients with active pulmonary tuberculosis. One study randomly assigned health care workers to either a surgical mask or an N95 mask. *(JAMA* 2009; 302 [November 4]: 1865-1871). Surgical masks were found to be noninferior to N95 masks in terms of protecting health care workers from influenza. However, investigators from Australia and China have described a yet-to-be published study in which health care workers were randomly assigned to wear either surgical masks, a fit-tested N95, or a plain N95 when caring for flu patients. Use of N95 masks was associated with a 75% decrease in the development of symptomatic flu. Based in large part on this study, the Centers for Disease Control and Prevention and the Institute of Medicine recommend use of N95 masks for health care workers when caring for flu patients. The Occupational Health and Safety Administration (OSHA) states that N95 masks should be worn when within 6 feet of flu patients. By OSHA rules, these masks should be discarded after each use. However, there are not enough N95 masks in the world to satisfy this requirement. If your supply of N95 masks starts to run low, one approach would be to use N95 masks for all influenza encounters but to wear surgical masks with eye guards on top of the N95 masks, and to swap out those surgical masks between encounters. (Reviewer-).
Among patients admitted to hospitals in China with seasonal flu, 30% continued to shed virus in their respiratory secretions beyond 7 days after fever resolution, even among those patients who had received antiviral medications.

During the 2009 novel H1N1 influenza outbreak, one of the major preventive strategies being taught to patients and health care workers alike is, “Stay home when you’re sick.” **Staying Home:** Physicians have a duty to care for their patients, and they often misinterpret this duty as an obligation to show up in the office or on the wards, regardless of how awful they feel. Yet, it is precisely this duty that mandates they protect their patients by staying away when sick. At the University of Washington Medicine, we have a very detailed coverage plan in case of health care worker illness, both for residents and faculty. A local residency program recently started its academic year with an orientation retreat for incoming interns. One participant had symptomatic H1N1 flu. Within about 1 week after the retreat, 19 of 33 interns were sick and had to be furloughed. The residency program already had a terrific contingency plan in place, so patient care was not significantly impacted. Please consider how a respiratory illness would affect you in your practice model. In my experience, patients are usually understanding and even grateful to know that their physician has the guts to reschedule due to a potentially transmissible illness. **Returning to Work:** When is it safe for health care workers to return to work after the onset of flu? We generally say that the general public (including school children) should reenter society only when they can control their nasal secretions and have been afebrile without use of antipyretics for at least 24 hours. However, the Centers for Disease Control and Prevention recommends that health care workers return to work at 7 days of afebrile status, simply because our patients tend to be so vulnerable to poor outcomes if we transmit our flu to them. For many hospitals and private practices, a week’s leave beyond fever resolution may seem impossible. If so, the second best option might be to consider allowing health care workers to return once afebrile for 24 hours, but requiring them to wear a surgical mask for the next week and allowing them to work only as long as they have enough stamina to do the work and the ability to control their nasal secretions. This sounds harsh, but consider a paper published by Lee and colleagues (J Infect Dis 2009; 200 [August 15]: 492-500). Among patients admitted to hospitals in China with seasonal flu, 30% continued to shed virus in their respiratory secretions beyond 7 days of fever resolution, even among those patients who had received antiviral medications. (Reviewer-).
The intramuscular seasonal flu vaccine can be given to children aged 6 months to 19 years, pregnant women, adults aged ≥50 years, and people who live in nursing homes and long-term care facilities.

(Card 1 of 2) Influenza vaccination is a key portion of the influenza prevention plan every year. Guidelines for seasonal flu are slightly different than those for novel H1N1 influenza. Both seasonal flu and H1N1 vaccines have live-attenuated intranasal and inactivated intramuscular versions, all of which are made by different companies with different amounts of thimerosal. **Seasonal Flu Vaccination:** This year’s seasonal flu vaccine mix is very similar to last year’s. The influenza A portions are the same; only the influenza B antigen is different. Nonetheless, because the durability of influenza A following vaccination may wane over time, indications for the 2009 seasonal flu vaccine remain the same as for 2008, regardless of whether patients were vaccinated in 2008. The Advisory Committee on Immunization Practices (ACIP) recommends vaccinating anyone who wants a vaccination and who does not have a contraindication. They also ask that patients who are at increased risk for poor outcomes with influenza infection be targeted for vaccination. **Intramuscular Vaccination:** The intramuscular seasonal flu vaccine should be given to the following people: children aged 6 months to 19 years; pregnant women; adults aged ≥50 years; people of any age with certain chronic medical conditions including asthma, neuromuscular diseases, and immunosuppression (HIV and cancer); people who live in nursing homes and long-term care facilities; people who live with or care for those at high risk of complications from flu (health care workers, household contacts), and household contacts of children aged <5 years, especially household contacts of children aged <6 months. **Contraindications:** Contraindications for the seasonal flu shot include severe allergy to chicken eggs; a Guillain-Barré outbreak within 6 weeks of a previous flu shot or some other severe vaccination reaction; or current illness with a fever. In some states, there may also be additional legal restrictions on whether pregnant patients can receive a certain vaccine containing a certain amount of thimerosal. (Reviewer-).
FluMist® is a live-attenuated intranasal vaccine for seasonal influenza, is safe because the vaccine has been cold-adapted, meaning that it reproduces only in the nasal epithelial cells and not in the lower respiratory tract.

(Card 2 of 2) Influenza vaccination is a key portion of the influenza prevention plan every year. Guidelines for vaccinating for the seasonal flu differ between the intramuscular vaccine and the live-attenuated intranasal vaccine (FluMist®). **Intranasal Vaccine:** FluMist contains the same antigens as the intramuscular vaccine. Its safety is due to the fact that the vaccine has been cold-adapted, meaning that it reproduces only in the nasal epithelial cells and not in the lower respiratory tract. Nonetheless, because it contains live-virus particles and because it is a newer product with a shorter track record, it has a narrower target population. This vaccine is indicated for healthy people aged 2 to 49 years. Age restrictions for FluMist are narrower than for the intramuscular vaccine, and the list of host factors is also more restrictive. **Contraindications:** Patients should not get live-attenuated FluMist if they have reactive airways disease, are allergic to chicken eggs, are at increased risk of influenza complications (such as pregnancy), have HIV infection, or recently had a stem cell transplant. Health care workers who care for these patients generally can and should be vaccinated with either FluMist or the intramuscular vaccine. **FluMist for Health Care Workers:** Among health care workers caring for severely immunocompromised patients in certain exotic, protected environments (a stem cell transplant recipient or a baby in the neonatal ICU), those receiving FluMist should be furloughed for 7 days after vaccination. Although this has never been shown to hurt anyone, there is a theoretical concern that the virus might be passed from the nose of the health care worker into the respiratory tract of those very high-risk patients. **Miscellaneous:** FluMist is a superb vaccine for children because it is highly efficacious and very well tolerated. Some patients develop a bit of rhinorrhea or a sore throat after FluMist, but it is generally mild and brief. (Reviewer-).
The vaccine for the novel H1N1 influenza virus has 2 key points. Like the seasonal flu vaccine, the H1N1 vaccine also has both injectable and intranasal forms. In addition, the H1N1 vaccine has the same indications and contraindications as the seasonal flu vaccine. However, all of these recommendations presuppose an available stockpile of vaccine. In late October 2009, we were experiencing a very significant delay in the delivery of a robust quantity of both the live-attenuated and the intramuscular H1N1 vaccines. As of October 22, 2009, only about 11 million doses of these vaccines had been distributed nationwide. Many more doses were on order, and we were told that they would be delivered soon. Until that stockpile of vaccine grows significantly, clinicians and public health officers are faced with a challenging set of decisions regarding who should get vaccinated. Priority List: All guidelines that I have seen, including those from the Centers for Disease Control and Prevention, continued to keep 5 groups of patients at the top of the priority list. These groups included pregnant women, household and caregiver contacts of children aged <6 months, health care and emergency services personnel, individuals aged 6 months to 24 years, and individuals aged 25 to 64 years who had certain chronic medical conditions associated with high risk of complications (cancer, immunosuppression, etc). Others: All other patients should be vaccinated for novel H1N1 as well, including patients aged ≥65 years. However, because the relatively older crowd is somewhat protected against acquiring severe H1N1 flu, they should wait until the people at the top of the priority lists have consumed the early shipments of vaccine. Health Care Workers: Clearly, influenza vaccinations are safe, well tolerated, and significantly effective (although not entirely effective). Yet, according to position statements by the Infectious Disease Society of America, only about 2 of every 5 eligible health care workers undergo immunization annually. Help us improve this track record. Undergo immunization as soon as it is available in your community, and encourage your colleagues to do the same. (Reviewer-).
To prevent H1N1 influenza, offering postexposure prophylaxis, when appropriate, is a good preventive strategy. However, antiviral use does incur a potential price in terms of accelerating drug resistance.

During the 2009 outbreak of novel H1N1 influenza, offering postexposure prophylaxis, when appropriate, is one of several good preventive strategies. The risk of illness depends in some part on the type of exposure. An exposure is defined as coming within 6 feet of a symptomatic patient without wearing appropriate personal protective equipment. To help decide who should receive prophylaxis, ask the following questions. **Was the Exposure Real?** Has a medical doctor assessed the index patient and diagnosed flu based at least on clinical grounds? Generally, flu becomes a concern if the source patient has fever and is systemically ill. In addition, the exposed patient should have come within 6 feet of an infected individual. If these criteria are not met, then there is no need for prophylaxis. **When Was the Exposure? How Is the Exposed Patient Feeling?** If the exposure was >48 hours before presentation and if the exposed patient is feeling fine, then benefits of prophylaxis are very minimal. Instead, counsel this patient to contact you if he or she develops flu-like symptoms so that treatment can be started immediately. **Is the Exposed Patient at High Risk of Flu Complications?** These high-risk patients are the same individuals we target for influenza vaccination. For patients who are not at high risk for flu complications but are worried about it, prophylaxis is not required. However, for patients who are in a high-risk group, talk with them and select 1 of 2 courses. Either offer them prophylaxis on the spot or ask them to remain vigilant for signs and symptoms of flu and have them call you immediately if those symptoms should arise. **Judgment Calls:** When it comes to flu prophylaxis, use your judgment and rely on the relationship that you already have with the patient to craft an optimal plan. Some high-risk patients really want the recommended postexposure prophylaxis, which is fine. However, antiviral use does incur a potential price in terms of accelerating drug resistance. Nonetheless, I think that we should offer postexposure prophylaxis, especially when it is indicated for high-risk patients with a real exposure. **Drug Options:** If you offer prophylaxis, you can use either oseltamivir (75 mg by mouth once a day for 10 days in patients with normal renal function) or zanamivir (1 inhalation once a day for 10 days). The only contraindication to zanamivir is if the patient has reactive airway disease or if the patient cannot use the inhalation device. With oseltamivir, nausea may develop in some patients. This is temporary and generally mild. Most cases should respond to antinausea medication. (Reviewer-).
Many providers use the rapid influenza test to help test for influenza infection. However, the test was not developed with H1N1 in mind, so very frequently the results are falsely negative.

In 2009, the diagnosis of influenza remains a clinical diagnosis for most cases. A diagnosis of influenza is considered when the patient has a febrile illness with some combination of prostration, coryza, myalgias, cough, and diarrhea. This is true for both seasonal flu and H1N1 flu. H1N1 infection has no special clinical features that rapidly distinguish it from other influenza infections: no rash, no enanthem, and no splenomegaly. As of late October 2009, H1N1 is the predominant form of flu being spread in the community.

**Lab Tests:** Routine lab testing results are not specific for H1N1. White blood cell count, lactate dehydrogenase, and serum sodium levels do not offer reliable hints for the flu. Like all clinically important viruses, influenza is too small to be seen by light microscopy. **Rapid Flu Test:** It is possible to test specifically for influenza infection. For many providers, the test of choice has been the rapid influenza test because it is relatively affordable and can be performed at point of care. A positive result on a rapid flu test can be helpful in distinguishing influenza from other respiratory viral infections. However, the rapid flu test has a poor negative-predictive value. This test was not developed with H1N1 in mind, so very frequently we will see falsely negative results on the rapid flu test. **Recommended Tests & Specimens:** Two major testing options are recommended for the 2009 flu season: the direct fluorescent antibody test with viral culture backup or a reverse transcriptase polymerase chain reaction assay. Both testing options are run directly on respiratory specimens (nasopharyngeal wash or swab). Confirm with your local virology lab which specimen they prefer. If a wash is acceptable, have the patient tilt his chin up slightly and hold his breath, and then squirt about 10 mL of preservative-free normal saline into a nostril. The patient then leans forward, and the saline runs out of the nose and into a specimen cup. For a swab, insert a synthetic tip swab (not a cotton swab) into the nostril until you meet gentle resistance. Then twirl it a few times before removing it, and stick it into a tube with viral transport media. Most patients tend to ask for the swab rather than the wash. However, the swab is actually tolerated less well and has a much higher rate of lab rejection due to low epithelial cell counts. While performing both these procedures, the health care worker should be wearing proper personal protective equipment. (Reviewer-).

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The 2 major testing options recommended for the 2009 flu season are the direct fluorescent antibody test with viral culture backup and the reverse transcriptase polymerase chain reaction assay.

(Card 2 of 2) The testing options for influenza are few. However, a clinical diagnosis is almost always sufficient, so testing is only rarely required. Nonetheless, the 2 major testing options recommended for the 2009 flu season are (1) the direct fluorescent antibody (DFA) test with viral culture backup and (2) the reverse transcriptase polymerase chain reaction (RT-PCR) assay. **DFA Testing:** Most labs offer a DFA with culture rather than the RT-PCR because of operator experience, cost, and lab setup. The negative- and positive-predictive values of DFA with culture are far superior to those of the rapid flu test. However, if the DFA is negative, then subsequent culture results can take days to come back. **RT-PCR Testing:** In many cases, DFA and culture are negative, but the RT-PCR test is positive. RT-PCR is a great test based on its high sensitivity, rapid turnaround, and ability to type the flu if the lab offers type-specific primer. However, RT-PCR assays are not approved by the CLIA, so some labs are reluctant to offer them because of the required expertise with molecular testing. At the University of Washington, we rely on a homemade RT-PCR assay. We batch these tests every day at 10:00 AM, and the results come back no later than 6:00 PM the same day. **When to Submit Tests and Treat:** A DFA or RT-PCR test should be submitted when the patient is sick enough to be hospitalized or the patient will remain ambulatory and is at high risk for influenza complications and the clinical diagnosis is unclear. The results of both the DFA and RT-PCR tests will take time. However, for flu treatment to be beneficial, it must be initiated rapidly. Therefore, treat the patient on clinical grounds and start medications right away, even before the test comes back. Antiviral drugs can be discontinued if the test comes back negative. Or, if the suspicion for flu remains high and the patient is at high risk for poor outcomes, you may elect to continue treating for flu even with negative test results. Remember, no test has a perfect negative-predictive value. **Additional Testing:** For all patients who are seriously ill with suspected flu pneumonia, test aggressively for respiratory copathogens, especially for *Staphylococcus aureus*. In these critically ill patients, a deep pulmonary secretion specimen, such as bronchoalveolar lavage fluid or deep endobronchial suction material, should be examined by Gram stain and sent for culture. Poor outcomes happen even in flu pneumonia without bacterial coinfection. However, when copathogens are present, they must be targeted for treatment. (Reviewer-).
Antiviral treatment can be started immediately for patients who are at high risk for flu complications and are symptomatic at presentation, even if they present beyond 48 hours after symptom onset.

Most patients will recover from the flu on their own. For patients with mild illness, conservative therapy with rest, sensible hydration, and antipyretics and analgesics (acetaminophen or ibuprofen) as needed are a good choice. Treatment doses of aspirin should be avoided among flu patients because of the concern for Reye syndrome, causing more harm than benefit. However, doses of cardioprotective baby aspirin can be continued in flu patients. **Patient Selection:** Antiviral medications should be started immediately for patients with suspected flu if they are at high risk for complications of flu and poor outcomes. These patients include those presenting with severe flu, especially lower respiratory tract disease by exam or chest x-ray; patients who are sick enough to be hospitalized; women who are pregnant or up to 2 weeks postpartum; immunosuppressed patients, including those with HIV or cancer or taking immunosuppressive medications; patients with chronic lung disease; children aged <2 years; adults aged >65 years; and children or adolescents aged <19 years who are taking chronic aspirin for other reasons. For these patients, initiate therapy as soon as possible.

**When Is It Too Late to Start Treatment?** The greatest benefit to flu medications comes when the drug is started within 48 hours of symptom onset. For that reason, patients with mild illness and no risk for complications who may present beyond 48 hours of symptom onset will obtain a very small (if any) benefit from starting oseltamivir or zanamivir. Therefore, these patients generally should not be offered treatment. However, for patients who are at high risk for complications and who are still symptomatic when they present, antivirals can be started immediately, even if it is beyond 48 hours since symptom onset. Anyone sick enough with flu to be hospitalized should be put on treatment right away, regardless of how long they have been sick. (Reviewer-).
As of late October 2009, during the novel H1N1 influenza outbreak, oseltamivir and zanamivir are highly effective against virtually all of the H1N1 circulating in the community. Antiviral Resistance: In the Morbidity and Mortality Weekly Report published by the Centers for Disease Control and Prevention, there are a few case reports on patients who developed oseltamivir resistance while taking the drug. In at least 2 of these cases, resistance happened among severely immunocompromised hematopoietic stem cell transplant recipients with symptomatic flu who were treated with oseltamivir for weeks because of persistent symptoms and persistent viral shedding proven by testing. In several other cases, otherwise healthy school-age children at summer camp were taking oseltamivir prophylaxis because some of their fellow campers were ill with the flu, and these kids developed flu despite use of antiviral prophylaxis because there was so much intense oseltamivir use among their close contacts. Presumably, the same phenomenon could happen with zanamivir, although the neuraminidase resistance mutations that are described so far seem to be specific for oseltamivir rather than zanamivir. Therefore, I believe we have reason to use both of these drugs prudently. Old Antiviral Medications: Other classes of antiinfluenza medications used in the past are not reliably effective against H1N1, including adamantine, rimantadine, and amantadine. At this time, we do not recommend using rimantadine or amantadine for treating influenza during the 2009 flu season. However, as the season progresses, that situation may change. Effective Antiviral Medications: H1N1 remains very susceptible to both oseltamivir and zanamivir, and both of these drugs are well tolerated. Standard dosing is appropriate for virtually all patients, although higher dosing can be considered for the few critically ill patients you may encounter. Lack of an IV form of these medicines has been a problem in these circumstances. Fortunately, we now have access to a new drug, Peramivir IV. This IV drug is a neuraminidase inhibitor and is on the short list of drugs that treat infection caused by the H1N1 virus. (Reviewer-.)

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In your medical practice, you may encounter numerous questions regarding the influenza vaccine. Being prepared for these questions will only enhance your patients’ confidence in the safety of the influenza vaccine. **Question 1:** If I get the seasonal flu shot, am I more likely to catch swine flu? **Answer 1:** There is an unpublished but much publicized study in Canada which reportedly indicates that patients who underwent influenza vaccination last year are about twice as likely to acquire H1N1 infection this year compared with those who did not get the vaccine. However, these unpublished results have not been peer reviewed, and nothing like this has been confirmed in the United States, Britain, Australia, or anywhere else. Therefore, until more information comes out, I would simply ignore this report and reassure patients that they should undergo vaccination for seasonal and H1N1 flu as appropriate. **Question 2:** Does the swine flu vaccine cause Guillain-Barré syndrome? **Answer 2:** In 1976, which was the last year that a so-called swine flu widely circulated in the United States, a small number of vaccine recipients were diagnosed subsequently with Guillain-Barré. Whether this was causally related to the vaccine has never been fully established, but reasonable estimates state that the increased risk of Guillain-Barré among vaccine recipients in 1976 was about 1 added case per 100,000 vaccine recipients. Subsequently, intensive surveillance efforts have shown that the excess risk of modern flu vaccines is no more than 1 case per 1,000,000 vaccine recipients. In fact, a paper published in the *American Journal of Epidemiology* in 2009 analyzed 775 episodes of Guillain-Barré in Great Britain. The relative incidence of Guillain-Barré within 90 days of influenza vaccination was 0.76. By comparison, the relative incidence of Guillain-Barré within 90 days of an influenza-like illness was 7.35. This finding suggests that the flu infection, not the flu shot, is associated with a relatively low risk of Guillain-Barré. In fact, taken at face value, an effective flu vaccine seems to offer about a 10-fold protection against Guillain-Barré. Mainly for legal reasons, the Food and Drug Administration’s rules state that a prior episode of Guillain-Barré within 6 weeks of vaccination is currently considered to be a contraindication for any further flu vaccinations. **Reference:** Stowe, Andrews, et al. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenza-like illness using the United Kingdom General Practice Research Database. *Am J Epidemiol* 2009; 169 (February 1): 382-388. (Reviewer-).
As you recommend influenza vaccination to your patients, you will often be questioned about the necessity of the vaccine and about which form (intranasal versus intramuscular) is the most effective. How you answer these questions may often determine if the patient will elect to receive adequate influenza protection for the year. **Question 1:** If I had the swine flu last year, do I really need the shot this year? **Answer 1:** Guidelines from the Centers for Disease Control and Prevention (CDC) state that, if your patient has had a laboratory-proven case of H1N1 flu as shown by a positive reverse transcriptase polymerase chain reaction assay, then there is no need to vaccinate that patient again. The illness itself is a huge antigenic challenge. It confers a durable immunity to future flu infections with H1N1. However, a prior clinical illness that has not been proven to be H1N1 should not affect our decision to vaccinate that patient. It is unclear how many patients who believe that they have had the flu are actually correct. There is no readily available, reliable, specific serological test to tell who has been exposed to what antigens. If such a test existed, it would probably cost more than the vaccine. The vaccine is safe and well tolerated, covers multiple strains in the case of seasonal flu, covers the most important strain in the case of H1N1, and is a boost to the immune system. The bottom line is, yes, we recommend vaccinating regardless of the patient’s perceived infection history. **Question 2:** Which is better, the nasal or the intramuscular form of the vaccination? **Answer 2:** Both forms of the influenza vaccine work well, and either one is much better than getting nothing at all. However, according to a paper published in 2009 (*JAMA* 2009; 301 [March 2]: 945-953), adults who received the intramuscular vaccine were 2 times better protected against acquiring flu as those who received the intranasal vaccine. This finding was highly unexpected. It is actually the opposite of our current thinking about influenza vaccine efficacy in children, where the nasal vaccine seems to be slightly more effective than the intramuscular form. But again, this is a relatively fine point. I think you should vaccinate with whatever the patient will accept and, frankly, with whatever you can get your hands on. (Reviewer-).

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Keywords: Influenza Vaccination, Intranasal vs Intramuscular Efficacy

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Most patients should do whatever they can to avoid catching the flu, including receiving influenza vaccinations regardless of the season. Remember, H1N1 outbreaks are being reported during traditional off-peak seasons.

Many rumors exist regarding the safety of influenza vaccinations. In addition, the popular media tend to give out conflicting information regarding influenza vaccines. This means that patients will come to you with questions about vaccinations. The better prepared you are for their questions, the more confident your patients will be with your answers. Question 1: Some patients in March, April, or even May of 2010 may ask you whether getting vaccinated is worth the effort at that time of the year. They are seeing you late in the season when flu outbreaks are typically done. So is there really any need to get vaccinated? Answer 1: They may be right, if they are lucky. Even seasonal flu can peak in March in some regions of the United States. However, the bigger point is that the H1N1 virus has demonstrated that the flu no longer watches the calendar as reliably as the seasonal flu has in the past. We simply do not know how or where it may surge back to life. Therefore, these patients should not worry so much about epidemiology. Tell your patients that they should focus on whether they want to get the flu. How would acquiring a case of influenza impact their life, their school, their income, and their childcare duties? When you state the problem this way, most patients do whatever they can to avoid catching the flu, which includes receiving influenza vaccinations, regardless of the time of year. Question 2: Some patients have heard that oseltamivir can make an individual crazy or commit suicide. Is this true? Answer 2: This is a real question, and the answer is “no.” Reports from Japan in 2008 actually suggested that adolescents receiving oseltamivir for treatment of flu had an unexpectedly high incidence of psychosis, psychotic break, and self-harm, including suicide attempts. However, subsequent investigations into this topic did not substantiate a clear link with the drug as the cause of these clinical findings. The oseltamivir package insert discusses this topic and advises caution when dosing adolescents who have an underlying case of psychosis. However, my interpretation of this cautionary note is that it is more of a legal than a scientific disclaimer. (Reviewer-).

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Keywords: Influenza Vaccination, Off-Season Vaccination, Oseltamivir, Self-Harm

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Pregnant women should get an influenza vaccination. The vaccine injection is both safe and highly effective in pregnancy. It does not cause the flu in the mother, and no link has been found between autism and the vaccine.

Women who are pregnant frequently have many concerns about receiving the influenza vaccine. They are concerned about whether they should actually receive the influenza vaccination in their condition. They may also fear catching a case of the flu from the shot. One of their big fears is that their baby will develop autism resulting from the mother being vaccinated. **Pregnancy & Vaccination:** Pregnant women should get an influenza vaccination. They are at an unusually high risk for poor outcomes with H1N1 flu. Although we do not understand exactly why this is true, we do know that it actually does happen. The good news is that the influenza vaccine injection is both safe and highly effective in pregnancy. It cannot cause the flu. **Vaccination & Autism:** Despite an exhaustive search by scientists around the world, no link has been established between thimerosal (a mercury-containing preservative in the vaccine) and autism. A series of biological and epidemiological studies have demonstrated that this fear of autism is unfounded. The American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the Infectious Disease Society of America urge pregnant women to get vaccinated as soon as possible. On a personal note, a child in my own family has autism, and I always insist that this child and the whole family get vaccinated for flu each year. **Intranasal Vaccine:** The nasal FluMist® vaccine is probably safe in pregnant women, but it has not been studied in this population. Therefore, FluMist is relatively contraindicated in pregnant women. (Reviewer-).
The 2009 H1N1 influenza vaccine has been made with the same technology used to manufacture the seasonal flu vaccine for many years. To date, the vaccine has no reported unusual or severe adverse events.

One of the rumors circulating about the H1N1 influenza vaccination is that the vaccine is not safe because it has not yet been tested thoroughly. Because of this, some patients will tell you that they are not interested in receiving the vaccine until it is proven safe. **Fact:** The 2009 H1N1 flu shot was brought to market in record time, which is a huge triumph for medical science. Undoubtedly, it will prevent many illnesses, and it has been made with the same technology used for seasonal flu vaccine for many years. During the vaccine’s manufacturing process, the H1N1 virus is grown in chicken eggs, and when the chicken eggs are purified, the virus is killed and moved into the vaccine vehicle. Clinical safety trials have been performed in the H1N1 vaccine, including at the University of Washington School of Medicine in Seattle. As of late October 2009, there are no reported unusual or severe adverse events associated with the vaccine. In the future, we possibly may find some reports of very rare adverse events, but by definition, we do not know if this will happen. In general, every year, we never know if that will happen. What we do know is that the risk of flu is very real, and that there is every reason to think that the H1N1 vaccine will be totally safe. **Safety Monitoring:** In August 2009, the Centers for Disease Control and Prevention (CDC) stated that vaccine safety monitoring is a shared responsibility among the federal government, state and local health departments, vaccine manufacturers, health care providers, and other partners. They established the Vaccine Adverse Event Reporting System as a frontline monitoring system for collecting and analyzing voluntary reports of adverse events following the 2009 H1N1 vaccination. The CDC will also monitor adverse events using the Vaccine Safety Datalink, which is a collaborative effort between the CDC and 8 large managed care organizations representing approximately 3% of the U.S. population. Many other safety-monitoring measures are at work. (Reviewer-).