WISCONSIN MEDICAL JOURNAL

Seasonal Influenza in Primary Care Settings: Review for Primary Care Physicians

Jonathan L. Temte, MD, PhD; Jacob P. Prunuske, MD, MSPH

ABSTRACT

Context: Influenza is a common and significant respiratory pathogen in primary medical care. Better understanding of influenza epidemiology, clinical characteristics, prevention, and management is essential for effective ambulatory care.

Evidence Acquisition: Review of the current literature was performed through PubMed queries and based on the authors' background and experience with influenza. In addition, summary data were presented from existing surveillance of influenza in Wisconsin.

Results: Seasonal influenza presents in annual epidemics with significant features of fever and cough. Prevention can be achieved through avoidance, influenza vaccine, and chemoprophylaxis. Diagnoses can be made on clinical grounds when appropriately supported by public health surveillance. Other diagnostic methods have limited use in primary care. Antiviral medications can have significant effects on illness course if started early, but may be limited by resistance.

Conclusions: Influenza is commonly prevented, diagnosed, and treated in the primary care arena. A combined approach to influenza response requires background knowledge on influenza epidemiology, prevention, diagnosis, and management, coupled with up-to-date information based on public health surveillance.

INTRODUCTION

Influenza is a significant and ubiquitous respiratory pathogen in humans. Despite great familiarity with this common infection, influenza never fails to surprise even the most seasoned observer. Primary care clinicians are on the front line for implementing influenza prevention and control efforts. An understanding of the basic concepts[1] will enhance the primary care physician's ability to better anticipate, provide prophylaxis against, and respond to seasonal and pandemic influenza, thereby contributing to public health efforts.

Author Affiliations: University of Wisconsin School of Medicine and Public Health, Madison, Wis.
Corresponding Author: Jonathan L. Temte, MD, PhD, University of Wisconsin School of Medicine and Public Health, Madison, WI; phone 608.263.3111; fax 608.263.6663; e-mail jon.temte@fammed.wisc.edu.

BASIC EPIDEMIOLOGY OF INFLUENZA

Influenza A and B viruses consist of 8 single strands of RNA enveloped in a lipid/glycolprotein membrane studded with 2 dominant and antigenic proteins.[2] Hemaglutinin (H), with 16 known antigenic types in human influenza A, allows attachment of the virus to host respiratory mucosa. Neuraminidase (N), with 9 antigenic types, allows the budding and separation of newly formed influenza viruses from the host cell.

Antigenic Drift

Influenza A viruses are prone to mutation.[3,4] Conversely, the genome of influenza B is more highly conserved. Mutations in the genes coding for either H or N proteins can alter their antigenic character. Slight to significant changes occur in surface antigens of influenza A viruses over time making antibodies formed during past infection or prior immunization for a given H or N antigen less effective. As a consequence, antigenic drift reduces previously acquired immunity, thus necessitating annual vaccination to adequately protect against circulating influenza viruses.

Antigenic Shift

Antigenic shift occurs with reassortment of 2 or more influenza A genomes within a host cell that is simultaneously infected.[3] This shift can produce novel combinations of H and N, along with genetic material that can confer significant virulence and pathogenicity. A significant antigenic shift is accompanied by very low rates of naturally occurring immunity and sets the stage for pandemic spread of influenza.

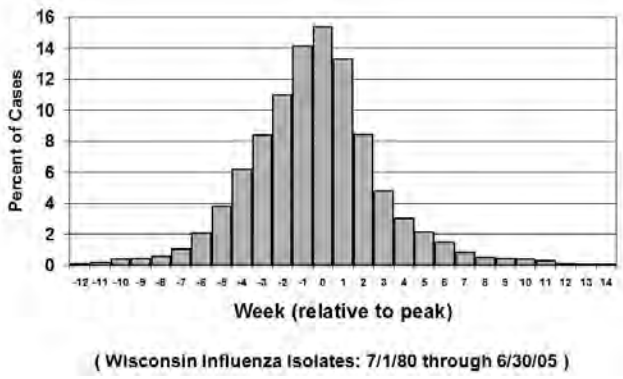

Figure 1. The shape of a typical influenza epidemic curve based on the 25-year average of influenza A in Wisconsin.

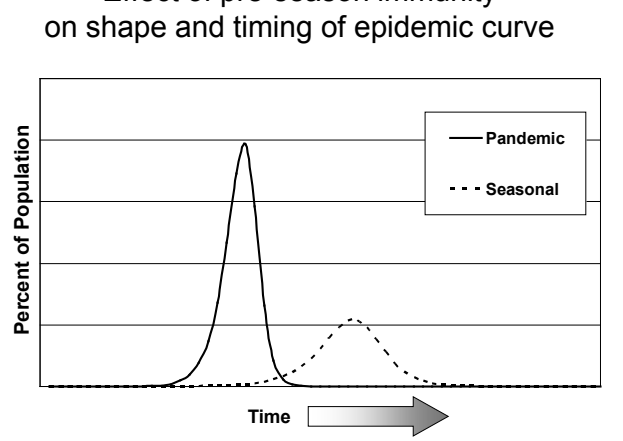

Figure 2. The theoretical effect of altering population immunity on the shape of the epidemic curve in the subsequent influenza season. (Unpublished model based on Wisconsin influenza A data.)

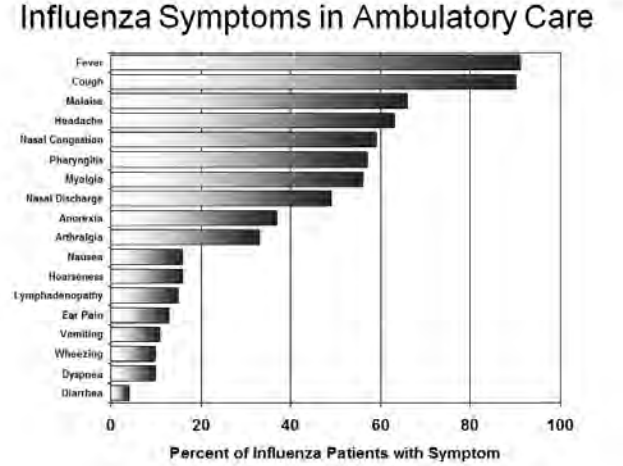

Figure 3. Symptoms associated with influenza A and B infections within primary care populations. (Unpublished data from the Wisconsin State Laboratory of Hygiene.)

Antigenic Gift

Influenza viruses have reservoirs within a wide variety of other mammalian and avian hosts, including domesticated animals such as swine and poultry. On occasion, influenza will jump species and produce significant human infection such as the smoldering avian influenza A(H5N1) zoonoses occurring in southeast Asia.[5]

Transmission Characteristics

Like most respiratory viruses, influenza is spread from person to person through respiratory droplets.[3,6] An individual with influenza can shed virus from 1 day before to 5-6 days after symptom onset. Peak shedding occurs with the peak of symptoms during day 2 or 3 of clinical illness.[7] Prolonged shedding, however, can occur in patients hospitalized with severe disease.[8]

Seasonality and Timing

Influenza is a highly seasonal virus with most transmission limited to late fall and winter across temperate latitudes.[3,6] Cool, dry air facilitates transmission in laboratory studies.[9] This results in peak influenza activity in late January and early February in the United States.[10] On average, initial cases are detected 12 weeks prior to the peak and continue for 14 weeks following the peak. An estimated 86% of cases occur during a 9-week period within a given locality (Figure 1). High levels of surveillance, however, such as during the 2009 pandemic of influenza A (H1N1), can detect low levels of community transmission of non-pandemic influenza viruses even during summer months.[11]

Pandemics of Influenza

Antigenic shifts or "gifts" (zoonoses) can result in the introduction of novel antigenic combinations for which there is no pre-existing immunity (Figure 2). Widespread and explosive outbreaks can occur at unexpected times of the year, circling the globe in a matter of weeks.[12,13]

CLINICAL CONSEQUENCES OF INFLUENZA

Pathogenesis

After an incubation period averaging 1.4 days (range: 1-3 days),[14] desquamation of infected respiratory mucosa and ciliated cells initiates early local symptoms. Interluekin-6 and interferon-α levels peak at 2 days correlating with mucus production, temperature, and symptom scores.[15] This release of inflammatory cytokines results in the sudden onset of the pronounced malaise and fever characteristic of influenza infection.

Symptoms

Influenza-like illness (ILI) is defined as fever accompanied by a cough and/or sore throat.[10] Influenza

symptoms are well defined and include fever, cough, malaise, headache, nasal congestion, sore throat, and myalgia (Figure 3).[3,6,16] The positive predictive value of various clinical signs and symptoms generally support the use of fever with cough as an indicator of influenza illness when circulation has been confirmed in the community.[17,18]

Consequences

Most individuals have mild to moderate symptoms and either continue with their daily activities or return to these after a short absence. Nevertheless, uncomplicated influenza infection can be associated with prolonged peripheral airway dysfunction and hyper-reactivity lasting up to 7 weeks.[19] Emerging from numerous mild to moderate cases in the community are the estimated 226,000 annual influenza-related hospitalizations and 36,000 annual deaths.[10] While attack rates are highest for older children, adolescents, and young adults, hospitalization and case fatality rates are highest for infants, young children, and older adults.[10] The annual medical and indirect costs have been estimated at $10.4 billion and $76.7 billion, respectively.[20]

PREVENTION OF INFLUENZA

Prevention is the key in managing influenza. Prevention can generally be accomplished in 3 ways: avoidance, vaccination, and chemoprophylaxis.

Avoidance

Avoiding exposure to respiratory droplets prevents infection (Box 1). Because influenza can survive on dry inanimate surfaces for 1-2 days,[21] hand washing and the use of facemasks limit nosocomial spread by physicians and other health care workers (HCW) who often continue to work when infected with influenza.[22] HCWs with influenza symptoms, however, should simply refrain from working since they interact with individuals at high risk for influenza complication. A recent randomized, controlled study detected no differences in the protection offered by simple surgical masks and N-95 respirators in hospital settings.[23] Either soap and water or alcohol-based sanitizers are effective; antibacterial soaps are no more effective than standard products.[24]

Immunization

Vaccines are developed annually in anticipation of the 3 strains of influenza [A(H1), A(H3) and B] that will most likely be in circulation during the coming influenza season.[10] In addition, monovalent vaccines may be produced in response to pandemic threats such

Box 1. Tips for Avoiding Influenza

- Stay at least 3-6 feet away from sick people, farther if possible.
- Avoid touching your eyes, nose, or mouth, especially without washing your hands first.
- Stay away from crowded or confined spaces such as malls, subways, airplanes, or buses during influenza peaks.
- Avoid sharing food, drinking glasses, towels, or other personal care items with others.
- In the doctor's office, keep your distance from other patients who may be ill.
- Use a facemask to reduce contact with respiratory droplets.
- Use a facemask to reduce spreading influenza if you are ill.
- Use a humidifier to increase humidity as influenza virus thrives in dry air.

Additional Tips for Heath Care Workers

- Wash hands frequently.
- Get vaccinated as early as possible each year.
- Stay home if you have an influenza-like illness.

Box 2. Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for the following individuals using an appropriate vaccine[10]

- Adults who want to reduce their risk of becoming ill with influenza or transmitting influenza to others
- All children 6 months to 18 years of age
- All adults ≥50 years of age
- Children and adolescents 6 months to 18 years of age receiving long-term aspirin therapy who might therefore be at risk for Reyes syndrome after influenza infection
- Women who will be pregnant during the influenza season
- Children, adolescents, and adults with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus)
- Children, adolescents, and adults who are immunosuppressed, including those receiving immunosuppressive drugs and those with HIV infection
- Children, adolescents, and adults with any condition that can compromise respiratory function or handling of respiratory secretions or increase the risk for aspiration (eg, cognitive dysfunction, spinal cord injuries, seizure disorders, other neuromuscular disorders)
- Children, adolescents, or adults who are residents of nursing homes and other chronic-care facilities
- Health care workers
- Household contacts and caregivers of children <5 years of age (especially contacts of children <6 months of age)
- Household contacts and caregivers of adults ≥50 years of age
- Household contacts and caregivers of individuals with medical conditions that put them at high risk for severe influenza complications

as for influenza A (H5N1) and influenza A (H1N1). Vaccination is now universally recommended by the Advisory Committee on Immunization Practices[25] and is especially important people at high risk for severe illness, hospitalization, or death from influenza, as well as their contacts and health professionals who can transmit illness to others (Box 2). Children aged 6 months to 8 years should receive 2 doses of vaccine, separated by 4 weeks, if they have not been vaccinated previously at any time or if, during the preceding year, they received a first and only influenza vaccine dose.

Influenza vaccination prevents death, hospitalizations, and physician visits in high-risk patients.[26] It is effective in elderly populations when the vaccine is well matched to the circulating influenza strains.[27] Vaccine reduces influenza-like illness, pneumonia, hospital admission, and influenza or pneumonia-related deaths in nursing home patients, and reduces the risk of hospitalization for influenza or pneumonia and risk of death among community-dwelling elderly persons. Vaccinating physicians and staff who provide care to elderly patients in nursing homes may also reduce nursing home resident mortality from pneumonia and all cause death.[28] Vaccine induced immunity persists in elderly, supporting early vaccination timing.[29]

In healthy adults, influenza vaccine reduces influenza and reduces work absence.[30] Vaccination of pregnant women decreases respiratory illness in the mother and reduces influenza in infants during the first 6 months of life.[31] Influenza vaccination of children in daycare or school may reduce morbidity in children and household contacts.[32,33] Live attenuated influenza vaccine appears to be more effective than the trivalent inactivated vaccine in preventing influenza in children.[34,35]

Chemoprophylaxis

Chemoprophylaxis is an option for patients who have either not been vaccinated or have had exposure to influenza in the 2 weeks following vaccination. Prophylaxis should be continued for at least 10 to 14 days following exposure in home settings and at least 1 week past the end of an institutional outbreak.[36]

The adamantine antivirals (amantadine and rimantadine) are active against influenza A; however, the Centers for Disease Control and Prevention (CDC) has advised not using adamantanes due to widespread resistance in A(H3) viruses.[37] Adverse effects with adamantanes include insomnia, light-headedness, nervousness, difficulty concentrating, delirium, hallucinations, and seizures, but are less common with rimantadine.

The neuraminidase inhibitors (oseltamivir and zanamivir) are generally effective against influenza A and B and may be more effective than the adamantanes in preventing influenza, but resistance patterns need to be kept in mind.[38] Adverse effects of oseltamivir include nausea, vomiting, and headache, while zanamivir is associated with nausea, vomiting, diarrhea, headache, respiratory tract irritation, and infection. Oseltamivir is FDA approved for children ≥1 year; reports of an association with adverse behavioral complications in children[39] have not confirmed in large cohort studies.[40,41] In the 2008-2009 season, high resistance to oseltamivir in seasonal A(H1) viruses emerged.[42] Zanamavir is FDA approved for children at least 5 years of age but is not recommended for patients with underlying airway disease. Oseltamivir, rimantadine, and amantadine doses must be adjusted for renal function.

CLINICAL MANAGEMENT OF INFLUENZA

Successful management of patients presenting with ILI depends on the clinician's situational awareness, diagnostic approach, advice for supportive measures, and judicious use of antiviral medications.

Awareness

Perhaps the greatest impediment to the appropriate management of influenza is the failure to recognize this common pathogen as a primary cause of fever and cough. This is evidenced by the 86-fold range in state-by-state estimates of H1N1 incidence during 2009.[43] The key is awareness of community patterns of disease. Excellent surveillance information is available from the CDC (FluView: www.cdc.gov/flu/weekly), many state and local public health departments, and novel tools such as Google FluTrends (www.google.org/flutrends).

Diagnosis

Diagnosis can be made on clinical grounds or through laboratory testing. Fever with cough in adults and children—when influenza is circulating in the community—is highly suggestive of influenza infection with a positive predictive value of 80%.[17,18,44] Laboratory approaches include rapid antigen tests for influenza (RATi), direct fluorescent antibody testing (DFA), polymerase chain reaction (PCR), and culture. Of these, only RATi are applicable to the time constraints of ambulatory care. In a recent comparative study, 6 commercially available RATi had sensitivities of 67% to 71% for influenza A and 30% for influenza B.[45] Specificities were uniformly high. Sensitivity, however, declines substantially with declining levels of virus in the respiratory mucosa[46] indicating the importance of timing specimen collection relative to the course of illness.

Table 1. Antiviral Dosing for Prophylaxis and Treatment of Influenza

Antiviral Agent		Age Group (years) 1-6	7-9	10-12	13-64	65 and Older
Zanamivir[a]	Treatment, influenza A and B	N/A[b]	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	Chemoprophylaxis, influenza A and B	**Ages 1-4** N/A	**Ages 5-9** 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir	Treatment[b], influenza A and B	Dose varies by child's weight[c]	Dose varies by child's weight[c]	Dose varies by child's weight[c]	75 mg twice daily	75 mg twice daily
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight[d]	Dose varies by child's weight[d]	Dose varies by child's weight[d]	75 mg/day	75 mg/day
Amantadine[e]	Treatment, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses[f]	5 mg/kg body weight/day up to 150 mg in 2 divided doses[f]	100 mg twice daily[g]	100 mg twice daily	≤100 mg/day
	Prophylaxis, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses[f]	5 mg/kg body weight/day up to 150 mg in 2 divided doses[f]	100 mg twice daily[g]	100 mg twice daily[c]	≤100 mg/day
Rimantadine[h]	Treatment,[i] influenza A	N/A[j]	N/A	N/A	100 mg twice daily[g,k]	100 mg/day
	Prophylaxis, influenza A	5 mg/kg body body weight/day up to 150 mg in 2 divided doses[f]	5 mg/kg body body weight/day up to 150 mg in 2 divided doses[f]	100 mg twice daily[g]	100 mg twice daily[c]	100 mg/day[l]
Duration of Treatment		Recommended duration for antiviral treatment is 5 days.				
Duration of Chemoprophylaxis		Recommended duration is 5-7 days after the last known exposure. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the last known case was identified.				

(http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm)

[a] Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease.

[b] A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance less than 30 mL/min.

[c] The treatment dosing recommendation for children who weigh <15 kg is 30 mg twice a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh >40 kg, the dose is 75 mg twice a day.

[d] The chemoprophylaxis dosing recommendation for children who weigh <15 kg is 30 mg once a day. For who weigh >15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh >40 kg, the dose is 75 mg once a day.

[e] The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/ min/1.73m^2.

[f] 55 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/22 lbs.

[g] Children aged 10 years and older who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight/day.

[h] A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance <10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

[i] Only approved by Food and Drug Administration (FDA) for treatment among adults.

[j] Not applicable.

[k] Rimantadine is approved by the FDA for treatment among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children. Studies evaluating the efficacy of amantadine and rimantadine in children are limited, but they indicate that treatment with either drug diminishes the severity of influenza A infection when administered within 48 hours of illness onset.

[l] Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged 65 years and older, if they experience possible side effects when taking 200 mg/day.

Table 2. Key Recommendations for the Clinician

Recommendation	SORT[a]	References
Immunization is highly effective in preventing influenza	A	26,27,30,31,34
Chemoprophylaxis with antiviral medications can prevent influenza	A	38
Influenza can be diagnosed based on symptoms of fever and cough when influenza is present in the community	B	17,18,44
Antiviral medications are effective in reducing the symptoms and illness duration of influenza	A	38,48,51,52,53
Antiviral medications are limited by timing of initiation	B	54
Antiviral medications are limited by resistance	C	37,42
Public health surveillance can assist in diagnosis and rational choice of antiviral	C	17,18,44,55

[a]Strength of Recommendation Taxonomy: A – Recommendation based on consistent and good-quality patient-oriented evidence; B – Recommendation based on inconsistent or limited-quality patient-oriented evidence; C – Recommendation based on consensus, usual practice, disease-oriented evidence, case series for studies of treatment or screening, and/or opinion.

Box 3. Case Presentation

In mid-March 2008, a 64-year-old man with a history of mild asthma presented to the emergency department (ED) of a hospital with complaints of progressive dyspnea and fever. He started feeling ill 24 hours ago after returning home from a cruise in Florida. In the ED, he was noted to have a temperature of 102.2ºF. He was slightly tachycardic with a pulse rate of 104. Oxygen saturation on room air was 86%, rising to 96% with 2 liters/minute of oxygen per nasal cannula. A chest X-ray showed questionable hazy infiltrates. He was provided intravenous fluid and started on piperacillin/tazobactam by the ED physician for a presumptive pneumonia.

The admitting family physician noted the abrupt onset of symptoms, the lack of definite consolidation on the chest X-ray (CXR), and the presence of an influenza-like illness during a period of circulation of multiple strains of influenza. A nasopharyngeal swab was obtained for influenza testing. Due to knowledge of circulating strains and antiviral resistance patterns, the family physician empirically started the patient on oseltamivir and amantadine.

By the following morning, the patient felt significantly improved. He no longer required oxygen. A direct fluorescent antibody test was positive for influenza A, and he was discharged to home that morning with a continuation of oseltamivir and amantadine for a total of 5 days.

Supportive Measures

Most authorities recommend rest, fluids, and antipyretics as supportive measures for influenza. Antipyretics can reduce fever and myalgia and make the patient feel subjectively better. A systematic review indicated benefit from acetaminophen and ibuprofen in the management of acute sore throat.[47] Aspirin products should be avoided, especially in children, due to the risk of Reyes syndrome.

Antiviral Medications

Influenza antivirals can be effective in treating influenza infection, but their effectiveness is highly time dependent and complicated by the emergence of resistant strains. Moreover, their use should be based on the potential benefits from treatment. In large meta-analyses, these medications reduce the length of influenza illness, on average, by approximately 1 day.[48-53] For benefit, they have to be started within 36 to 48 hours of illness onset. Early initiation of therapy is associated with profound reductions in illness and return to full function.[54] Initiation of therapy prior to a clinical visit—in selected patients—may provide 1 avenue for early intervention.[55] There is emerging evidence that even antivirals started late in the course of hospitalized patient can reduce morbidity and mortality.[56]

The specific antivirals are discussed in the section on chemoprophylaxis; dosing is provided in Table 1. The adamantane antivirals are ineffective against influenza B viruses. Resistance to this antiviral class in influenza A(H3) viruses extended to 100% by 2009.[37] Accordingly, adamantanes should be used only for seasonal A(H1) viruses. Widespread resistance to oseltamivir by seasonal influenza A(H1) viruses was also noted in 2009.[42] Only zanamivir is effective against all strains of influenza, but is not recommended for children >7 years and in patients with respiratory problems such as asthma and chronic obstructive pulmonary disease (COPD).

The conundrum for the clinician, therefore, is choosing the correct antiviral therapy with insufficient information; there is no point-of-care test that will identify subtypes or resistance patterns. Consequently, empiric therapy must be based on up-to-date surveillance and a willingness to consider combination therapy (See Table 2).[57] An example of a case of influenza presenting to the emergency department is available in Box 3.

PUBLIC HEALTH SURVEILLANCE OF INFLUENZA EPIDEMIOLOGY

There is a long history of partnerships between primary care clinicians, local and state public health departments, public health laboratories, and the CDC Influenza Branch, resulting in a highly functional, accurate, and timely monitoring of influenza. The US Outpatient Influenza-like Illness Surveillance Network (ILINet) started in 1974 as a cooperative agreement between the CDC and the Ambulatory Sentinel Physician Network. Over the years, this program has grown to be an essential component of influenza surveillance in the United States.[58] When combined with virological surveillance, the ultimate product is highly accurate monitoring of influenza prevalence, strain assessment, and resistance patterns. Surveillance information available at www.cdc.gov/flu/weekly can assist the primary care clinician in making rational treatment decisions regarding patients presenting with fever and cough during the influenza season. Clinicians should also stay in close contact with their local and state health departments during the influenza season for a more detailed, local picture of influenza trends and recommendations.

Financial Disclosures: None declared.
Funding/Support: None declared.

REFERENCES

1. Temte JL. Basic rules of influenza: how to combat the H1N1 influenza (swine flu) virus. *Am Fam Physician.* 2009;79(11):938-939.
2. Bouvier NM, Palese P. The biology of influenza viruses. *Vaccine.* 2008;26 Suppl 4:D49-53.
3. Kilbourne ED. *Influenza.* New York, NY: Plenum Medical Book Company;1987:359.
4. Chen J, Deng YM. Influenza virus antigenic variation, host antibody production and new approach to control epidemics. *Virol J.* 2009;6:30.
5. Beigel JH, Farrar J, Han AM, et al. Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med.* 2005;353:1374-1385.
6. Glezen WP, Couch RB. Influenza viruses. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control.* 4th ed. New York, NY: Plenum Medical Book Company;1987:473-505.
7. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol.* 2008;167:775-785.
8. Lee N, Chan PKS, Hui DSC, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis.* 2009;200:492-500.
9. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog.* 2007;3:1470-1476.
10. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR.* 2009;58(RR-8):1-52.
11. Ghedin E, Wentworth D, Halpin RA, et al. Unseasonal transmission of H3N2 influenza A virus during the swine-origin H1N1 pandemic. *J Virol*. 2010 Mar 17. [Epub ahead of print] PMID: 20237080.
12. Kilbourne ED. Influenza pandemics of the 20th century. *Emerg Infect Dis.* 2006;12:9-14.
13. World Health Organization. Pandemic (H1N1) 2009 - update 93. Weekly update. http://www.who.int/csr/don/2010_03_26/en/index.html. Accessed July 29, 2010.
14. Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis.* 2009;9:291-300.
15. Hayden FG, Fritz R, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J Clin Invest.* 1998;101:643-649.
16. Dolin R. Influenza: current concepts. *Am Fam Physician.* 1976;14:72-77.
17. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med.* 2000;160:3243-3247.
18. Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. *Clin Infect Dis.* 2006;43:564-568.
19. Little JW, Hall WJ, Douglas RG Jr, et al. Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. *Am Rev Respir Dis.* 1978;118:295-303.
20. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine.* 2007;25:5086-5096.
21. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? a systematic review. *BMC Infect Dis.* 2006;6:130.
22. Yassi A, Mcgill M, Holton C, Nicolle L. Morbidity, cost and role of health care worker transmission in an outbreak in a tertiary care hospital. *Can J Infect Dis.* 1993;4:42-56.
23. Loeb M, Dafoe N, Mahony J, et al. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. *JAMA.* 2009;302:1865-1871.
24. Larson EL, Lin SX, Gomez-Pichardo C, Della-Latta P. Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms. *Ann Intern Med.* 2004;140:321-329.
25. CDC. ACIP provisional recommendations for the use of influenza vaccines. http://www.cdc.gov/vaccines/recs/provisional/default.htm#acip. Accessed July 29, 2010.
26. Hak E, Buskens E, van Essen GA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions. The PRISMA Study. *Arch Intern Med.* 2005;165:274-280.
27. Jefferson T, Rivetti D, Rivetti A, et al. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet.* 2005;366:1165-1174.
28. Hayward AC, Harling R, Wetten S, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ.* 2006;333:1241.
29. Skowronski DM, Tweed SA , De Serres G. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? *J Infect Dis.* 2008;197:490-502.
30. Demicheli V, Di Pietrantonj C, Jefferson, et al. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub3.

31. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med.* 2008;359:1555-1564.
32. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med.* 2006;355:2513-2522.
33. Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA.* 2010;303:943-950.
34. Jefferson T, Rivetti A, Harnden A, et al. Vaccines for preventing influenza in healthy children. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD004879. DOI: 10.1002/14651858.CD004879.pub3.
35. Fleming DM, Crovari P, Wahn U, et al; the CAIV-T Asthma Study Group. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J.* 2006;25:860-869.
36. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2008;57(RR-7):1-60.
37. Nelson MI, Simonsen L, Viboud C, et al. The origin and global emergence of adamantane resistant A/H3N2 influenza viruses. *Virology.* 2009;388:270-278.
38. Jefferson T, Demicheli V, Rivetti D, et al. Antivirals for influenza in healthy adults: systematic review. *Lancet.* 2006;367:303-313.
39. FDA MedWatch 2006 Jan 4: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152874.htm. Accessed July 29, 2010.
40. Smith JR, Sacks S. Incidence of neuropsychiatric adverse events in influenza patients treated with oseltamivir or no antiviral treatment. *Int J Clin Pract.* 2009;63:596-605.
41. Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. *Med Gen Med.* 2007;9:23.
42. Dharan NJ, Gubareva LV, Meyer JJ, et al; Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA.* 2009;301:1034-1041.
43. Temte JL. Heterogeneity in estimating H1N1. BMJ [rapid response]. Posted on 8/16/2009 at: http://www.bmj.com/cgi/eletters/339/jul14_3/b2840. Accessed July 29, 2010.
44. Zambon M, Hays J, Webster A, et al. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. *Arch Intern Med.* 2001;161:2116-2122.
45. Hurt AC, Alexander R, Hibbert J, et al. Performance of 6 influenza rapid tests in detecting human influenza in clinical specimens. *J Clin Virol.* 2007;39:132-135.
46. Centers for Disease Control and Prevention (CDC). Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009. *MMWR* 2009;58:826-829.
47. Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract.* 2000;50:817-820.
48. Matheson NJ, Harnden AR, Perera R, et al. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev.* 2007;(1):CD002744.
49. Bettis R, Iacuzio D, Jung T, et al. Impact of influenza treatment with oseltamivir on health, sleep and daily activities of otherwise healthy adults and adolescents. *Clin Drug Investig.* 2006;26:329-340.
50. Halloran ME, Hayden FG, Yang Y, et al. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am J Epidemiol.* 2007;165:212-221.
51. Cooper NJ, Sutton AJ, Abrams KR, et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ.* 2003;326:1235.
52. Shun-Shin M, Thompson M, Heneghan C, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomized controlled trials. *BMJ.* 2009339:b3172.
53. Burch J, Corbett M, Stock C, et al. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet Infect Dis.* 2009;9:537-545.
54. Aoki FY, Macleod MD, Paggiaro P, et al; IMPACT Study Group. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother.* 2003;51:123-129.
55. Temte JL. Telephone triage of patients with influenza. *Am Fam Physician.* 2009;79:943-945.
56. McGeer A, Green KA, Plevneshi A, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis.* 2007;45:1568-1575.
57. Poland GA, Jacobson RM, Ovsyannikova IG. Influenza virus resistance to antiviral agents: a plea for rational use. *Clin Infect Dis.* 2009;48:1254-1256.
58. Buffington J, Chapman LE, Schmeltz LM, Kendal AP. Do family physicians make good sentinels for influenza? *Arch Fam Med.* 1993;2:858-865.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.