

CME ARTICLE

Diagnostic Testing for Influenza: Review of Current Status and Implications of Newer Treatment Options

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AUDIENCE

This article is intended for all clinicians caring for patients at risk for or infected with influenza.

GOAL

To review the accuracy and utility of diagnostic tests for influenza and to compare them with clinical diagnosis.

OBJECTIVES

1. Discuss the epidemiology and scope of influenza infection.
2. Discuss available diagnostic tests for influenza.
3. Discuss the implications of newer options for prevention and therapy.

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Each year millions of Americans are infected with the influenza virus, and 20,000 die from complications of the disease.¹ Despite the major public health importance of influenza, accurate diagnostic tests and specific treatment options have been limited.² Vaccination is the primary method for preventing influenza and its complications. Vaccination levels among persons at high risk have improved in the past decade. Until optimal compliance is realized, however, reducing excess morbidity and mortality from influenza should excite and challenge the medical and public health communities.

Prior to this year, physicians confronted with patients presenting with a "flu-like" illness might have considered state-of-the-art treatment to be a sympathetic nod and the sage advice of "drink plenty of fluid, get lots of rest, and next year remember to get your flu shot." This influenza season, however, clinicians have available to them new, specific treatments and may have expanded options for prevention of disease in the face of an influenza epidemic.

A wide variety of viral and bacterial respiratory pathogens are prevalent during the time of year when influenza outbreaks occur. Thus, the ability to identify illness caused by the influenza viruses will become increasingly important because the new treatments are effective against influenza and not other pathogens. Discussions of relative efficacy, cost effectiveness, and patient preference will become driving forces governing the care of patients with symptoms that may be attributable to influenza. To make appropriate decisions regarding coverage for diagnosis and therapy of influenza and influenza-like illnesses, managed care organizations must understand the burden of the disease, diagnostic strategies, and treatment options.

The objective of this paper is to review the available tests and compare their accuracy with that of

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history and physical examination. Diagnostic strategies that will enhance cost effectiveness and patient quality of life will be explored.

... BIOLOGY OF INFLUENZA ...

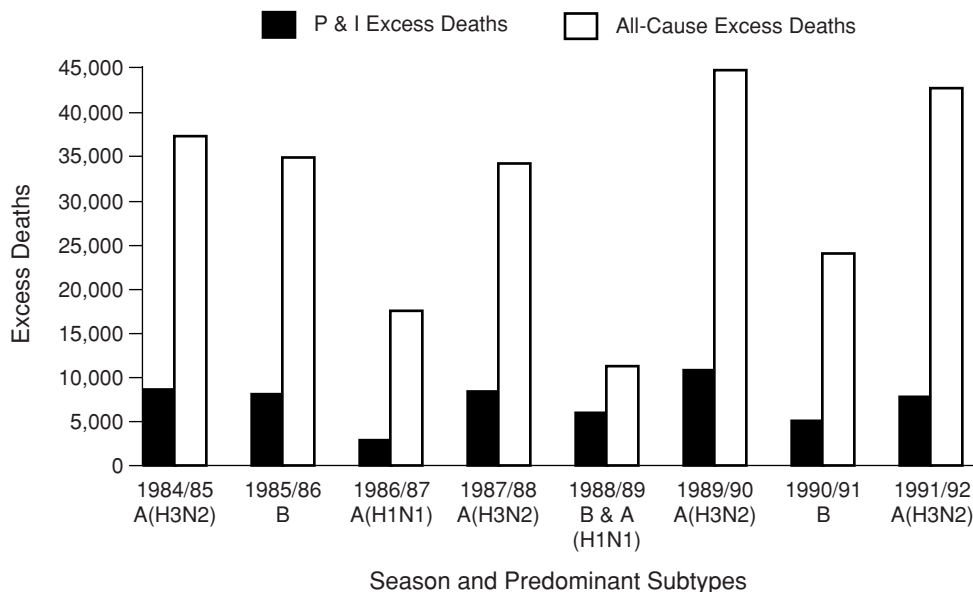
Influenza is a viral respiratory disease characterized by acute onset, fever, myalgias, and cough. The pathogen is a group of RNA viruses that is further classified into types A, B and C. Only types A and B have been associated with regional or widespread epidemics. The envelope of the virus contains 2 glycoproteins: hemagglutinin and neuraminidase. These glycoproteins are used to classify the strains of influenza, and they have important functions in determining virulence of the organism. Hemagglutinin has a role in viral attachment to cells; neuraminidase is responsible for releasing virus from infected cells and may also reduce the ability of respiratory mucous to inactivate the virus.³ Thus, inhibitors of the neuraminidase glycoprotein are effective against both the A and B strains of the influenza virus. The neuraminidase inhibitors zanamivir (Relenza,[®] GlaxoWellcome, Inc., Research Triangle Park, NC) and

oseltamivir (Tamiflu,[®] Roche Pharmaceuticals, Nutley, NJ) are effective in both ameliorating the symptoms of disease (if given early in the course of the illness) and preventing infection during an epidemic.⁴⁻⁶ Although more expensive than the older antivirals amantadine and rimantadine (\$45-\$55 vs \$8-\$30), their broader spectrum, fewer side effects, and less potential for generating drug-resistant strains has the potential to alter not only the course of the disease but also the clinical approach to individuals with flu-like symptoms and their resultant disease-related expenditures.

... MEDICAL AND ECONOMIC BURDEN OF INFLUENZA INFECTION ...

Influenza-related mortality is generally estimated using *International Classification of Diseases* (ICD) codes corresponding to a list of diagnoses termed "pneumonia and influenza" mortality.⁷ The Figure shows the estimated number of excess deaths attributable to pneumonia and influenza as well as all-cause mortality for the influenza seasons of 1984-1992. The all-cause mortality demonstrates

Figure. Pneumonia and Influenza (P&I) Related and All-Cause Excess Mortality Estimate for 8 Influenza Seasons: United States, 1979 through 1992



Source: Reference 7.

the maximum impact of influenza on mortality because many influenza-related deaths may be ascribed to cardiovascular disease or other diagnoses rather than to pneumonia and influenza diagnoses.⁸ As can be seen from the Figure, in most years the number of preventable deaths ranges from 20,000 to 40,000.

The aging of the population and the longer life spans of persons with diseases such as congestive heart failure and human immunodeficiency virus (HIV) infection may result in significant future increases in influenza-attributable mortality. In a recent study of women 15-64 years of age enrolled in a Tennessee Medicaid program from 1974 to 1993, Neuzil and colleagues identified 2045 excess deaths due to selected cardiopulmonary causes.⁹ This influenza-attributable mortality translates into 2.4 excess deaths annually per 10,000 high-risk women overall (high-risk women are those for whom annual influenza immunization is currently recommended by the Centers for Disease Control and Prevention) and 4.0 excess deaths annually per 10,000 high-risk women aged 45-64 years. Among low-risk women, excess deaths due to influenza complications were rare.

Influenza-associated morbidity is significantly more difficult to quantify than mortality.¹⁰ Studies evaluating the effectiveness of vaccine suggest that the actual impact of influenza on morbidity may be much larger than that reported in observational studies.¹¹ The heterogeneity of symptom severity in infected individuals makes estimating the true burden of the disease quite difficult. Only about 20% of the total number of cases will be sufficiently severe to produce significant medical expenditures. In addition to visits to ambulatory clinics and emergency rooms, the cost of antibiotics inappropriately prescribed for upper respiratory symptoms presumed to be caused by a bacterial infection, but actually caused by influenza, must be included.

Determination of the economic burden of influenza presents a great challenge. With most clinical conditions, direct medical expenditures explain much of the costs of illness. Influenza, however, requires careful consideration of indirect costs relating to lost productivity. Many infected individuals do not undergo a formal medical evaluation, but incur significant morbidity and work loss. In addition to the burden of illness on the patient, the caregivers of individuals with influenza incur loss of productivity. Meltzer et al modeled the economic impact of a future pandemic in the United States.¹² Without large-scale immunization, the total eco-

omic impact was estimated to range from \$71.3 to \$166.5 billion, depending on the attack rate of the virus. At any given attack rate, 83% of the estimated losses were attributed to loss of life. Outpatient care, ill persons not seeking care but experiencing loss of productivity, and inpatients accounted for the remainder of the economic losses.

... LABORATORY DIAGNOSIS ...

Not all flu-like symptoms are caused by the influenza virus; a substantial proportion of patients may be infected with parainfluenza, adenovirus, or respiratory syncytial virus. Even during the winter months, when incidence of upper respiratory infections caused by influenza infection is high, studies show that up to 70% of patients with influenza-like symptoms may not be infected with the virus.¹³ Symptoms such as malaise, myalgias, and cough are common in influenza, but they are also common in noninfluenza illnesses. The challenge of distinguishing influenza from other viral respiratory diseases is critical to prescribing appropriate treatment. Moreover, issues of accuracy, cost, and ease of testing will further determine the cost effectiveness of treatment. The introduction this flu season of neuraminidase inhibitors, drugs that are well tolerated and effective for treatment and prevention of both common strains of influenza, highlights the problems and payoffs of influenza diagnosis.

The ideal diagnostic method would have high sensitivity and specificity for the identification of influenza, would be relatively simple to administer, and would be rapid and inexpensive. The timeliness of results is critical because, in order to be effective, the newer therapies (as well as the more traditional antiviral therapies for influenza A must be started within 48 hours after onset of symptoms. As test accuracy improves or cost falls, the argument for diagnostic testing is enhanced. Regardless of the sensitivity and specificity of each test, the positive predictive value of any test will improve when the prevalence of influenza in the community is high. On the other hand, as the likelihood of influenza illness increases (such as in major outbreaks), the effectiveness and tolerability of treatment improve, or the cost of treatment decreases, an advantage is realized for empiric treatment based on clinical characteristics alone.

There are 4 main methods for identification of influenza infection: enzyme immunoassay (EIA), direct immunofluorescence (DIF), viral culture, and

polymerase chain reaction (PCR) (Table). The EIA and DIF technologies have been adopted for use in the office-based setting, which allows for rapid and simple reporting of results. These tests must be performed in a laboratory meeting the standards of the Clinical Laboratory Improvement Act, which may prove a hindrance to wide introduction into certain clinical settings. No published study has directly compared the sensitivity, specificity, positive predictive value, and negative predictive value of these office-based tests for detecting influenza in clinical specimens. Each of the methods has unique advantages and disadvantages. An understanding of these diagnostic methods has become more important as our treatment options for influenza infection expand.

Enzyme Immunoassay

Enzyme immunoassay testing is both rapid and simple. This technique relies on the ability to detect free viral antigen in nasopharyngeal secretions. Secretions are obtained by instilling saline into the nasopharynx and aspirating back. The secretions are tested for influenza antigen using commercially available EIA kits. These kits are easy to use and have excellent technical documentation. This allows even novices to rapidly become proficient enough with the technique to produce accurate results with minimal training. Processing the specimens is simple, results can be obtained in hours, and the test is relatively inexpensive (under \$100).

When compared with viral culture, EIA routinely achieves sensitivity of 85% with specificity of 100% for both influenza A and B.^{14,15}

The disadvantage of EIA rests with the difficulty and unpleasantness of obtaining nasopharyngeal aspirates. Clinicians may be tempted to substitute pharyngeal swab specimens for the aspirates, but the swabs contain fewer epithelial cells, resulting in decreased sensitivity.

Direct Immunofluorescence

Direct immunofluorescence depends on the ability to directly detect viral antigen on pharyngeal columnar epithelial cells. Nasopharyngeal aspirates are the preferred specimen source, but unlike EIA, the specimen is not considered acceptable for further testing unless a threshold level of epithelial cells is present in a concentrated aspirate. The epithelial cells in the aspirate are directly stained for viral antigen with fluorescent antibody. As with EIA, the results can be obtained within hours, allowing for same-day diagnosis. The sensitivity of 60-80% and specificity of 90% of DIF are somewhat lower than the sensitivity and specificity of EIA.¹⁶ Direct immunofluorescence testing is the least expensive (\$20) of the available influenza tests.

As with the other rapid influenza tests, DIF has disadvantages. DIF interpretation can be particularly difficult and subtle. Technical expertise is necessary to determine positively stained cells. Specimens require extensive processing to concentrate the epithelial cells of the aspirate, increasing the time and technical difficulty of the method.¹⁷ Because of these problems, DIF is not widely used in clinical practice.

Viral Culture

Viral culture of influenza has traditionally been considered the gold standard for isolation and identification. Like the other testing modalities, viral culture begins with nasopharyngeal aspiration or swabbing. The secretions are then washed and purified before inoculation into live monkey kidney cells. After 1-3 days, the cell culture is analyzed for signs of viral infection. The cost of

Table. Laboratory Methods for the Identification of Influenza Virus

Characteristic	EIA	DIF	Culture	PCR
Sensitivity	85%	70%	100%	100%*
Specificity	100%	90%	100%	100%
Time	hours	hours	days	1 day
Ease of Use	++++	+	++	++
Cost	++	+	+++	++++

EIA = enzyme immunoassay; DIF = direct immunofluorescence; PCR = polymerase chain reaction. *PCR may be more sensitive than culture, the traditional "gold standard" for diagnosis.

an influenza culture is approximately \$100 per specimen.

Advantages of this technique include its reproducibility, relatively high availability, favorable sensitivity and specificity, and acceptable cost. Tissue culture, however, is not the ideal test. Results can be obtained only after several days of processing, rendering this method relatively useless for early treatment of disease. In addition, viral culture requires technical expertise as well as facilities for growing the culture, limiting its availability to large clinical laboratories. Although viral culture has been used as the gold standard against which to judge sensitivity, recent studies using the newer technique of PCR have indicated that the sensitivity of viral culture is less than 100%.

Although not optimal from a treatment perspective, viral culture techniques remain critical because only cultures yield viruses that can be characterized to provide specific information on circulating influenza subtypes and strains. This information is critical for determining the presence and characteristics of an epidemic and assessing the match between current circulating strains and vaccine antigens, data that are used to formulate vaccine composition for the coming year.

Polymerase Chain Reaction

Recently investigators have begun to apply the techniques of molecular biology to the detection of influenza infection. Polymerase chain reaction may prove to be both more sensitive and more specific than standard culture.^{18,19} Among patients tested by viral culture, 10-20% of those who test negative will test positive for influenza virus by PCR.²⁰ Although PCR is the most sensitive of the available tests, it is labor-intensive and costly to perform. Accurate results depend on skilled technique and avoidance of contamination. If technical aspects improve, costs decrease, or both, PCR may evolve to become the preferred method for diagnosing influenza.

... CLINICAL DIAGNOSIS ...

The signs and symptoms most often associated with influenza (ie, fever, myalgias, fatigue, headache, cough) may be present in patients infected by noninfluenza viruses such as parainfluenza, respiratory syncytial virus, and adenovirus, as well as in patients with bacterial infections such as mycoplasma or even pneumococcal pneumonia. The likelihood that a patient with any of these symptoms has influenza depends on the prevalence

of influenza at that time in a particular locale. In the setting of an outbreak, individuals with the constellation of symptoms of fever, cough, headache, and myalgias without some other clinically apparent infection have been considered to be appropriate candidates for antiviral influenza treatment.²¹

Multiple outbreaks of influenza A have provided investigators with the opportunity to validate the "epidemiological diagnosis of disease." When applied to a population of individuals aged 60 years and older in the Netherlands, cough, fever, and an acute onset were found to be the most predictive set of symptoms when compared with several well-established clinical diagnostic criteria.²² An analysis conducted during the French influenza epidemics of 1995-1996 reported a positive predictive value of 40% using a temperature of >38.9°C, respiratory signs, and myalgias. The negative predictive value was 80%. In this study, the less sensitive DIF and EIA were used to validate a case of influenza, which may account for the surprisingly low positive predictive value of the symptom constellation.²³ In the more recent series of therapy studies of zanamivir, clinical criteria were used to select cases for inclusion when influenza had been identified in the community; 65-70% of those cases were positive for influenza when cell culture isolation or PCR was used.⁵ A recent evaluation, using data from these studies, indicated that cough and fever were the best predictors of influenza positivity, achieving a positive predictive value of 79%.⁵ Given that symptoms achieve positive predictive values approaching those of the currently available rapid diagnostic tests, determining treatment based on clinical criteria may well be appropriate at this time.

... APPROACH TO THE PATIENT WITH INFLUENZA-LIKE ILLNESS ...

Vaccination is the most cost-effective method of ameliorating the clinical and economic burden of influenza. The effectiveness of the vaccine in a given year depends on the degree of vaccination coverage in the population as well as the antigenic match between the predominant circulating virus strains and the composition of that year's vaccine.¹ The effectiveness of the vaccine in the elderly population, who are at higher risk for influenza morbidity and mortality, is lower than average even in the best of circumstances. Despite programs to increase vaccination in the high-risk and general population, infections with influenza and other respiratory infec-

tions will present diagnostic and treatment challenges to clinicians.

Epidemiologic, clinical, and economic issues must be considered in any future disease management algorithm. An effective disease management should improve care and reduce the use of inappropriate antibiotics and other unnecessary therapy. The cost effectiveness of the neuraminidase inhibitors will depend on the extent to which the drugs are prescribed for individuals who actually have influenza infection and who are at greatest risk of morbidity and mortality. To maximize cost effectiveness, clinicians must become aware of the prevalence of influenza in their communities and must develop systems that do not impede access to treatment, particularly for high-risk individuals. The Centers for Disease Control and Prevention web site for weekly influenza surveillance data (www.cdc.gov/ncidod/diseases/flu/fluivirus.htm) affords clinicians easy access to influenza outbreak information. Procedures for triaging phone calls and scheduling visits to ambulatory care sites should be implemented. This is particularly important because it is necessary to prescribe therapy early in the clinical episode, within 48 hours of onset of symptoms.

Outbreak information, individuals' risk of influenza complications, and clinical presentation should indicate whether empiric treatment or expeditious laboratory testing is warranted on clinical and economic grounds. Laboratory testing, in the setting of a compatible history and outbreak information (particularly in an individual with cardiac disease, lung disease, or diabetes), might only add to the cost of the episode without further informing the decision-making process. Empiric therapy is already used in this high-risk group, only the therapy often is antibiotics, which are unnecessary and potentially harmful in the setting of influenza.

The use of antivirals as an alternative to or in addition to vaccination for influenza prophylaxis may be more controversial than their use in treatment of acute illness. The benefits of influenza vaccination for both the high-risk and the working populations are well documented.²⁴⁻²⁷ Influenza vaccine has been shown to be safe and to have 70-90% efficacy in the prevention of influenza when a good antigenic match exists between vaccine composition and epidemic viruses for that season. Unfortunately, the most extensive vaccine coverage in high-risk groups only approaches 75%, and excess mortality will continue to plague us in the 21st century. Broader access to and greater acceptability of the vaccine for both high-risk and healthy individuals will be necessary to

decrease the proportion of the population susceptible to the virus and therefore capable of transmitting disease. The introduction of a live, inhaled influenza vaccine should support this objective.

The neuraminidase inhibitors have been demonstrated to be efficacious and well tolerated when used for influenza prophylaxis over a period of weeks. It is unlikely that they will be extensively used in this manner, except in outbreaks in nursing homes or institutions where they may be used in addition to vaccine. Studies are currently under way to show that the neuraminidase inhibitors are effective for use in households for short-term prophylaxis for exposed family members. No formal cost-effectiveness analysis of neuraminidase inhibitors as prophylactic agents has been conducted. Such an analysis, as well as systematic comparison of the two preventive approaches, will be required for definitive conclusions to be made.

... CONCLUSIONS ...

Influenza is a common infection whose significance, especially in terms of morbidity and economic impact, has been difficult to quantify. Vaccination has been demonstrated to be cost effective in reducing the impact of the disease and should remain the primary method for prophylaxis. Indeed, the concept of targeting vaccination only to high-risk populations is being rethought, and the American Academy of Family Physicians has revised its recommendations to include all adults over age 50 years.

The scrutiny given to new interventions for treatment and prophylaxis will promote the collection of better data on the clinical and economic burden of the disease. Appropriate use of all available treatments requires a rational approach to the diagnosis of influenza. Issues of patient preference and cost effectiveness should determine whether both diagnostic testing and new therapies become available to the general population or to groups at higher risk. Economic evaluations of these innovations must include a societal perspective that recognizes the substantial contribution of indirect costs attributable to this disease. Implementing cost-effective prophylactic and treatment strategies based on clinical and epidemiologic data will be critical to mitigating the suffering and cost due to influenza.

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CME QUESTIONS: TEST #059912

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Instructions

After reading the article "Diagnostic Testing for Influenza: Review of Current Status and Implications of Newer Treatment Options" select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. Annual influenza-related mortality in the United States is:

- a) 2,000
- b) 20,000
- c) 200,000
- d) 2,000,000

2. The cost of a future influenza pandemic has been estimated to be:

- a) \$10 million
- b) \$100 million
- c) \$100 billion
- d) \$1 trillion

3. Common viruses that may mimic influenza infection include all of the following *except*:

- a) respiratory syncytial virus
- b) parvovirus
- c) adenovirus
- d) parainfluenza virus

4. After symptom onset, antiviral therapy should be initiated:

- a) within 4 hours
- b) within 48 hours
- c) within 4 days
- d) within 1 week

5. The traditional gold standard for diagnosis of influenza is:

- a) polymerase chain reaction
- b) direct immunofluorescence
- c) enzyme immunoassay
- d) viral culture

6. Using symptoms to formulate a diagnosis of influenza is a reasonable alternative to diagnostic testing:

- a) true
- b) false

(CME QUESTIONS CONTINUE ON FOLLOWING PAGE)

CME TEST FORM

AJMC Test #059912

Diagnostic Testing for
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Current Status and
Implications of Newer
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(Test valid through
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Please circle your answers:

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- 3. a b c d
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- 7. a b c d
- 8. a b c d
- 9. a b c d
- 10. a b

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(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

7. Which of the following agents is active against influenza B:

- a) amantadine
- b) acyclovir
- c) rimantadine
- d) oseltamivir

8. The effectiveness of influenza vaccine in preventing disease is:

- a) <50%
- b) 50-70%
- c) 70-90%
- d) >90%

9. "Epidemiologic diagnosis" of influenza is favored by all of the following symptoms except:

- a) myalgias
- b) cough
- c) sore throat
- d) fever

10. The cost of influenza is primarily related to direct medical expenses.

- a) true
- b) false