



Laura M. Gunder, DHSc, PA-C
Assistant Professor

Bonnie A. Dadig, EdD, PA-C
Associate Professor
and Department Chair

Physician Assistant Department
Medical College of Georgia
Augusta

Rapid Flu Testing

For patients who present within 48 hours of influenza symptom onset, rapid flu testing can rule out bacterial infections and open the door for helpful treatment options.

Continued on page 6



Each year in the United States, seasonal influenza accounts for 200,000 hospitalizations and 36,000 deaths,¹ despite the fact that this illness is preventable by vaccination.^{2,4} While most influenza infections are self-limiting, the potential for morbidity and mortality, loss of productivity, monetary loss due to missed work days, and physical discomfort make early diagnosis important. Additionally, when diagnosed early, influenza is treatable by specific antivirals that can shorten the course of disease and ameliorate symptoms.^{2,3,5}

Current CDC guidelines recommend rapid influenza testing for persons who present within 48 hours of symptom onset.⁶ Rapid testing for influenza at the point of patient care facilitates early diagnosis during this period.^{2,6,7}

Influenza is often difficult to diagnose based on clinical presentation alone due to the common occurrence of other respiratory illnesses, such as mycoplasma pneumonia, adenoviruses, respiratory syncytial virus, rhinovirus, and parainfluenza viruses.^{3,4,8} The predictive value of rapid flu testing is greater during a period of influenza outbreak and when the test is performed in patients who exhibit the typical physical symptoms: fever, muscle aches, nonproductive cough, sore throat, headache, and fatigue.^{3,4,8,9} Rapid testing for influenza should be carried out only when the results will influence a clinical decision.

RAPID FLU TESTING

At present, multiple “waived” rapid test systems are available as diagnostic and screening tests for influenza A and B virus infection⁷ (see table,^{2,7} page 7). These tests are often referred to as *point-of-care* tests since they are not performed at a centralized laboratory facility, but in facilities that include the outpatient clinic, urgent

care center, or emergency department. These tests are simple to perform and relatively sensitive and specific. They can provide results in 30 minutes or less.^{2,7,9-14}

As a group, these tests can detect influenza A, influenza B, or influenza A and B. Influenza A and B antigens are detectable in the respiratory secretions of infected persons. There is evidence that these rapid flu tests also react with the novel influenza A (H1N1) virus (“swine flu”) but with a lower sensitivity than seen in other strains of influenza A and influenza B.¹⁵

In any case, the methodologies for rapid flu testing are immunoassays that employ monoclonal antibodies.^{2,9-14} This methodology is highly specific for influenza types A and B with no significant cross reactivity to normal flora of the respiratory tract or to other respiratory pathogens.^{2,9-14} After collection of respiratory secretions from the nose, viral antigens are extracted from the swab collection device. When any extracted particles react with reagent antibody, a color change appears in the test system.^{13,14} Antigens must be present in sufficient number to be detectable. This necessary threshold directly affects the sensitivity of the test. For specimens in which antigen levels fall below the lower threshold of reactivity, the test will yield a negative result. All of the rapid flu test systems contain a built-in control.^{2,13,14}

Not every patient who exhibits flu-like symptoms requires rapid flu testing. Rather, the test should be performed only when it will provide information that will help the clinician make a treatment decision.^{3,9,16}

For example, in a patient who has been ill for four days, it is unlikely that antivirals will shorten the duration or severity of illness; in this situation, supportive care is usually indicated. For a patient who presents on the first day of illness with flu-like

symptoms and whose family member has had positive results on a rapid flu test, the patient may be tested or given pharmacotherapy. In the case of a patient who has no history of influenza contact and who presents at the onset of flu-like symptoms, the test may help to distinguish between influenza infection and other causes of respiratory illness.

Rapid flu testing may also be used to confirm clinical diagnoses during community outbreaks of influenza.^{3,9,16} This surveillance can help to control these outbreaks and may support the development of public health recommendations.

Specimen Collection

The rapid influenza test may be performed on multiple specimen types, collected as nasal swabs, nasal lavage, nasopharyngeal swabs, or sputum. Test results may vary based on specimen type, due primarily to variation in the amounts of detectable antigen among specimens. The highest-quality specimens contain the largest numbers of cells and, presumably, the greatest concentration of antigen.^{2,9-14} Swabs generally yield the least amount of antigen.

Regardless of type, specimens should be collected as early as possible following onset of symptoms to maximize the amount of viral antigen obtained. After four to five days of clinical illness, viral shedding decreases drastically in adults, although it typically lasts longer in children.^{9,16}

Test Results, Expected Values, and Limitations

Negative test results occur when (1) no influenza antigens are present or (2) influenza antigens are not present in sufficient quantity to be detected.⁹⁻¹⁴ The rapid tests are reactive with a wide range of recently identified human influenza strains because they are designed to detect

Table. Types and Levels of Influenza Testing Available^{2,7}

Test type	CLIA-waived?	Specificity/sensitivity	Ease of performance	Performance site	Specimen site	Time to diagnosis
BinaxNOW [®] Influenza A & B	Yes	High	Easy	Point of care, office-based	NP swab, nasal wash or aspirate	< 15 min
QuickVue [®] Influenza A+B	Yes	High	Easy	Point of care, office-based	NP swab, nasal wash or aspirate	< 15 min
Immunofluorescence DFA Testing, A and B	No	High	Moderate	Reference laboratory	NP swab, nasal or bronchial wash, nasal aspirate, sputum	2 – 4 h
RT-PCR, A and B	No	More sensitive than culture	Moderate	Reference laboratory	NP swab, nasal or bronchial wash, nasal aspirate, sputum	2 – 4 h
Viral cultures, A and B	No	“Gold standard”	Moderate	Reference laboratory or state health department laboratory	NP swab, nasal or bronchial wash, nasal aspirate, sputum	3 – 10 d
Serology	No	High	Moderate	Reference laboratory	Paired acute and convalescent serum	≥ 2 wk

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; NP, nasopharyngeal; DFA, direct fluorescent antibody; RT-PCR, real-time polymerase chain reaction.

Data extracted from: CDC. Rapid diagnostic testing for influenza. 2009²; Clinical Laboratory Improvement Amendments. 2009.⁷

a common antigen of all influenza A viruses or B viruses. However, rapid tests cannot distinguish among the human influenza subtypes.¹⁷

While some nonhuman influenza viruses (eg, avian influenza) are not necessarily detected with the rapid assay, other nonhuman influenza viruses show some cross reactivity.¹⁷ For example, the novel influenza A (H1N1) has been shown to react with the influenza A immunoassay but at lower sensitivities than seasonal influenza subtypes.^{15,17} Confirmation of infection with novel influenza A (H1N1) may be necessary for patients who are critically ill, immunocompromised, or pregnant or lactating.^{2,8}

Test Validity

Clinical accuracy of an influenza diagnostic test is determined by the

sensitivity and specificity of the test to detect an influenza virus infection when compared with the “gold standard” (ie, a viral culture, in the case of influenza) and in consideration of the overall incidence of the illness in the community (see table).

Sensitivity is demonstrated by the number of positive test results in the presence of true influenza cases. *Specificity* is demonstrated by the number of negative test results in the absence of true influenza cases. The sensitivity of CLIA-waived rapid flu assays varies between 70% and 75%.⁹ This is much lower than the sensitivity of viral culture methods. Conversely, the average specificity of CLIA-waived rapid flu tests is 90% to 95%.⁹ The low sensitivity contributes to the number of false-negative results with this system, while the

high specificity makes the rapid flu test a good screening test for patients who exhibit symptoms.

The *predictive value* of a test takes into account the overall prevalence of the disease. For example, when a high percentage of patients with clinical signs and symptoms of influenza also test positive for influenza by the rapid test method, the test has a high positive predictive value. The percentage of patients who test negative in the absence of disease reflects the negative predictive value. During periods of influenza outbreak, the positive predictive value of rapid flu testing is highest.^{2,9} Conversely, during periods without high incidence of influenza illness, the negative predictive value is higher.

Characteristics of test performance should be evaluated or adapted in the



setting in which the test is employed.⁹ As evidenced by the recent epidemics of the novel influenza A (H1N1), influenza viruses that cause disease in humans continue to evolve. This necessitates continuous reevaluation of the rapid diagnostic tests to gain an understanding of their sensitivity, specificity, and overall predictive value in the clinical setting.¹⁷

For surveillance purposes, more influenza testing to identify subtype may be required by state or local protocols.⁸

CONCLUSION

Rapid testing for influenza virus can assist in guiding the clinical treatment and care of patients in inpatient and outpatient settings. These diagnostic tests are most effective when performed within 48 hours of symptom onset, since they make it possible to incorporate antiviral use in the treatment plan when appropriate. In addition, positive test data provide a diagnosis for the patient, who can then be advised to take extra precautions to avoid infecting others. Positive test results also preclude the use of antibiotics, thus helping to avoid increased microbial resistance.

During an influenza outbreak, rapid test results provide surveillance data that, when distributed to the general public, give persons an incentive to take prophylactic measures against influenza infection, such as vaccination. Confirmatory testing for seasonal influenza should be considered on an individual basis, taking into account the potential value of the information as it pertains to patient treatment or surveillance. 

REFERENCES

1. National Institute of Allergy and Infectious Diseases, NIH. Flu (influenza) (2009). www3.niaid.nih.gov/topics/Flu/default.htm. Accessed October 13, 2009.
2. Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza (2009). www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm. Accessed October 14, 2009.
3. Montalto NJ. An office-based approach to influenza: clinical diagnosis and laboratory testing. *Am Fam Physician*. 2003;67(1):111-118.
4. Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet*. 2003;362(9397):1733-1745.
5. World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis (2005). www.who.int/csr/disease/avian_influenza/guidelines/RapidTestInfluenza_web.pdf. Accessed October 9, 2009.
6. Centers for Disease Control and Prevention. Interim guidance for the detection of novel influenza A virus using rapid influenza diagnostic tests (2009). www.cdc.gov/h1n1flu/guidance/rapid_testing.htm. Accessed October 9, 2009.
7. US Department of Health and Human Services. Clinical Laboratory Improvement Amendments—Currently Waived Analytes (2009). www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/analyteswaived.cfm. Accessed October 13, 2009.
8. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(8):1003-1032.
9. Gavin PJ, Thomson RB Jr. Review of rapid diagnostic tests for influenza. *Clin Appl Immunol Rev*. 2003;4:151-172.
10. Landry ML, Cohen S, Ferguson D. Comparison of BinaxNOW and Directigen for rapid detection of influenza A and B. *J Clin Virol*. 2004;31(2):113-115.
11. Reina J, Padilla E, Alonso F, et al. Evaluation of a new dot blot enzyme immunoassay (directigen flu A+B) for simultaneous and differential detection of influenza A and B virus antigens from respiratory samples. *J Clin Microbiol*. 2002;40(9):3515-3517.
12. Smit M, Beynon KA, Murdoch DR, Jennings LC. Comparison of the NOW Influenza A & B, NOW Flu A, NOW Flu B, and Directigen Flu A+B assays, and immunofluorescence with viral culture for the detection of influenza A and B viruses. *Diagn Microbiol Infect Dis*. 2007;57(1):67-70.
13. QuickVue® Influenza A+B Test [package insert]. Quidel Corporation. San Diego, CA: CLIAwaived, Inc; 2009.
14. BinaxNOW® Influenza A & B Test Kit [package insert]. San Diego, CA: CLIAwaived, Inc; 2008.
15. Chan KH, Lai ST, Poon LL, et al. Analytical sensitivity of rapid influenza antigen detection tests for swine-origin influenza virus (H1N1). *J Clin Virol*. 2009;45(3):205-207.
16. Rodriguez WJ, Schwartz RH, Thorne MM. Evaluation of diagnostic tests for influenza in a pediatric practice. *Pediatr Infect Dis J*. 2002;21(3):193-196.
17. Uyeki TM, Prasad R, Vukotich C, et al. Low sensitivity of rapid diagnostic test for influenza. *Clin Infect Dis*. 2009;48(9):e89-e92.