Seasonal influenza testing

Clinical Policy ID: CCP.1330

Recent review date: 3/2022

Next review date: 7/2023

Policy contains: Biofire; reverse-transcription polymerase chain reaction; seasonal influenza.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

The diagnosis of seasonal influenza by laboratory assay is clinically proven and, therefore, medically necessary when the results of the assay will influence management decisions (e.g., initiating antiviral therapy, prescribing antibiotics, performing other diagnostic tests, or implementing infection control measures), and the following criteria are met (Uyeki, 2019):

- In the outpatient setting for members who present with either:
  - Signs or symptoms suggestive of uncomplicated influenza (e.g., acute onset of respiratory symptoms with or without fever), and either exacerbation of chronic medical conditions or known complications of influenza (e.g., pneumonia).
  - Atypical signs or symptoms or complications associated with influenza in high-risk* members who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without fever).
- In the emergency department, for members who present with Influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without a fever), have no increased risk for influenza complications, and will likely be discharged if either:
  - The test results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic tests, and length of time in the emergency department.

    - The test results might influence antiviral treatment or chemoprophylaxis decisions for high-risk members of the patient's household.
- In hospitalized members with any of the following indications:
    - Acute respiratory illness, including pneumonia, with or without fever.
    - Acute worsening of chronic cardiopulmonary disease.
    - An immunocompromised status or at high risk* of complications, who present with an acute onset of respiratory symptoms, whether febrile or afebrile.
    - Acute onset of respiratory symptoms (with or without fever) or respiratory distress, without a clear alternative diagnosis.

*High risk is defined as either (Fiore, 2011):

- Children < 5 years of age.
- Adults ≥ 65 years of age.
- Members with chronic illness.
- Members with known complications of influenza, such as pneumonia.
- The immunosuppressed (e.g., human immunodeficiency virus infection).
- Pregnant or within two weeks postpartum.
- Younger than 19 years of age and receiving long-term aspirin or salicylate-containing therapy.
- American Indians/Alaska Natives.
- Morbidly obese (i.e., body mass index ≥ 40).
- Institutional residence (e.g., nursing homes or long-term care facilities).

Limitations

Respiratory viral panel testing using reverse-transcription polymerase chain reaction assay targets, including influenza virus, is medically necessary for testing performed in an inpatient facility, observation, or emergency setting only.

The following limitations apply to seasonal influenza testing:

- In outpatients:
    - Providers should use rapid molecular assays (nucleic acid amplification tests) rather than rapid influenza diagnostic tests (antigen detection tests) to improve detection of influenza virus infection, preferably within four days of symptom onset (Uyeki, 2019).
- To increase influenza virus detection, nasopharyngeal specimens are preferred over other specimens (Uyeki, 2019). Testing of specimens for influenza from nonrespiratory sites such as blood, plasma, serum, cerebrospinal fluid, urine, and stool is not medically necessary, except when ordered by an infectious disease specialist.
- In hospitalized members (Uyeki, 2019):
- Providers should use reverse-transcription polymerase chain reaction or other molecular assays to improve detection of influenza virus infection.
    - In immunocompromised members, providers should use multiplex reverse-transcription polymerase chain reaction assays to target a panel of respiratory pathogens, including influenza viruses.
    - In inpatients who are not immunocompromised, providers can consider using multiplex reverse-transcription polymerase chain reaction assays to target a panel of respiratory pathogens, including influenza viruses, if it might influence care.

    - Clinicians should not use immunofluorescence assays for influenza virus antigen detection except when more sensitive molecular assays are not available. Follow-up testing with reverse-transcription polymerase chain reaction or other molecular assays should be performed to confirm negative immunofluorescence test results.
    - Clinicians should not use rapid influenza diagnostic tests in hospitalized members except when more sensitive molecular assays are not available. Follow-up testing with reverse-transcription polymerase chain reaction or other molecular assays should be performed to confirm negative rapid influenza diagnostic test results.
- Clinicians should not use viral culture for initial or primary diagnosis of influenza, but viral culture can be considered to confirm negative test results from rapid influenza diagnostic tests and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization.
- Clinicians should not use serologic testing for diagnosis of influenza, because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera two to three weeks apart are needed for serological testing.

Alternative covered services

- In-network routine and preventive health services by a primary care or specialty provider.
- Infectious disease consultation.

Background

Influenza is an acute respiratory illness caused by influenza A or B viruses that occurs in outbreaks and epidemics worldwide, mainly in winter. During an influenza outbreak, acute febrile respiratory illnesses can be diagnosed as influenza with a high degree of certainty by clinical criteria (Ebell, 2012). In comparison, sporadic cases of influenza cannot be differentiated from infections caused by other respiratory viruses on clinical grounds alone.

Symptoms of influenza typically include fever (100.4° or higher temperature, or feeling feverish/chills), and one or more of the following: cough, sore throat, headaches and/or body aches; difficulty breathing or shortness of breath; fatigue; and runny or stuffy nose (Centers for Disease Control and Prevention, 2020c).

Influenza diagnostic tests include molecular assays (rapid molecular assays, reverse transcription polymerase chain reaction, and other nucleic acid amplification tests) and antigen detection tests (including rapid influenza diagnostic tests and immunofluorescence assays) (Centers for Disease Control and Prevention, 2020a). Molecular assays provide the highest sensitivity and specificity for influenza viruses, but their ability to detect and discriminate between infections with influenza A and B viruses varies. Among these, reverse-transcriptase polymerase chain reaction-based testing is the most sensitive and specific though there are constraints of expense and adequate laboratory facility and personnel that can impact access.

Reverse-transcriptase polymerase chain reaction-based testing may be ordered as single pathogen-specific tests or as a multiplex panel designed to detect a predefined number of organisms associated with an infectious syndrome. Multiplex panels may simplify testing algorithms and improve the sensitivity and speed of diagnosis compared to those of conventional methods, but they are limited in the ability to allow customized ordering. They have the potential to be more cost-effective and may help standardize patient care, particularly in smaller hospitals, clinics, and provider offices. Several approved multiplex panels have received a Clinical Laboratory Improvement Amendments waiver by the U.S. Food and Drug Administration (2020) for the simultaneous detection and identification of five or more respiratory pathogens in outpatient settings, including office-use.

Three multiplex assays have received Emergency Use Authorization for simultaneous detection of influenza viruses and SARS-CoV-2 using respiratory specimens collected from individuals suspected of COVID-19 by their

provider (Centers for Disease Control and Prevention, 2020b). One is the CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay that detects and differentiates ribonucleic acid from SARS-CoV-2, influenza A virus, and influenza B virus in upper or lower respiratory specimens. The assay provides a sensitive, nucleic-acid-based diagnostic tool for evaluation of specimens from patients in the acute phase of infection. It is available for public health purposes only. Two other tests are commercially available through authorized laboratories certified to perform high or moderate complexity tests. They are the BioFire Respiratory Panel 2.1 (RP2.1) and the QIAstat-Dx Respiratory SARS-CoV-2 Panel.

Rapid antigen and immunofluorescence testing can be performed at the site of patient care such as the physician's office or emergency department. Early diagnosis at the point-of-care can have a positive impact on the efficacy of therapy (in general, earlier treatment is more effective than later), but these tests are constrained by a lack of test sensitivity (Abraham, 2016; Nicholson 2014, Petrozzino, 2010). Detection of influenza virus antigen does not necessarily indicate detection of viable infectious virus or on-going influenza viral replication, and none of the rapid influenza diagnostic tests provide any information about influenza A virus subtypes (Centers for Disease Control and Prevention, 2020a). Given the limited sensitivity of the rapid antigen tests for influenza, a negative result should be interpreted with caution given the potential for a false-negative result and empiric treatment for most symptomatic patients may be a foregone conclusion whether testing is conducted or not (Abraham, 2016).

Neither serological testing nor viral culture provides timely, reliable results to help with clinical decision-making and is generally reserved for research and public health investigations (Centers for Disease Control and Prevention, 2020a).

Findings

There is scant medical evidence in support of routine point-of-care testing for influenza in adults and children presenting with acute febrile respiratory conditions. Most analyses do not support routine or screening use of point-of-care tests for influenza; nor do they find compelling evidence of efficacy with regard to improved prescribing of anti-viral medications, avoidance of organism resistance, or in improved clinical outcomes in either adult or child.

The Centers for Disease Control and Prevention (2016) and the Infectious Diseases Society of America (Harper, 2009) have promulgated guidelines regarding influenza testing and treatment. The Centers for Disease Control and Prevention identify reverse-transcriptase polymerase chain reaction-based testing as a preferred method, and note the current drawbacks of rapid testing modalities. The Infectious Diseases Society of America guidelines are more patient-focused and identifies who and when to test and treat.

Recent systematic reviews/meta-analyses showed accuracy of these tests to be essentially unchanged at sensitivity 61%, specificity 99% (Bruning, 2017), and sensitivity 69%, specificity 97% (Gentilotti, 2021). Another systematic review of rapid molecular tests (results available in under three hours) for influenza noted a higher degree of accuracy (sensitivity 90%, specificity 96%) (Vos, 2019).

A systematic review/meta-analysis of 162 studies found pooled sensitivity for influenza A and B was highest for rapid nucleic acid amplification tests (91.6% and 95.4%), compared with digital immunoassays (80.0% and 76.8%) and traditional rapid influenza diagnostic tests (54.4% and 53.2%). Pooled specificities were uniformly greater than 98%) (Merckx, 2017).

A systematic review of 30 studies showed positive results of rapid point-of-care tests for influenza led to increased use of antiviral drugs, and decreased use of antibiotics (Egilmezer, 2018).

A systematic review of 11 studies (n = 9,106) showed point-of-care testing for influenza had no effect on admissions, returning for care, or antibiotic prescribing. Testing was associated with increased prescribing of antivirals, and less subsequent testing for full blood counts, blood cultures, and chest radiography (Lee, 2019). In 2017, the U.S. Food and Drug Administration required rapid influenza diagnostic tests to achieve at least 80% sensitivity compared to reverse transcriptase polymerase chain reaction tests. It also requires, compared with viral culture, at least 90% sensitivity for detecting influenza A and 80% sensitivity for detecting influenza B viruses. Required specificity rates are 95% (Centers for Disease Control and Prevention, 2019).

Several Medicare Local Coverage Determinations declare influenza testing is not needed for all patients with signs and symptoms of influenza to make antiviral treatment decisions, and that a clinical diagnosis of influenza can be made for outpatients with signs and symptoms consistent with suspected influenza, especially during periods of peak influenza activity in the community. In addition, influenza testing is most appropriate for hospitalized patients if a positive test would result in a change in clinical management, and that antiviral treatment should not be withheld from patients with suspected influenza awaiting test results during peak influenza periods in the community (Centers for Medicare & Medicaid Services, 2019/2020).

We did not identify any new relevant publications in 2018. The policy ID changed from 07.01.08 to CCP.1330.

In 2019, we updated one professional society guideline. The Infectious Diseases Society of America updated its guidelines regarding seasonal influenza testing as indicated below. All of these recommendations, but one, are categorized as A-III:

- In outpatients, including patients seen in the emergency department, clinicians should test for influenza in the following groups:
- High-risk patients, including immunocompromised people with signs of influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without fever), if the test result will influence clinical management (A–III).
- Patients who present with acute onset of respiratory symptoms, febrile or afebrile, and one of these:
- Exacerbation of chronic medical conditions (such as asthma, chronic obstructive pulmonary disease, or heart failure).
- Known complications of influenza (such as pneumonia) if the result will influence clinical management (A-III).
- Clinicians can consider influenza testing for those who are not at increased risk for influenza complications, who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (for example, cough and afebrile) and who are either:
- Likely to be discharged if the test results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department, or
- If the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (C-III).
- In hospitalized patients, clinicians should test on admission all of the following patients:
- With acute respiratory illness, including pneumonia, febrile or afebrile (A-II).
- With acute worsening of chronic cardiopulmonary disease (including chronic obstructive pulmonary disease, asthma, coronary artery disease, or heart failure), as there is an association between influenza and exacerbation of these chronic diseases (A-III).
- Who are immunocompromised or at high risk of complications and present with acute onset of respiratory symptoms, febrile or afebrile, as the signs of influenza in such patients are not characteristic of those in immunocompetent individuals (A-III).

In addition, unlike the 2009 version, the updated guideline of the Infectious Diseases Society of America (2019) include recommendations for the types of influenza assays to be used according to the patient or population being tested. The following have been added to the policy limitations:

- In outpatients, providers should use rapid molecular assays (nucleic acid amplification tests) rather than rapid influenza diagnostic tests to improve detection of influenza virus infection (A-II).
- In hospitalized patients, providers should use reverse-transcription polymerase chain reaction or other molecular assays to improve detection of influenza virus infection.
- In immunocompromised inpatients, providers should use multiplex reverse-transcription polymerase chain reaction assays to target a panel of respiratory pathogens, including influenza viruses (A-III).
- In inpatients who are not immunocompromised, providers can consider using multiplex reverse-transcription polymerase chain reaction assays to target a panel of respiratory pathogens, including influenza viruses, if it might influence care (B-III).
- Clinicians should not use immunofluorescence assays for influenza virus antigen detection, except when more sensitive molecular assays are not available (A-II), and follow-up testing with reverse-transcription polymerase chain reaction or other molecular assays should be performed to confirm negative immunofluorescence test results (A-III).
- Clinicians should not use rapid influenza diagnostic tests in hospitalized patients except when more sensitive molecular assays are not available (A-II). Follow-up testing with reverse-transcription polymerase chain reaction or other molecular assays should be performed to confirm negative rapid influenza diagnostic test results (A-II).
- Clinicians should not use viral culture for initial or primary diagnosis of influenza (A-III), but viral culture can be considered to confirm negative test results from rapid influenza diagnostic tests and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization (C-II).
- Clinicians should not use serologic testing for diagnosis of influenza because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera two to three weeks apart are needed for serological testing (A-III).

In 2020, we identified no newly published, relevant literature to add to the policy. We clarified the criteria for inpatient and outpatient testing defined by the Infectious Diseases Society of America 2019 guideline regarding the appropriate use of seasonal influenza testing, including the use of multiplex reverse transcription polymerase chain reaction testing that has been approved and Clinical Laboratory Improvement Amendments-waived for office use.

In 2021, we modified the coverage to limit use of respiratory viral panel testing using reverse-transcription polymerase chain reaction assay targets to testing performed in an inpatient facility, observation, or emergency setting only.

References

On December 20, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Influenza, Human/diagnosis"[MAJR], “seasonal influenza,” “assay,” and “test.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Abraham MK, Perkins J, Vilke GM, Coyne CJ. Influenza in the emergency department: vaccination, diagnosis, and treatment: Clinical practice paper approved by American Academy of Emergency Medicine Clinical Guidelines Committee. *J Emerg Med*. 2016 Mar;50(3):536-42. Doi: 10.1016/j.jemermed.2015.10.013.

Bruning AHL, Leeflang MMG, Vos JMBW, et al. Rapid tests for influenza, respiratory syncytial virus, and other respiratory viruses: A systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(6):1026-1032. Doi: 10.1093/cid/cix461.

Centers for Disease Control and Prevention. Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm. Published February 4, 2019.

Centers for Disease Control and Prevention. Overview of influenza testing methods. https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm. Reviewed August 31, 2020. (a)

Centers for Disease Control and Prevention. Table 4. Multiplex assays authorized for simultaneous detection of influenza viruses and SARS-CoV-2 by FDA. https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html. Reviewed December 10, 2020. (b)\

Centers for Disease Control and Prevention. Algorithm to assist in medical office telephone evaluation of patients with possible influenza. https://www.cdc.gov/flu/professionals/antivirals/office-evaluation.htm. Reviewed August 31, 2020. (c)

Centers for Medicare & Medicaid Services. Nucleic Acid Amplified Tests for Respiratory Viral Panels. Local Coverage Determinations L37315, L37318, L37713, and L37764. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37348&ver=13&keyword=nucleic%20acid%20amplified%20tests%20for%20respiratory%20viral%20panels&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Effective various dates, 2019 and 2020.

Ebell MH, Afonso AM, Gonzales R, Stein J, Genton B, Senn N. Development and validation of a clinical decision rule for the diagnosis of influenza. *J Am Board Fam Med*. 2012;25(1):55-62. Doi: 10.3122/jabfm.2012.01.110161.

Egilmezer E, Walker GJ, Bakthavathsalam P, et al. Systematic review of the impact of point-of-care testing for influenza on the outcomes of patients with acute respiratory tract infection. *Rev Med Virol*. 2018;28(5):e1995. Doi: 10.1002/rmv.1995.

Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60(1):1-24. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm.

Gentilotti E, De Nardo P, Cremonini E, et al. Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections. A systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;S1198-743X(21)00551-6. Doi: 10.1016/j.cmi.2021.09.025.

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):1003-32. Doi: 10.1086/598513.

Lee JJ, Verbakel JY, Goyder CR, et al. The clinical utility of point-of-care tests for influenza in ambulatory care: A systematic review and meta-analysis. *Clin Infect Dis*. 2019;69(1):24-33. Doi: 10.1093/cid/ciy837.

Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: A systematic review and meta-analysis. *Ann Intern Med*. 2017;167(6):394-409. Doi: 10.7326/M17-0848.

Nicholson KG, Abrams KR, Batham S, et al. Randomized controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. *Health Technol Assess*. 2014;18(36):1-274, vii-viii. Doi: 10.3310/hta18360.

Petrozzino JJ, Smith C, Atkinson MJ. Rapid diagnostic testing for seasonal influenza: an evidence-based review and comparison with unaided clinical diagnosis. *J Emerg Med*. 2010;39(4):476-490.e1. Doi: 10.1016/j.jemermed.2009.11.031.

U.S. Food and Drug Administration. 510(k) Premarket Notification database searched using product code OCC. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. *Clin Infect Dis*. 2019;68(6):895-902. Doi: 10.1093/cid/ciy874.

Vos LM, Bruning AHL, Reitsma JB, et al. Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: A systematic review of diagnostic accuracy and clinical impact studies. *Clin Infect Dis*. 2019;69(7):1243-1253. Doi: 10.1093/cid/ciz056.

Policy updates

8/2017: initial review date and clinical policy effective date: 10/2017

9/2018: Policy references updated. Policy ID changed.

9/2019: Policy references updated. Limitations added to coverage.

9/2020: Policy references updated. Coverage section reorganized by inpatient and outpatient indications.

4/2021: Policy references updated. Limitations section modified.

3/2022: Policy references updated.