Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests for the 2010-2011 Influenza Season

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Background

Rapid influenza diagnostic tests (RIDTs) are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and display the result in a qualitative way (positive vs. negative). In the United States, a number of RIDTs are commercially available. (See “Table 1: Influenza Virus Testing Methods” and "Table 2: Characteristics of Rapid Influenza Diagnostic Tests".) The reference standards for laboratory confirmation of influenza virus infection are reverse transcription-polymerase chain reaction (RT-PCR) or viral culture. RIDTs can yield results in a clinically relevant time frame, i.e., approximately 15 minutes or less. However, RIDTs have limited sensitivity to detect influenza virus infection and negative test results should be interpreted with caution given the potential for false negative results.

Advantages and Disadvantages of RIDTs

Advantages

- Produce quick result in 15 minutes or less, simple to perform
- Some RIDTs are approved for office/bedside use

Disadvantages

- Sub-optimal test sensitivity, false negative results are common, especially when influenza activity is high
- Although specificity is high, false positive results can also occur, especially during times when influenza activity is low
- Some RIDTs distinguish between influenza A or B virus infection while others do not. RIDTs that provide results on type of influenza virus (e.g. influenza A or B virus), do not provide information on influenza A virus subtype (e.g. A/H1N1 versus A/H3N2) or specific strain information (e.g. degree of similarity to vaccine strains)

Use of RIDTs in Clinical Decision-making

RIDTs may be used to help with diagnostic and treatment decisions for patients in clinical settings, such as whether to prescribe antiviral medications. However, due to the limited sensitivities and predictive values of RIDTs, negative results of RIDTs do not exclude influenza virus infection in patients with signs and symptoms suggestive of influenza. Therefore, antiviral treatment should not be withheld from patients with suspected influenza even if they test negative. More information about antiviral drugs and recommendations on their use during the 2010-2011 season are available at Antiviral Drugs, Information for Health Care Professionals at http://www.cdc.gov/flu/professionals/antivirals/index.htm.

Testing is not needed for all patients with signs and symptoms of influenza to make antiviral treatment decisions (See Figures 1-4). Once influenza activity has been documented in the community or geographic area, 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.

Use of RIDTs for Public Health Purposes to Detect Influenza Outbreaks

RIDTs can be useful to identify influenza virus infection as a cause of respiratory outbreaks in any setting, but especially in institutions (i.e., nursing homes, chronic care facilities, and hospitals), cruise ships, summer camps, schools, etc. Positive RIDT results from one or more ill persons with suspected influenza can support decisions to promptly implement prevention and control measures for influenza outbreaks. However, negative RIDT results do not exclude influenza virus infection as a cause of a respiratory outbreak because of the limited sensitivity of these tests. Testing respiratory specimens from several persons with suspected influenza will increase the likelihood of detecting

influenza virus infection if influenza virus is the cause of the outbreak. Public health authorities should be notified of any suspected institutional outbreak and respiratory specimens should be collected from ill persons (whether positive or negative by RIDT) and sent to a public health laboratory for more accurate influenza testing.

Factors Influencing Results of RIDTs

Many factors can influence the accuracy of RIDTs, including:

- Clinical signs and symptoms consistent with influenza
  - Having clinical signs and symptoms consistent with influenza increases the pre-test probability of influenza virus infection, which increases the reliability of a positive RIDT result.
- Prevalence of influenza activity in the population tested
  - Influenza activity varies seasonally, which directly affects the predictive values of RIDTs (See algorithms below [Figures 3 and 4], and "Prevention Strategies for Seasonal Influenza in Heath Care Settings" at http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm)
- Time from illness onset to collection of respiratory specimens for testing
  - Testing specimens collected within 48-72 hours of illness onset (when influenza viral shedding is highest) is more likely to yield positive RIDT results.
- Type of respiratory specimen tested
  - RIDTs have different specifications for acceptable specimens (e.g. nasopharyngeal, nasal or throat swab/aspirate). The package insert for the RIDT test used should be reviewed to ensure that an appropriate specimen is collected, and test procedures are followed. Some tests may require specimen collection using a special swab (some RIDTs must be used with a swab supplied with the test kit; some swab material can interfere with RIDT results).
  - RIDTs must also ensure that the appropriate viral transport media or other media is used, consistent with test specifications, if testing is done at a different location from where the specimen is collected from the patient.
  - Collection of good quality respiratory specimens (e.g. nasopharyngeal or nasal swab/aspirate/wash or combined nasal/throat swab specimens) also will increase accuracy of RIDT results.
  - Some RIDTs require that the entire collected specimen be used in the test. Consider whether a second specimen should be collected for confirmatory testing using viral culture and/or RT-PCR.
- Accuracy of the test compared to a reference test ("gold standard" = RT-PCR or viral culture)
  - Sensitivity of the RIDT
    - Proportion of positive RIDT results of all positive “gold standard test” results (RT-PCR or viral culture)

        - Fixed characteristic of a test; generally low to moderate (10-70%) for RIDTs
            - An RIDT with low sensitivity will produce negative results in patients with influenza (false negatives)
    - Specificity of the RIDT
        - Proportion of negative RIDT results of all negative "gold standard test" results (RT-PCR or viral culture)
        - Fixed characteristic of a test; generally very high for RIDTs (90-95%)
            - An RIDT with very high specificity will not produce many positive results in patients who do not have influenza (few false positives)

Interpretation of Rapid Test Results

The reliability of RIDTs depends largely on the conditions under which they are used. Understanding some basic considerations can minimize being misled by false-positive or false-negative results.

- Sensitivities of RIDTs are generally 40-70%, but a range of 10-80% has been reported compared to viral culture or RT-PCR. Specificities of RIDTs are approximately 90-95% (range 85-100%). Thus false negative results occur more commonly than false positive results.
    - Negative results of RIDTs do not exclude influenza virus infection and influenza should still be considered in a patient if clinical suspicion is high based upon history, signs, symptoms and clinical examination.
- False-positive (and true-negative) results are more likely to occur when disease prevalence in the community is low, which is generally at the beginning and end of the influenza season and during the summer.
    - The negative predictive value of an RIDT (the proportion of patients with negative results who do not have influenza) is highest when influenza activity is low.
    - The positive predictive value of an RIDT (the proportion of patients with positive results who have influenza) is lowest when influenza activity is low.
- False-negative (and true-positive) results are more likely to occur when disease prevalence is high in the community.
    - The positive predictive value of an RIDT (the proportion of patients with positive results who have influenza) is highest when influenza activity is high
    - The negative predictive value of an RIDT (the proportion of patients with negative results who do not have influenza) is lowest when influenza activity is high

Minimize False Results

- Collect specimens as early in the illness as possible (ideally less than 4 days from illness onset).
- Follow manufacturer's instructions, including acceptable specimens, and handling.
- Follow-up negative results with confirmatory tests (RT-PCR or viral culture) if a laboratory-confirmed influenza diagnosis is desired.

Information on Local Influenza Activity

Clinicians should contact their local or state health department for information about current influenza activity. Information on national influenza activity is available on the CDC Influenza Activity & Surveillance page at http://www.cdc.gov/flu/weekly/fluactivitysurv.htm.

When to Consider Further Influenza Testing

Consider sending respiratory specimens for influenza testing by viral culture or RT-PCR to confirm results of an RIDT when:

- A patient tests negative by RIDT when community influenza activity is high and laboratory confirmation of influenza is desired.
- A patient tests positive by RIDT and the community prevalence of influenza is low, and a false positive result is a consideration.
- A patient has had recent close exposure to pigs or poultry or other animals and novel influenza A virus infection is possible (e.g. influenza viruses circulate widely among swine and birds, including poultry, and also can infect other animals such as horses and dogs)

Hospitalized patients

Influenza testing is recommended for hospitalized patients with suspected influenza. However, empiric antiviral treatment should be initiated as soon as possible without the need to wait for any influenza testing results (see Antiviral Drugs, Information for Health Care Professionals at http://www.cdc.gov/flu/professionals/antivirals/index.htm). Antiviral treatment should not be stopped based on negative RIDT results given the limited sensitivities of RIDTs. Infection control measures should be implemented immediately upon admission for any hospitalized patient with suspected influenza even if RIDT results are negative (see "Prevention Strategies for Seasonal Influenza in Heath Care Settings" at http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm). Respiratory specimens can be tested for influenza by immunofluorescence, RT-PCR or viral culture. Serology should not be performed for clinical management. Clinicians should understand that negative results of influenza testing do not exclude influenza virus infection, especially if the time from illness onset to collection of respiratory specimens is more than 5 to 7 days, or if upper respiratory specimens were tested and the patient has lower respiratory tract disease. If influenza is suspected, testing of

clinical specimens collected from different respiratory sites can be done (e.g. upper and lower respiratory tract) and can be collected on more than one day to increase likelihood of influenza detection; intubated patients should have endotracheal aspirate specimens tested if influenza is suspected, but not yet confirmed.

Detection of influenza virus infection and prompt implementation of control measures is critical to prevention of nosocomial influenza outbreaks. When there is influenza activity in the community, clinicians should consider influenza testing, including viral culture, for patients who develop signs and symptoms of influenza while they are in a health care facility. This should be done as part of a broader surveillance strategy for influenza as discussed in "Prevention Strategies for Seasonal Influenza in Heath Care Settings" at http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm)

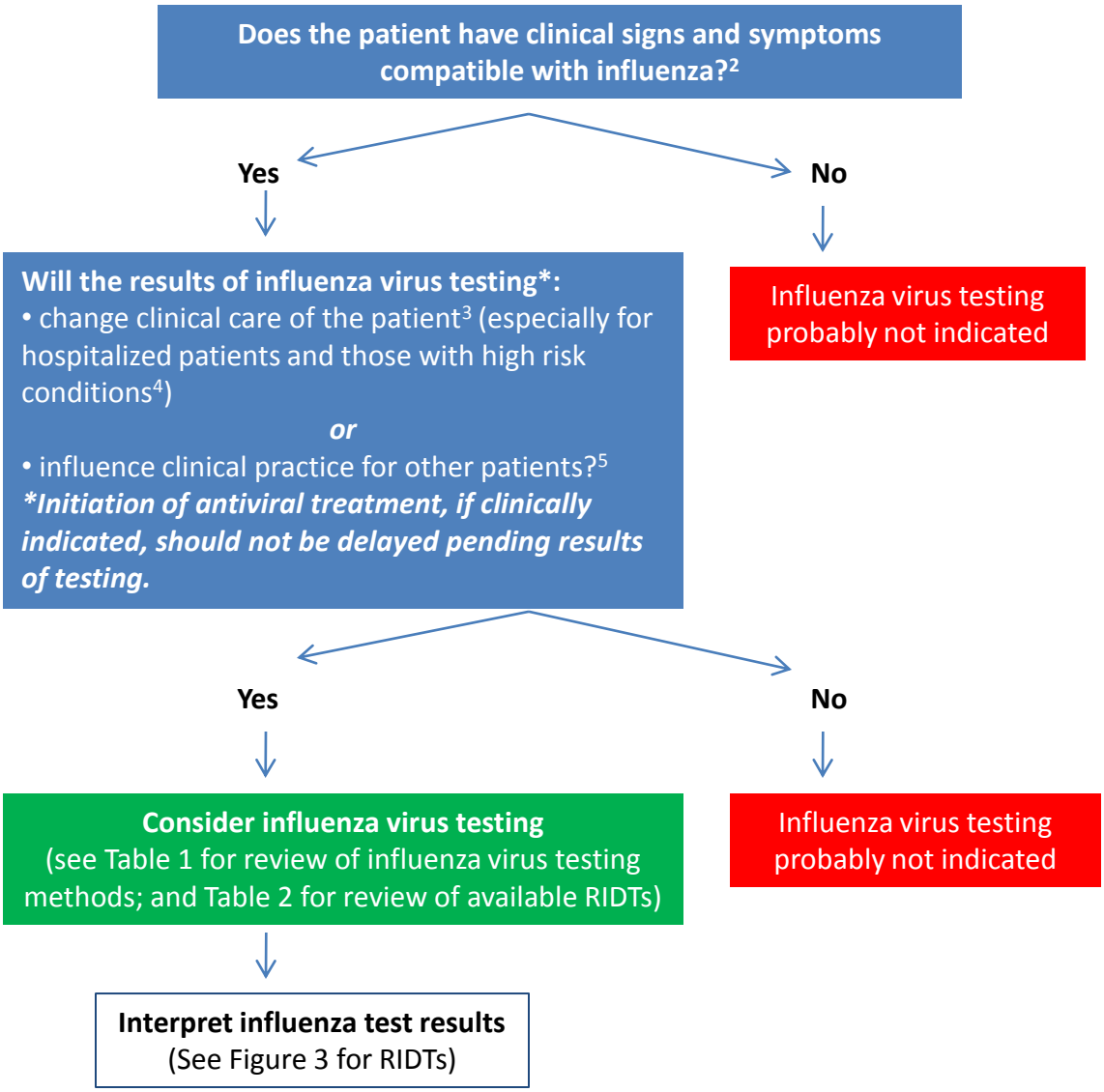
Suspected influenza institutional outbreaks

For suspected influenza outbreaks in institutions, respiratory specimens should be collected from patients with suspected influenza as early as possible once the outbreak is suspected (See Figure 2). If RIDTs are used in these settings, clinical specimens should also be sent for influenza testing by viral culture and RT-PCR to provide detailed information on specific influenza A virus subtype and strains, and antiviral susceptibility data and to verify RIDT test results. Surveillance for suspected influenza illness and collection of specimens from patients with suspected influenza should continue through at least 2 weeks after implementation of control measures to assess effectiveness of the measures and to monitor for potential emergence of antiviral resistance. See "Prevention Strategies for Seasonal Influenza in Heath Care Settings" at http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm)

Influenza Surveillance

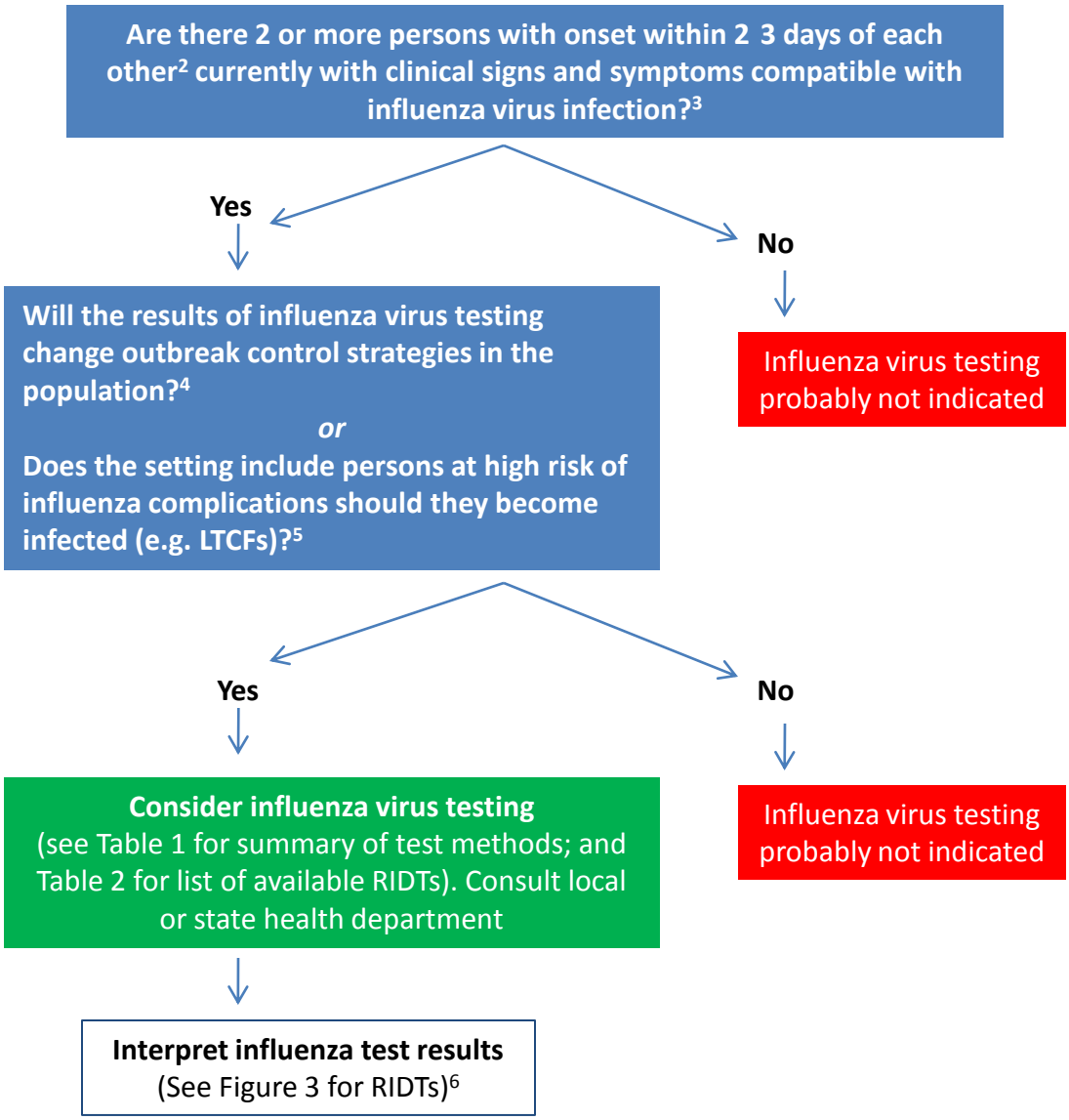
Laboratory-based surveillance for influenza viral isolates is critically important to the selection of viruses for the next season's influenza vaccine. Virus isolates are needed in order to characterize the circulating influenza virus subtypes and strains and to determine how well they are matched to vaccine strains. Isolates are also needed for obtaining information on the emergence and prevalence of antiviral resistant strains, and the identification of human infection with novel influenza A virus (e.g. an influenza A virus of animal origin that may occasionally cause illnesses in people) that may have pandemic potential. This information is needed from specimens sent for viral culture and RT-PCR year round for identification of novel strains or antigenically-drifted variant strains, including during times of low influenza activity such as at the beginning and end of influenza seasonal activity. Information on national influenza activity is available on the CDC influenza website Flu Activity & Surveillance page at http://www.cdc.gov/flu/weekly/fluactivitysurv.htm.

Figure 1. Guide for considering influenza virus diagnostic tests for individual patients when influenza viruses are circulating in the community[1]



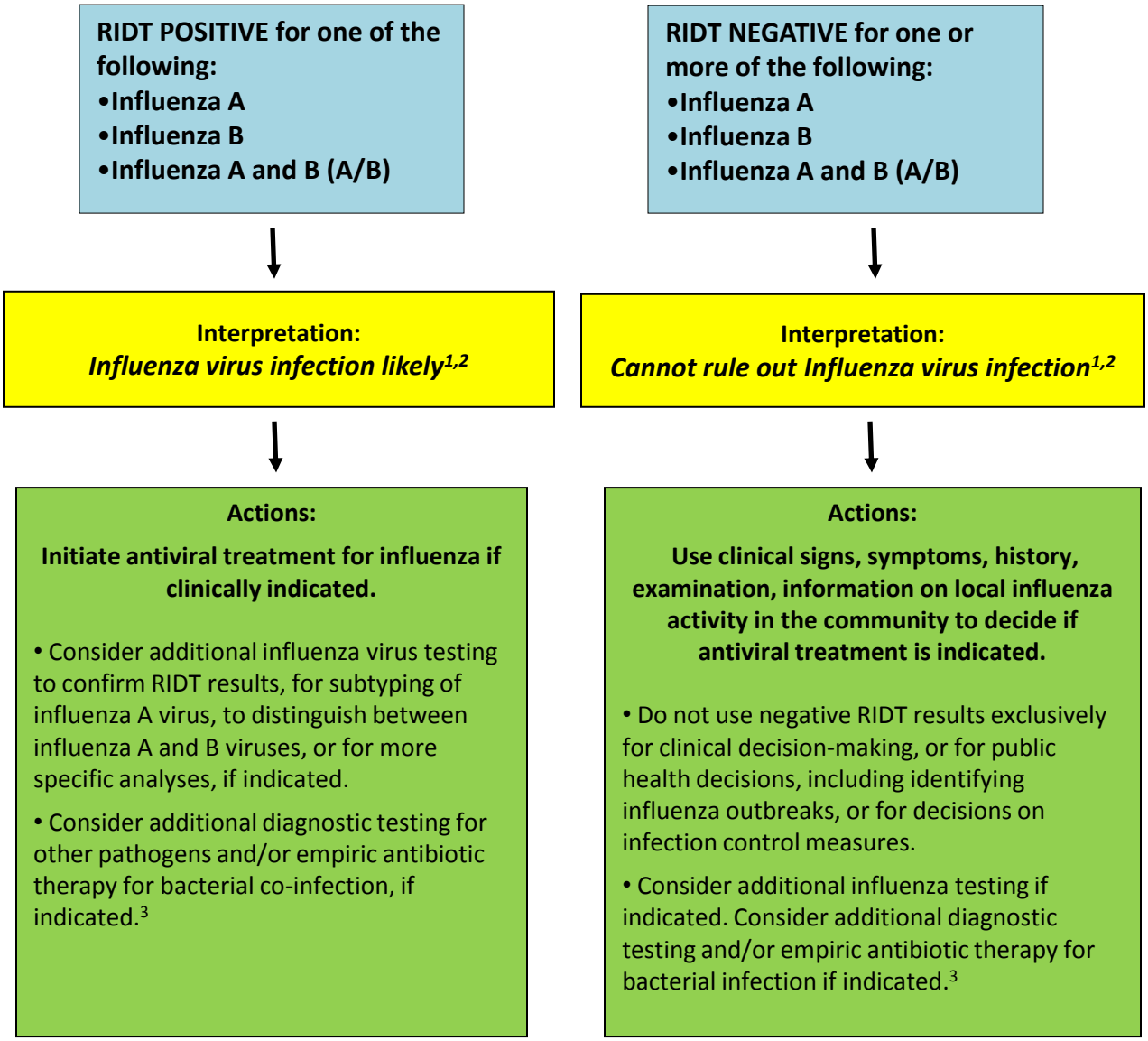
1. Confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications. Decisions to administer antiviral medications for influenza treatment or chemoprophylaxis , if indicated, should be based upon clinical illness and epidemiologic factors, and start of therapy should not be delayed pending testing results. (*place link to CDC website guidance*). **Respiratory specimens should be collected from an ill patient as early as possible after onset of symptoms (ideally <48-72 hours after onset) to help maximize influenza testing sensitivity.**
2. Influenza like-illness (history of feverishness or documented fever with either cough or sore throat), fever with other respiratory symptoms, etc. Note that some persons may have atypical presentations (e.g. elderly , very young infants, immunosuppressed, and patients with certain chronic medical conditions). Fever is not always present (e.g. premature infants, young infants, elderly, immunosuppressed). Other symptoms associated with influenza include myalgias, headache, fatigue. Complications include exacerbation of underlying chronic disease, (e.g. congestive cardiac failure, asthma), pneumonia, bacterial co-infection, bronchiolitis, croup, encephalopathy, seizures, myositis, and others.
3. e.g. Decisions on use of antibiotics or antiviral medications, on conducting further diagnostic tests, on recommendations for home care, or on recommendations for ill persons living with persons with high-risk conditions. Consult IDSA, ATS, AAP, ACIP for antibiotic guidance.
4. Persons ≥65 years or <2 years; pregnant women; persons with chronic lung disease (including asthma), heart disease, renal, metabolic, hematologic and neurologic disease; immunosuppression; and morbid obesity.
5. e.g. Decisions on changing infection control practices (such as in hospitalized patients); if a positive influenza test result is used for confirming influenza virus circulation in the community which might inform clinical practices related to home care guidance, hospital infection control practices, future testing practices, etc

Figure 2. Guide to use of influenza virus diagnostic tests in investigating outbreaks in institutional or other closed settings[1]



1. Examples of institutional or closed settings include long-term care facilities, nursing homes, schools, correctional facilities, hospitals, ships.
2. In settings where persons at high-risk of influenza complications reside, a single case of suspected influenza is sufficient for triggering influenza testing and consideration of implementation of empiric control measures, including active surveillance for new illness cases.
3. e.g., Influenza like-illness (fever with either cough or sore throat), fever with other respiratory symptoms, etc. Note that some persons may have atypical presentations (e.g. elderly , very young infants, immunosuppressed, and patients with certain chronic medical conditions). Fever is not always present. Other symptoms associated with influenza include myalgias, headache, fatigue. Complications include exacerbation of underlying chronic disease, (e.g. congestive cardiac failure, asthma), pneumonia, bacterial co-infection, bronchiolitis, croup, encephalopathy, seizures, myositis, and others.
4. e.g., use of antivirals empirically for treatment or for chemoprophylaxis of influenza, changes in infection control practices (isolation or cohorting of ill, quarantine of exposed), changes in admission or staffing policies, or changes in social distancing recommendations , etc.
5. Persons ≥65 years or <2 years; pregnant women; persons with chronic lung disease (including asthma), heart disease, renal, metabolic, hematologic and neurologic disease; immunosuppression; and morbid obesity.
6. In an outbreak setting, because of the low sensitivity of RIDTs, use of the tests on specimens from more than one ill person is recommended. The presence of any influenza positives among persons with clinically compatible illnesses is supportive of influenza as the probable cause of the outbreak. Confirmation of RIDT results by more specific influenza testing is indicated.

Figure 3. Algorithm to assist in the interpretation of RIDT results and clinical decision-making during periods <u>when influenza viruses are circulating</u> in the community[1]



1. During periods when influenza activity is high and influenza viruses are circulating among persons in the community (see 3. below), the positive predictive value of a test result is high (that is, the chance that a positive result indicates that the patient has influenza is high), and the negative predictive value of a test result is low (the chance that a negative result is a true negative is low) due to low sensitivity of RIDTs to detect influenza virus in respiratory specimens compared to RT-PCR or viral culture**: false negative results are common**.
2. Influenza virus infection may include seasonal influenza A (H3N2), 2009 H1N1, influenza B, or rarely, a novel influenza A virus infection. The interpretation of RIDTs will, in part, depend on the test used - some will detect influenza A, some will detect influenza B and some will detect both A and B viruses. If tests for both influenza A and influenza B are positive, refer specimen to a public health laboratory for resolution, as dual infections are uncommon.
3. Consult local or state health departments or other sources (e.g. virology testing at a local hospital) for local activity on other respiratory pathogens associated with acute respiratory illness. Empiric antibiotic coverage should include coverage for *Streptococcus pneumoniae*, *Staphylococcus aureus* (including MRSA), Group A *Streptococcus*, and others, especially for hospitalized adult patients per IDSA/ATS CAP guidelines.

Figure 4. Algorithm to assist in the interpretation of RIDT results and clinical decision-making during periods when influenza viruses are not circulating or influenza activity is low in the community[1]

1. During periods when influenza activity is low and there is low influenza virus circulation among persons in the community, the positive predictive value of a rapid influenza diagnostic test is low (that is, the chance that a positive result indicates that the patient has influenza is **low**), and the negative predictive value is high (the chance that a negative result is a true negative is high). Even though RIDTs have high specificity, **false positive RIDT results are more common when influenza activity is low.**
2. Influenza virus infection may include seasonal influenza A (H3N2), 2009 H1N1, influenza B, or rarely, a novel influenza A virus infection. The interpretation of RIDTs will, in part, depend on the test used - some will detect influenza A, some will detect influenza B and some will detect both A and B viruses. If tests for both influenza A and influenza B are positive, refer specimen to a public health laboratory for resolution, as dual infections are uncommon.
3. Consult local or state health departments or other sources (e.g. virology testing at a local hospital) for local activity on other respiratory pathogens associated with acute respiratory illness. Empiric antibiotic coverage should include coverage for *Streptococcus pneumoniae*, *Staphylococcus aureus* (including MRSA), Group A *Streptococcus*, and others, especially for hospitalized adult patients per IDSA/ATS CAP guidelines.

Table 1. Influenza Virus Testing Methods

Method[1]	Types Detected	Acceptable Specimens[3]	Test Time[3]	CLIA Waived
Viral cell culture (conventional)	A and B[2]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	No
Rapid cell culture (shell vials; cell mixtures)	A and B[2]	As above	1-3 days	No
Immunofluorescence, Direct (DFA) or Indirect (IFA) Antibody Staining	A and B[2]	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[4] (singleplex and multiplex; real-time and other RNA-based)	A and B[2]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (Generally 1-6 hours)	No[5]
Rapid Influenza Diagnostic Tests[6]	A and B	NP swab, (throat swab), nasal wash, nasal aspirate	<30 min.	Yes/No

1. Serologic (antibody detection) testing is not recommended for routine patient diagnosis.
2. May be adapted to identification of specific subtypes
3. Ref: Leland, et al. 2007, Clin Micro Rev 20: 49-78. **Approved respiratory specimens vary among FDA cleared influenza assays.**
4. Reverse transcriptase polymerase chain reaction, including FDA-approved test systems, reference laboratory testing using ASR or lab-developed reagents
5. Random-access, single cartridge tests may be moderately complex
6. Immunochromatographic lateral flow and membrane-based immunoassays

Table 2. Characteristics of Rapid Influenza Diagnostic Tests[1]

Procedure Manufacturer/Distributor	Influenza Virus Types Detected	Approved Specimens[1]	Test Time
3M™ Rapid Detection Flu A+B Test[4,6] (3M)	A and B	NP[2] swab/aspirate Nasal wash/aspirate	15 minutes
BinaxNOW® Influenza A&B[5,6] (Alere)	A and B	NP[2] swab Nasal wash/aspirate/swab	15 minutes
Clearview®Exact Influenza A & B[4,6] (Alere)	A and B	Nasal swab	15 minutes
Directigen™ EZ Flu A+B[4,6] (Becton-Dickinson)	A and B	NP[2] wash/aspirate/swab Throat swab	15 minutes
OSOM® Influenza A&B[4,6] (Genzyme)	A and B	Nasal swab	10 minutes
QuickVue® Influenza Test[3,5] (Quidel)	A or B	Nasal wash/ aspirate/swab	10 minutes
QuickVue® Influenza A+B Test[5,6] (Quidel)	A and B	NP[2] swab Nasal wash/ aspirate/swab	10 minutes
SAS™FluAlert A&B[4,6] (SA Scientific)	A and B	Nasal wash/aspirate	15 minutes
SAS™FluAlert A[3,5] (SA Scientific)	A only	Nasal wash/aspirate	15 minutes
SAS™FluAlert B[3,5] (SA Scientific)	B only	Nasal wash/aspirate	15 minutes
TRU FLU®[4,6] (Meridian Bioscience)	A and B	NP[2] aspirate/swab Nasal wash	15 minutes
XPECT™ Flu A&B[4,6] (Remel/Thermofisher)	A and B	Nasal wash/swab Throat swab	15 minutes

1. List may not include all test kits approved by the U.S. Food and Drug Administration. Discontinued tests not included. Approved respiratory specimens according to manufacturer's package insert. Note that test performance may vary if other respiratory specimens are used.
2. NP = nasopharyngeal.
3. Does not distinguish between influenza A and B virus infections when used alone.
4. Moderately complex test – requires specific laboratory certification.
5. CLIA-waived test. Can be used in any office setting. Requires a certificate of waiver or higher laboratory certification.
6. Distinguishes between influenza A and B virus infections.

Disclaimer: Use of trade names or commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention or the Department of Health and Human Services.

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