

## REVIEW ARTICLE

### RAPID INFLUENZA DIAGNOSTIC TESTS - INDICATIONS, CLINICAL IMPLICATIONS AND USEFULNESS

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#### Abstract

Influenza is a common, acute infectious disease causing seasonal epidemics. The clinical diagnosis of influenza is mainly based on the presence of non-specific influenza-like symptoms and the knowledge regarding prevalence of influenza viruses in a population. To improve accuracy of the clinical diagnosis of influenza, more sensitive laboratory test should be conducted, including real time RT-PCR method and rapid influenza diagnostic tests (RIDTs). RT-PCR method is recommended, but is expensive, time consuming and not always available. RIDTs are more accessible and usually are office-based, however their results should be interpreted carefully. Many factors may influence the RIDT results - patient age, duration of symptoms and the type of specimen. In the epidemic season positive results of RIDT confirm the presumptive diagnosis of influenza while negative results do not exclude it. Regardless of RIDTs' limitations, they may be used both in hospital and ambulatory care settings to guide treatment decisions and rationalize the use of antivirals (neuraminidase inhibitors).

**Keywords :** flu, diagnostics, clinical assessment, point of care test

#### Context

Influenza occurs globally affecting yearly about 5-10% of the general population and 20-30% children, during epidemics and even more during sporadic pandemics. It affects all age groups and can cause serious complications in "high risk" individuals including children in first two years of life, pregnant women, the elderly or those with concomitant diseases (e.g. chronic respiratory disease, diabetes, neuromuscular disorder, and immunodeficiency). It is estimated that 250,000-500,000 die in result of influenza infection. (1) Typical symptoms include: fever, cough, sore throat, nasal congestion or rhinorrhoea, headache, muscle pain and malaise. Immunization is the primary measure to prevent morbidity and mortality from influenza (1,2). Antiviral treatment of patients belonging to risk groups brings clear benefits and should be preferably started within 48 hours of onset of symptoms. (1,2). The diagnosis of influenza is usually based upon clinical presentation but the sensitivity and specificity of clinical diagnosis is limited due to overlap with symptoms of other diseases. The diagnostic accuracy may be improved by awareness of local epidemiology of influenza and use of lab tests, including rapid viral tests.

#### Objective

Assessment of indications, clinical implications and usefulness of rapid influenza diagnostic tests in children.

#### Methods and Data Sources

A narrative literature review of evidence about Rapid Influenza Diagnostic Tests in children was

conducted. The most recent clinical guidelines from professional societies were complemented by meta-analyses, systematic reviews, and randomized clinical trials. To identify evidence-based articles, the MEDLINE, and EMBASE were searched through January 2016 using the following Medical Subject Headings terms: "influenza" AND "diagnostic tests" OR "rapid test" OR laboratory test".

#### Results

##### 1. Influenza

Influenza has been likened to 'the last uncontrolled plague in human history' (Dr. Kevin Sullivan), each year 3-5 million individuals develop severe disease and 250,000-500,000 die in result of influenza infection. (1) Yearly there are influenza epidemics or pandemics. The seasonality of infections depends on geographical location, in temperate climates epidemics occur mainly during the winter, however in tropical climates epidemics can be irregular and occur at any time of the year. While the sequelae risk in the general population is estimated to be around 6%, most patients remain asymptomatic or develop self-limiting acute febrile illness. Influenza can affect all age groups; at risk of severe complications are those in the extremes of age - those below 2 years of age or above 65, pregnant women or those with impaired immune systems or with chronic medical diseases. (1,2) However, mortality from influenza in the paediatric population is rare; during the 2003/2004 epidemic in the United States, the mortality was estimated at around 2.1/100,000. The most common sequelae in the paediatric population are acute otitis media, sinusitis, bronchiolitis, myositis, pneumonia, febrile seizures and exacerbations of asthma symptoms. (1,2) Evidence supports benefits of antiviral treatment of high risk patients. (2) In light of this, the quick diagnosis and prompt treatment of this disease is paramount in both the hospital and outpatient clinic settings.

##### 2. Diagnosing influenza infection

In ambulatory care the diagnosis of influenza is usually based on clinical presentation. Typical patient complaints are abrupt fever onset and dry cough, but patients may present with some or all of influenza-like illness symptoms including fever, cough, chills, sore throat, nasal congestion or rhinorrhoea, weakness, fatigue, generalized or frontal headache, arthralgia, muscle pain and malaise. (1-3) The severity, intensity and frequency of the symptoms vary and clinical diagnosis may be difficult due to lack of specificity. (3) The leukocyte count may be normal or decreased. Although influenza-like symptoms are well known, the accuracy of clinical diagnosis based on symptoms alone may be limited due to overlap with symptoms of other diseases and the clinical findings may not be sufficient to confirm or exclude diagnosis of influenza (likely reliable evidence based on

systematic review). (3) A systematic review of 6 studies evaluating diagnosis of influenza based on clinical signs and symptoms in 7,105 patients with reference diagnosis made by laboratory confirmation (by culture, polymerase chain reaction, immunofluorescent antibody, and/or 4-fold increase in diagnostic antibody titer) found that in patients of any age, no clinical finding is associated with increased likelihood of influenza (defined as summary likelihood ratio > 2), but absence of fever, absence of cough and absence of nasal congestion were associated with decreased likelihood of influenza (defined as summary likelihood ratio < 0.5). (3)

While influenza should be suspected in children with typical symptoms such as fever and cough during influenza season in the community, a definitive diagnosis should be based upon testing. However according to the World Health Organization (WHO) and Center for Disease Control (CDC), once influenza activity has been documented in a community or geographic area, clinical diagnosis of influenza without testing is acceptable, especially during periods of peak influenza activity. (4,5)

**3. Laboratory tests**

An accurate diagnosis of influenza purely basing on symptoms alone is near impossible as the symptoms are protean and non-specific, it is estimated that while in adults during flu season the symptom specificity is about 80%, but it may be as low as 20% in children under 3. (6). In light of this, laboratory tests should be used to determine infection. According to the WHO, nasal aspirates, nasal washes, sputa and nasopharyngeal swabs, especially those specimens containing cellular material, are preferable to nasal and throat swabs. (4,5) Testing should be carried out within the first 4-5 days of illness in adults. (4) Commercially available tests vary in specificity, sensitivity, time to obtain results, specimen used, and cost. The current gold standard test is viral tissue cell culture, with a test time of 3-10 days. (3,5) This method has been used since 1933, but only culture isolates can provide specific information concerning circulating strains and subtypes of the virus. Other methods include RT-PCR and fluorescent antibody staining, with test times of several hours, however these tests are not easily available in the outpatient clinic or to small, local hospitals. This is where the Rapid Influenza Diagnostic Tests (RIDTs) shine – they are readily available to small clinics, they are easy to perform, provide results within 15-30 minutes of performing them, and they are cheaper to use in large scale or closed setting infections scenarios (i.e. illness outbreak on a cruise ship, nursing home or summer camp). (1,4,5,7-10) Rapid tests can be used in physician’s office and enable an approach to influenza with therapeutic decisions guided by results of the test. Influenza testing is recommended for hospitalized or high-risk

children, especially that the sensitivity of RIDTs is higher in children in comparison with adults. (7,8) The best approach is testing by viral culture or reverse transcriptase polymerase chain reaction (RT-PCR). (3-5,7-9) RT-PCR has been reported to be most sensitive and specific test for influenza and recommended as the test of choice by Infectious Diseases Society of America (IDSA) (10). Rapid influenza diagnostic tests produce quick results and are simple to perform. (4,5,7-9) Times needed to obtain results in different influenza tests have been compared in Table 1.

**Table 1. Influenza virus testing methods and their respective test times.**

Method	Influenza types tested	Test time
Viral tissue cell culture	A and B	3-10 days
Rapid cell culture	A and B	1-3 days
Florescent antibody staining	A and B	1-4 hours
RT-PCR	A and B	Variable, minutes to hours
Rapid molecular assay	A and B	<30 minutes
RIDT (Rapid Influenza Diagnostic Tests)	A, B, or A and B	<30 minutes

**4. Characteristics of Rapid Influenza Diagnostic Tests**

The appearance of RIDTs – “point of care” immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens yielding results within 15 to 30 minutes (depending on the assay used) enables immediate patient management. In comparison with the reference standards of viral culture or reverse transcription-polymerase chain reaction (RT-PCR), tests which may take hours to days (depending on local availability), the speed at which the results are revealed can be clinically relevant, and may alter the physician’s decision-making process in suspected influenza infection. This is especially true in light of the disease’s rapid clinical course and its pandemic potential. (1,2) Some of the RIDTs can be used to detect only influenza A, while others can detect both A and B types. (4,5) In general, the sensitivity of rapid tests (the percentage of “true influenza cases” detected as positive by a test) is variable (median 50–75%) and lower than that of cell culture, while their specificity (the percentage of “true non-influenza cases” detected as being negative by a test) is high (median 90–95%).

(4,5,7-9) The greatest limitation of this influenza detection method is its sensitivity. In a recent meta-analysis of 119 articles evaluating 26 different commercially available RIDTs in comparison with the gold standard RT-PCR or viral culture, the RIDTs had a 62.3% sensitivity and a high specificity of 98.2%. (8) This means that there is a relatively high risk of false negative results (almost 4 in 10 negative RIDT result), whereas a positive result is rarely false positive.

In light of this, if there is a negative result of RIDT in an at-risk individual with highly suspect influenza symptoms, testing using gold standard methods should be carried out. (9,10) To improve low-moderate sensitivity of RIDTs, nasopharyngeal and nasal specimens rather than throat swab specimens should be used since they have higher yields for rapid detection. (4) In children lower nasal swabs are accurate compared to nasopharyngeal swabs for identifying influenza and respiratory syncytial virus (RSV) (likely reliable evidence) and appear less uncomfortable (mid-level evidence). (11) Nasal secretions and nasal cavity washings may also be used instead of nasopharyngeal swabs. (4)

RIDTs can supplement clinician judgement and in patients with influenza-like symptoms, can aid to confirm influenza. However, as previously mentioned they are not reliable to definitively rule out the disease. In consequence to the low specificity, RIDTs have a tendency for increased false negative results during seasons of peak influenza activity. The accuracy of RIDTs is related to influenza prevalence in the local community, it is estimated that the tests are optimally accurate when influenza prevalence exceeds >10% in the populace. When the prevalence is around 5%, the positive and negative predictive value of RIDTs (the percentage of test positive cases that have influenza) is around 50%, whereas when prevalence is <2% - the predictive value are 25% and 99% respectively. (4,8)

## 5. Costs

The costs of diagnostic tests differ widely between RIDTs, office-based techniques for detecting influenza A and B viruses (enzyme immunoassay and direct immunofluorescence) being the cheapest. According to our own Internet search their cost ranges from US\$ 7-25 per test depending on the manufacturer and order size. The costs of polymerase chain reaction (PCR) based rapid influenza tests are higher, ranging from US\$ 30 to 60 per test. The culture techniques are more expensive. The cost-utility analyses revealed that antiviral treatment is superior to no treatment in high risk populations whether based on clinical judgement, RIDTs or treating all. (12)

## Conclusion

In conclusion, the use of the RID tests is mired by their sensitivity, which influences the negative and positive predictive values depending on the influenza status of the populace. Positive RIDT's results in a patient with appropriate symptoms during an epidemic may influence clinician judgement in decreasing overuse of antibiotics or auxiliary testing, while increasing the use of antiviral medication. However the problem arises with negative test results, which may or may not be indicative of lack of the disease. Moreover, in areas where there is unknown local influenza prevalence, or in countries with inadequate influenza surveillance, clinical differentiation of influenza is likely to be confounded by other pathogens. (1,2) Summarizing, the use of rapid influenza testing should not rule out good clinician judgement, or the use of gold standard influenza detection methods. Nevertheless, the use of RIDTs increases physician confidence in the diagnosis of influenza and may increase antiviral treatment rate. Since the therapeutic decision depends on local influenza prevalence, from practical point of view, physicians using office-based tests would benefit not only from the single result in an individual patient but also from estimates of the disease in local population. We present our value care advice for RIDTs use in children below.

### Value Care Advice for use of RIDTs in children:

1. RIDTs as quicker and cheaper tests in comparison to RT-PCR may be useful especially in feverish children with non-specific symptoms when influenza incidence is high - the moderate sensitivity of RIDTs is still higher than clinical examination based on symptoms in children, which has a low sensitivity especially in small children.
2. The sensitivity of RIDTs can be improved by better material collection:
  - collection of the specimen during the first days of disease
  - use of nasal secretions
  - use of saline to rinse the nasal cavity instead of nasopharyngeal swabs
  - use of combined nasal/throat swab specimens
  - use of test on specimens from more than one person in outbreak setting
3. Positive result of RIDTs has a strong positive predictive value - i.e. it confirms the diagnosis of influenza during influenza season
4. Negative result of RIDTs must be interpreted with caution. If a child presents typical signs and symptoms of flu during peak influenza activity, the negative result does not exclude influenza since statistically almost every second child with influenza will have false negative result. Children who belong to high-risk groups of severe course of the disease should be started on antivirals despite negative RIDT result.

5. Typical clinical picture during influenza season or epidemiological link (e.g. contact with patient with confirmed influenza) is sufficient to diagnose influenza and to initiate anti-viral therapy.

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