



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Influenza

Diagnosis & Case Definition

by

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TABLE 191.2 Clinical Manifestations of Influenza

Symptoms	Infants	Children	Adults
Fever	++	+++	+++
Cough	+	++	+++
Myalgias	—	+	++
Sore throat	—	+	++
Headache	—	++	++
Conjunctivitis	++	++	++
Cervical adenopathy	+	+	—
Anorexia	++	++	+
Diarrhea	++	+ ^a	— ^a
Vomiting	++	+ ^a	— ^a
Rhinitis	++	+	+
Malaise/lethargy	++	+	+
Neurologic symptoms	+	— ^a	—

^aCommon (++) with 2009 pandemic influenza.

—, rare; +, uncommon; ++, common; +++, very common.

From McCullers JA. Influenza. In: Elzouki AY, Harfi HA, Nazer H, et al., eds. *Textbook of Clinical Pediatrics*. 2nd ed. New York: Springer; 2012.



Clinical Criteria for Diagnosing Influenza

Core Symptom Triad

Most predictive when occurring together:

- ▶ **Abrupt onset of fever** (often $>38^{\circ}\text{C}$)
- ▶ **Cough** (usually dry)
- ▶ **Myalgias**

These three symptoms form the backbone of most case definitions.



Additional Supportive Symptoms

- ▶ Chills or rigors
- ▶ Headache
- ▶ Fatigue or malaise
- ▶ Sore throat
- ▶ Nasal congestion or rhinorrhea
- ▶ Gastrointestinal symptoms (more common in children)

Clinical Diagnosis & Differential Diagnosis

Clinical Diagnosis & Differential Diagnosis

- ▶ Because influenza can manifest as a variety of clinical syndromes, the differential diagnosis is broad.
- ▶ This is particularly true in **infants**, who may not have common signs of infection, such as **cough**.
- ▶ Depending on the specific disease manifestations, many other pathogens can be either the **primary cause** or a **co-pathogen**.

Clinical Diagnosis & Differential Diagnosis

- ▶ Differential Diagnosis for upper respiratory tract infections,
 - ▶ Etiologic Based
 - ▶ parainfluenza viruses,
 - ▶ Respiratory Syncytial Virus,
 - ▶ Human Metapneumovirus,
 - ▶ Rhinoviruses,
 - ▶ Coronaviruses (including SARS- CoV- 2),
 - ▶ System-Based Infection
 - ▶ upper respiratory tract infections
 - ▶ Otitis Media
 - ▶ Croup
 - ▶ Encephalitis, Meningitis
 - ▶ Sepsis

particularly if they are circulating in the community at the same time frame.

Clinical Diagnosis & Differential Diagnosis

- ▶ **The accuracy of clinical diagnoses** of specific respiratory viruses is very poor, with a **sensitivity** for diagnosing influenza as low as **38%** and **a positive predictive value** of only **32%**.
- ▶ Influenza A and B viruses cannot be distinguished clinically by signs and symptoms of presentation.
- ▶ In general, testing for influenza is valuable to recognize when influenza is **circulating** in a community.
- ▶ Still, testing is not necessary to establish the diagnosis in every patient once an epidemic is underway.

Clinical Diagnosis & Differential Diagnosis

- ▶ Bacterial causes of epiglottitis, must also be considered in the child with croup, particularly if acutely ill such as
 - ▶ *H. influenzae*
 - ▶ *S. aureus*
 - ▶ *S. pneumoniae*
- ▶ common lower respiratory tract as co-pathogens or primary agents with influenza
 - ▶ *S. pneumoniae*
 - ▶ *S. aureus*
 - ▶ *S. pyogenes*
 - ▶ *Mycoplasma pneumoniae* (and *Chlamydophila pneumoniae*)

Clinical Diagnosis & Differential Diagnosis

- ▶ Fever and Diarrhea
 - ▶ Numerous viral and bacterial pathogens can also present with fever and diarrhea, although GI symptomatology with influenza is generally mild and the diarrhea is nonbloody.
- ▶ The encephalopathy
 - ▶ The encephalopathy syndrome associated with influenza can mimic either bacterial meningitis or a viral encephalitis, so multiple causes must be considered.
- ▶ Neonates with Influenza
 - ▶ Finally, neonates with influenza can present with lethargy, poor circulation, and apnea without other typical signs of influenza, so other causes of sepsis must be considered.

Laboratory Findings

- ▶ Blood chemistries are typically normal unless dehydration or complications are present.
 - ▶ CBC
 - ▶ normal white blood cell count
 - ▶ Most children
 - ▶ leukopenia
 - ▶ leukocytosis
 - ▶ Leukocytosis with a predominance of neutrophils can be a sign of secondary bacterial infection, but can also occur with uncomplicated influenza.

Laboratory Findings

▶ LFT

- ▶ Mild elevations of hepatic transaminases occur commonly during acute influenza.
- ▶ Severe elevations, accompanied by steatosis, may be seen in Reye syndrome in the setting of salicylate exposure.

▶ Neurologic Involvement:

- ▶ Cerebrospinal fluid (CSF) examination
 - ▶ is typically normal or
 - ▶ reveals a mild pleocytosis
 - ▶ **virus** can be detected in **CSF** by **PCR** or in biopsy or autopsy material from affected brains in about **15% of cases**

Influenza Laboratory Diagnosis

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Types of Rapid Influenza Diagnostic Tests (RIDTs)

RIDTs detect influenza viral antigens in respiratory specimens and provide results in 10-15 minutes. They are commonly used in outpatient settings and during outbreaks.

Main categories:

- ▶ **Antigen-based RIDTs:** Immunoassays that detect viral nucleoprotein antigens.
- ▶ **Digital immunoassays (DIAs):** Enhanced antigen tests with automated readers.
- ▶ **Rapid molecular assays:** Detect viral RNA using isothermal amplification or PCR.

Rapid Influenza Diagnostic Tests (RIDTs)



Rapid Influenza Diagnostic Tests (RIDTs): Performance Summary

Test Type	Method	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)	Turnaround
Antigen-based RIDTs	Immunoassay (manual read)	50-70	90-95	50-90	70-95	10-15 min
Digital Immunoassays	Immunoassay (automated)	66-80	90-95	60-95	80-98	10-15 min
Rapid Molecular Assays	Isothermal/PCR-based	90-100	95-100	>95	>95	15-30 min

*PPV and NPV vary with influenza prevalence. During peak season, PPV increases and NPV decreases.



How to operate a Flu (Influenza) A/B Rapid Antigen Test



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Validated Case Definitions

CDC and WHO definitions typically include:

- ▶ **Acute respiratory illness with:**

- ▶ Fever ($\geq 38^{\circ}\text{C}$)
- ▶ Cough or sore throat
- ▶ Onset within the past 10 days
- ▶ No alternative diagnosis

BMJ meta-analysis findings:

- ▶ Fever + cough is the most sensitive combination
 - ▶ Fever + cough + myalgia improves specificity
 - ▶ Absence of cough significantly lowers the likelihood of influenza
-
- ▶ 🧒 Age-Specific Considerations
 - ▶ Children: GI symptoms and otitis media may be present
 - ▶ Older adults: Fever may be absent; confusion or functional decline may dominate



When to Confirm with Testing

- ▶ High-risk patients (e.g., immunocompromised, pregnant, elderly)
- ▶ Severe or progressive illness
- ▶ Institutional outbreaks
- ▶ When diagnosis will impact management (e.g., antiviral use, isolation)

Sources: CDC Clinical Guidance, WHO Guidelines, BMJ Open meta-analysis

Influenza case definitions

▶ Clinical Criteria

- ▶ Influenza-like illness (ILI)
- ▶ Acute respiratory infection (ARI)

▶ Epidemiological Criteria

▶ Laboratory Criteria

مشکوک ▶

احتمالی ▶

قطعی ▶

Influenza case definitions

Clinical Criteria

Influenza-like illness (ILI)

- . Sudden onset of symptoms
- ▶ *And* at least **one** of the following four **systemic symptoms**:
 - . Fever or feverishness
 - . Malaise
 - . Headache
 - . Myalgia
- ▶ *And* at least **one** of the following three **respiratory symptoms**:
 - . Cough
 - . Sore throat
 - . Shortness of breath

Influenza case definitions

Clinical Criteria

Influenza-like illness (ILI)

Acute respiratory infection (ARI)

- Sudden onset of symptoms
- ▶ *And* at least **one** of the following four **respiratory symptoms**:
 - Cough
 - Sore throat
 - Shortness of breath
 - Coryza
- ▶ *And* **a clinician's judgement** that the illness is due to an infection

Influenza case definitions

Laboratory Criteria

At least one of the following:

- 1) Isolation of influenza virus from a clinical specimen
- 2) Detection of influenza **virus nucleic acid** in a clinical specimen
- 3) Identification of **influenza virus antigen** by the DFA test in a clinical specimen
- 4) Influenza-specific antibody response

Sub-typing of the influenza isolate should be performed, if possible.

Influenza case definitions

▶ Epidemiological Criteria

- ▶ An epidemiological link by human-to-human transmission

Influenza case definitions

Case Classification

Possible case: مشکوک

- ▶ Any person meeting the clinical criteria (ILI or ARI)

Probable case: احتمالی

- ▶ Any person meeting the clinical criteria (ILI or ARI) and with an epidemiological link

▶ **Confirmed case:** قطعی

- ▶ Any person meeting the clinical (ILI or ARI) and the laboratory criteria