



eInfluenza Review

Presented by
The Johns Hopkins University
School of Medicine, The Institute
for Johns Hopkins Nursing & The
University of Tennessee
College of Pharmacy

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August 2007: VOLUME 1, NUMBER 10

Syndromic Diagnosis of Influenza in the Urgent Care Setting

In This Issue...

Although influenza continues to be the most common infectious cause of death in this country, our ability to recognize it remains limited. Yet correct diagnosis of influenza is important due to the availability of anti-viral treatment, the ability to reduce infectivity, and the need for monitoring for potential complications such as bacterial superinfections and exacerbations of underlying medical conditions.

In this issue, we review the literature regarding the signs and symptoms that can aid the clinician in the diagnosis of influenza infection, reporting on diagnostic data for both adults and children (as their clinical presentations may differ), and discussing the clinical symptoms (thus far determined) of avian influenza.

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 [ABX Guide Influenza-Info](#)

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the common clinical presentations of influenza in adults and children
- Discuss the limitations of clinical symptoms in the diagnosis of influenza
- Identify the risk factors and features of avian influenza

COMMENTARY

Influenza infections cause significant morbidity and mortality in the United States despite the availability of an effective vaccine. In fact, influenza-related deaths have increased 83% from the 1976-1977 through the 1997-1998 influenza seasons.¹ Although an estimated 1 in 5 individuals in this country will be infected with influenza each year, our ability to recognize the disease is still limited.² One factor may be the wide spectrum of clinical manifestations influenza presents. In one study of health care workers with serologic evidence of influenza infection, 59% of subjects did not report having had influenza, and 28% did not recall having any upper respiratory tract infection.³ On the other end of the spectrum, the mortality associated with this infection, particularly among the very young and elderly, is substantial.^{1,4}

The clinical diagnosis of influenza remains an imprecise science. The Monto and Ohmit studies examined the clinical "predictors" of influenza infection in adults and children, respectively, finding varying clinical presentations in different age groups.^{5,6} Call et al performed a comprehensive review of studies evaluating clinical findings of influenza.⁷ Poehling's investigation found that the bulk of influenza infections remain undiagnosed in children.⁸

The interpretation of these papers requires knowledge of key epidemiology terms, since they are used to describe the predictors of influenza. **Sensitivity** refers to the percentage of patients with influenza who will correctly be diagnosed with influenza by the test, or in this instance, clinical sign or symptom. **Specificity** is the percentage of patients without influenza who will be correctly diagnosed as not having influenza by the clinical finding. The **positive predictive value** (PPV) is the probability a patient with the sign or symptom will have influenza, whereas the **negative predictive value** (NPV) is the probability a patient without the sign or symptom will not have influenza. An important point is that predictive values are highly dependent on disease prevalence.⁹ The Centers for Disease Control and Prevention (CDC) tracks influenza cases on a weekly basis, and the most current data can be found on their website.¹⁰

Once the suspicion of influenza infection arises, clinicians must then consider other important factors. Should influenza testing be performed? Is this patient presenting within 48 hours of symptoms, such that antiviral therapy may be useful? Does this patient have close contact with particularly vulnerable populations such as those who are immunocompromised, or nursing home patients who may require post-exposure prophylaxis? Does this patient have a travel history that may have included areas where avian influenza has been reported?

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In conclusion, we remain limited in our ability to diagnose influenza on clinical findings alone. However, as the studies reviewed herein show, the presence or absence of certain signs and symptoms in the appropriate populations can influence clinical decision-making. The presence of both fever and cough have a high positive predictive value (though low sensitivity) for influenza in adults. A significant limitation in examining the clinical diagnosis of influenza is that the inclusion criteria of many studies include fever and/or acute respiratory illness. Thus, there may be a proportion of influenza infections that go undiagnosed due to atypical presentations. In practice, rapid diagnostic testing for influenza and/or empiric therapy with appropriate antiviral agents may be the best approach when influenza infection is suspected.

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PREDICTORS OF INFLUENZA INFECTION IN ADOLESCENTS AND ADULTS

Monto AS, Gravenstein S, Elliot E, Colopy M, Schweinle J. **Clinical signs and symptoms predicting influenza infection**. *Arch Intern Med*. 2000;160:3243-3247.



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Monto et al report on a retrospective, pooled analysis of data from 8 studies with 231 study centers involved in the phase 2 and 3 clinical trials for zanamivir. The age inclusion criteria for the studies varied from age ≥ 12 to ≥ 18 . Study eligibility required subjects to have fever ($T \geq 37.8^\circ \text{C}$ or 37.2°C if age ≥ 65 years old) or a symptom of feverishness, plus at least 2 of the following symptoms: headache, myalgia, cough, or sore throat. All participants underwent culture and serological testing for influenza. The authors analyzed the correlation between clinical symptoms and diagnosis of influenza in this large (though potentially heterogeneous) group of subjects.

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A total of 3744 subjects meeting the eligibility criteria were enrolled in the studies. Of these participants, 2470 (66%) had laboratory-confirmed influenza. The most common symptoms of patients with confirmed influenza included weakness (94%), myalgia (94%), cough (93%), loss of appetite (92%), and feverishness (90%). A higher proportion of subjects with influenza (versus those without) had cough (93% vs 80%), fever (68% vs 40%), both cough and fever (64% vs 33%), or nasal congestion (91% vs 81%). The authors performed a risk factor analysis to determine associations between influenza infection and symptoms. Fever ($T \geq 37.8$) had the strongest association with influenza, with an odds ratio of 3.26, though cough and nasal congestion were also significant, with odds ratios of 2.85 and 1.98, respectively. Equally important, headache, "feverishness," and myalgia did not appear to be associated with influenza infection.

The authors next attempted to develop predictors of influenza infection. They found that the combination of fever and cough, when onset was between 36 and 48 hours, had the highest positive predictive value (PPV) of 85.37% – meaning an 85.37% likelihood the patient had influenza when these symptoms are present. Although this combination of symptoms is specific, the sensitivity is only 50.3%, which means about half of patients with influenza will not have this combination of symptoms. Fever and/or cough appear to be important indicators of influenza, though the specificity (the probability of the subject not having the symptom when they do not have influenza) ranged from 20.41% for cough alone to 80.89% for fever and cough (when onset was 36-48 hours).

While this study is consistent with prior work by Monto¹ that determined fever and cough to be the best predictors of influenza infection, a key problem remains: the lack of sensitivity and specificity of these symptoms. If the combination of fever and cough does not describe over a third of patients with influenza (36% of patients with influenza did not have these symptoms), and misdiagnoses a third with influenza (specificity of both fever and cough was 67.19%), it still leaves a large degree of imprecision. Rapid diagnostics for influenza are available, though their implementation (and decision of when to prescribe antiviral therapy) in an urgent care setting versus acute care hospital presents additional challenges.

An important limitation of this study is the eligibility criteria. Since the data was pooled from clinical trials to test the efficacy of zanamivir, subjects needed to have multiple symptoms consistent with influenza – in particular, fever or feverishness. Thus, there may be a subset of people who may have had influenza without these common symptoms who are not represented in this analysis. Secondly, most of the subjects included in this analysis were unvaccinated; thus this data is primarily applicable only to this subgroup.

References

1. Monto AS, Ohmit SE. *The evolving epidemiology of influenza infection and disease*. In: Brown LE, Hampson AW, Webster RG, eds. *Options for the control of influenza III*. Amsterdam, the Netherlands: Elsevier Science BV; 1996:45-49.

CLINICAL FINDINGS OF INFLUENZA IN ADULTS

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Call SA, Vollenweider MA, Hornung CA, Simel DA, McKinney WP. **Does this patient have influenza?** *JAMA*. 2005;293(8):987-997.



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Call et al performed a systemic review of articles examining the clinical signs and symptoms of influenza from January 1966 through September 2004. The objective was to perform a comprehensive review of the predictive signs and symptoms, and rapid diagnostics, for influenza. Of 915 articles initially identified by their search strategy, 17 had sufficient data on signs and symptoms; 11 were excluded based on criteria established by the authors; and 6 articles were reviewed in full (including the study by Monto et al discussed above). The age ranges of patients in the individual studies varied from all ages to only those age ≥ 60 years. Data was extracted from studies to determine likelihood ratios (LRs) based on clinical presentation.

The likelihood ratio refers to how a particular result increases or decreases the odds of disease, with LR >1 increasing the likelihood of disease, LR <1 decreasing the likelihood, and LR =1 having no effect.

The most significant result is that no single clinical sign or symptom could "rule in" or "rule out" influenza. On examination of the data, the clinical studies including all ages found no individual sign or symptom with a LR >2 (meaning no finding increased the likelihood of having influenza two-fold). However, several signs and symptoms decreased the likelihood of influenza, including the absence of fever (LR 0.40, 95% confidence interval [CI] 0.25-0.66), cough (LR 0.42, 95% CI 0.31-0.57), or nasal congestion (LR 0.49, 95% CI 0.42-0.95).

In the 2 studies that limited age to ≥ 60 and 60-90 years, the clinical findings were more useful. The triad of fever, cough, and acute onset had a LR 5.4 (95% CI 3.8-7.7), whereas both fever and cough had a LR of 5.0 (95% CI 3.5-6.9). Fever by itself had a LR of 3.8 (95% CI 2.8-5.0) in this patient population. Other significant associations included malaise (LR 2.6, 95% CI 2.0-3.2) and chills (LR 2.6, 95% CI 2.0-3.2). Sneezing had a negative LR of 0.47 (95% CI 0.24-0.92), meaning its presence would decrease the likelihood a patient had influenza.

This study provides a useful summary of the clinical signs and symptoms that can influence the likelihood that a patient has influenza. The lack of predictors seen in the all-population studies may be due to the heterogeneity of clinical presentations depending on age. The studies with age ≥ 60 years, however, identified symptoms that can influence the clinician in the decision to perform influenza testing and/or prescribe antiviral therapy. Although the triad of fever, cough, and acute onset can increase the likelihood of influenza by five-fold, the sensitivity of this constellation of symptoms is still an abysmal 27%. If these symptoms are present in an elderly patient, they should raise high clinical suspicion for influenza, although their absence is not particularly telling.

THE UNDERDIAGNOSIS OF INFLUENZA IN CHILDREN

Poehling KA, Edwards KM, Weinberg GA, et al for the New Vaccine Surveillance Network. **The underrecognized burden of influenza in young children.** *N Engl J Med*. 2006;355:31-40.



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In this study, Poeling et al sought to determine the disease burden of influenza infection in children younger than age 5. The study included children in 3 US counties: Nashville, TN; Cincinnati, OH; and Rochester, NY. The surveillance included both inpatient and outpatient populations. For inpatients, researchers enrolled children within 48 hours of admission with an acute respiratory tract infection or fever. Children who had symptoms for more than 14 days, neutropenia due to chemotherapy, recent prior hospitalization (within 4 days), or newborns never discharged from the hospital, were excluded from the study. For the outpatient population, children with an acute respiratory tract infection or fever presenting to clinics or emergency departments during the 2002-2003 and/or 2003-2004 influenza

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seasons were eligible for enrollment. Study participants underwent nasal swab and throat swabs, with testing for influenza by reverse-transcriptase polymerase chain reaction (RT-PCR) and viral culture.

Based on census data of the population in the 3 counties, the average annual rate of hospitalization due to influenza was 0.9 per 1000 children. For every 1000 children, there were 50-95 clinic visits and 6-27 emergency department visits due to influenza, depending on the influenza season. Interestingly, although these studies were performed during influenza season and children were presenting with acute respiratory tract infections or fever, only 28% of inpatients and 17% of outpatients were diagnosed with influenza by the treating clinician.

Among hospitalized children who tested positive for influenza, most subjects had fever (93%), cough (87%), and rhinorrhea (83%). For those children age 0-5 months, cough was not as common as compared to children age 6-59 months (80% vs 94%). The median duration of symptoms prior to presentation ranged from 3-4 days, with a mean of 2 days or less. Among outpatients who had influenza, most had fever (95%), cough (96%), and rhinorrhea (96%). Ninety-one percent of subjects had both fever and cough. Other diagnoses of subjects with influenza included otitis media (28%), pneumonia (6%), and seizures (1%). Asthma was less common among children with influenza as compared to children without influenza (6% vs 12%).

This study illustrates how challenging it is to diagnose influenza in young children. Only about a fourth of inpatients and less than a fifth of outpatients were correctly diagnosed with influenza. Among hospitalized infants 0-5 months, 61% subjects with influenza had a lumbar puncture but only 28% had a discharge diagnosis of influenza. Since such young infants cannot give a clinical "history," invasive procedures are performed to rule out serious, life-threatening infections. However, as this study demonstrates, during the influenza season, a simple nasal swab or throat swab sampling for influenza, performed routinely in all patients with acute respiratory symptoms or fever, would aid tremendously in establishing the correct diagnosis. Further, influenza testing is particularly valuable in patients who may benefit from antiviral therapy.

PREDICTORS OF INFLUENZA INFECTION IN CHILDREN

Ohmit SE, Monto AS. **Symptomatic predictors of influenza virus positivity in children during the influenza season.** *Clin Infect Dis.* 2006;43:564-568.



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In this study, Ohmit and Monto sought to determine the clinical signs and symptoms that could predict influenza infection in children. Data from the clinical trials of zanamivir and oseltamivir, the 2 available neuraminidase inhibitors active against both influenza A and B, were analyzed, comparing the clinical signs and symptoms observed with a diagnosis of influenza confirmed by viral culture, serologic testing (acute and convalescent), and/or RT-PCR. For the zanamivir study, inclusion criteria were children 5-12 years of age with fever (temperature $\leq 37.8^{\circ}\text{C}$) and duration of illness ≤ 36 hours. In the oseltamivir trial, children 1-12 years of age were eligible to enroll if they had fever (temperature $\leq 37.8^{\circ}\text{C}$) and ≥ 1 respiratory symptoms of cough or nasal symptoms.

In the zanamivir study, fever and cough best predicted influenza infection, with PPV (positive predictive values) of 78% and 77% respectively. The presence of both symptoms had a PPV of 83%. Among those children who had white blood cell (WBC) counts performed, those with leukopenia (WBC < 4500 cells/mm³) had an increased risk of influenza infection, with OR 4.32 and PPV 89%. The combination of fever, cough, and leukopenia had a PPV of 95%, though with a low sensitivity of 27%.

The oseltamivir study included children with fever and at least one other respiratory or nasal symptom. Interestingly, by using the inclusion criteria, 66% and 67% of the children ages 5-12 years and age < 5 years had influenza, respectively. Among children ages 5-12 years, fever and cough had PPV of 69% and 70% respectively, with the presence of both fever and cough only raising the PPV to

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71%. The highest PPV in the oseltamivir trial in the 5-12 year age range was the triad of fever, cough, and headache, with a PPV 74%. Among the age range of 1-4 years, the clinical symptom with the highest PPV was myalgia (73%). The PPV for the other symptoms of fever, cough, or both fever and cough were $\leq 65\%$ in the younger age group.

The baseline symptom of cough had an odds ratio of 5.19 for laboratory-confirmed influenza in the zanamivir trial. Likewise in the oseltamivir trial, within the same age range of 5-12 years, cough had an OR of 10.94 ($p < 0.001$) for influenza infection. In stark contrast, for the age range of 1-4 years, cough is negatively associated with influenza, with an OR 0.61 (95% confidence interval 0.11-3.42). Thus, the diagnosis of influenza in children is particularly difficult, since it appears different age groups present with different clinical findings. These data indicate that aggressive testing for influenza in children may be the soundest approach.

AVIAN INFLUENZA: WHERE IS IT AND WHAT DOES IT LOOK LIKE?

The writing committee of the world health organization consultation on human influenza A/H5. **Avian influenza A (H5N1) infection in humans.** *N Engl J Med.* 2005;353:1374-1385.



Abstract: Not Available



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This review article summarizes the features of avian influenza based on information of known cases, including its incidence, transmission, clinical features, pathogenesis, case detection and management, and prevention. Appropriate to this month's issue, this discussion will focus on the epidemiology and clinical data presented.

Avian influenza A infections in humans have been identified primarily in Southeast Asia, although outbreaks have been seen in other regions. As of 2005, the largest numbers of cases and deaths had occurred in Vietnam, with a total of 90 cases and 40 deaths from December 2003 to August 2005. Avian influenza A (H5N1) infection appears to be transmitted via bird-to-human, potentially environment-to-human, and non-sustained, rare human-to-human transmission.

The clinical features are based on hospitalized patients only, and infections have mostly occurred in healthy children. Based on serologic testing, subclinical disease with avian influenza does occur, and avian influenza A (H5N1) can have uncommon presentations of encephalopathy and gastroenteritis. The incubation period for this virus is thought to range from 2-17 days, which is longer than currently circulating human influenza viruses. Initial symptoms include high fever ($T > 38.0^\circ \text{C}$) and respiratory illness, with almost all patients having cough and/or pulmonary infiltrates. Lower respiratory tract disease, including dyspnea, respiratory distress, tachypnea, and crackles, has frequently been found on presentation. Watery non-bloody diarrhea appears to be more common with avian influenza A (H5N1) as compared to other human influenza viruses.

Fortunately, efficient human-to-human transmission of avian influenza A (H5N1) has not yet occurred. However, other features required for a pandemic, such as presence of a new strain against which the population has no immunity and severe infection, are already present. Avian influenza A (H5N1) infection in humans appears to cause pneumonia frequently, although this conclusion is based on evaluating hospitalized patients only. Given that some people seroconvert without clinical symptoms, there is likely a spectrum of disease much like that seen with annual influenza epidemics. Thus, taking a travel history, which can be done fairly quickly, is critical in determining how to approach and manage a patient with acute respiratory illness, and should therefore be done routinely.

A patient with suspected avian influenza (versus annual influenza) will be treated very differently due to the public health ramifications. Keeping up to date by using the [Pandemic Flu website](#) as a reference is extremely useful, given how little we know thus far about avian influenza.

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- Identify the risk factors and features of avian influenza

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