# Clinical Diagnosis of Influenza in Adults

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# Context of the discussion

- Illness due to influenza is difficult to distinguish from other infections
- Antiviral agents are most effective when given early after onset of symptoms
- Antiviral agents are likely to be in short supply in most pandemic scenarios
- Additional uses of antivirals are proposed which are triggered by recognition of influenza
  - PEP for households
  - PEP for institutional clusters

# Desirable diagnostic features

- Accurate
  - Reasonable PPV for efficient use of scarce resource
  - Good NPV to prevent witholding of treatment
- Able to be applied to large numbers of patients
- Not require patients to travel to centers
- Ideally not require high skill level

# Laboratory Tools for Influenza Diagnosis

| Test | Advantages | Sensitivity | TAT |
|---|---|---|---|
| Culture | Gold standard<br>Isolate can be typed | 100% by definition | Turnaround still >48 hours, even with shell vial |
| RT-PCR | Most accurate<br>Can be multiplexed | > Culture<br>Limited availability | 2-4 hours |
| DFA | Turnaround 1-6 hours<br>Detects up to 7 viruses | 80-95% | 2-4 hours |
| EIA (rapid test) | Rapid turnaround (30 min)<br>Some CLIA waived | Median 70%<br>Range 50-90% | 30 min |
| Serology | Useful for epidemiologic studies | NA | >10 days |

# Factors that influence lab test performance

- Test platform
- Duration of symptoms
- Age of patients
  - Young children > older children > adults
- Type of specimen
  - Nasal wash > NP swab > nasal swab

# Clinical diagnosis influenced by:

- Population: Elderly vs younger adults
- Comorbid illness: Eg. COPD
- Severity: Outpatients vs hospitalized patients
- Prevalence
- Study design issues
  - Population studied
  - Selection bias
  - Spectrum bias
  - Seasonal variation?

# Clinical signs and symptoms predicting influenza

- Pooled data set from 8 clinical trials of zanamivir
- Enrollment only during after 2 confirmed flu cases
- Eligibility
  - Age 13 +
  - Fever ≥ 37.8 or feverishness plus at least 2 ILI symptoms
- 3744 patients included
- 2470 (66%) had culture confirmed influenza

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# Clinical signs and symptoms predicting influenza

| Symptom | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Fever | 67.8 | 60.4 | 76.9 | 49.1 |
| Cough | 93.2 | 20.4 | 69.4 | 60.9 |
| Fever and cough | 63.8 | 67.1 | 79 | 48.9 |
| Onset < 36 h | 63.3 | 67.5 | 77.3 | 51.3 |
| Onset > 36 h | 50.3 | 80.9 | 85.4 | 42.3 |
| Fever, cough and nasal congestion | 59.0 | 73.9 | 81.5 | 48.2 |
| Fever, cough and weakness | 59.8 | 71.5 | 80.2 | 47.9 |

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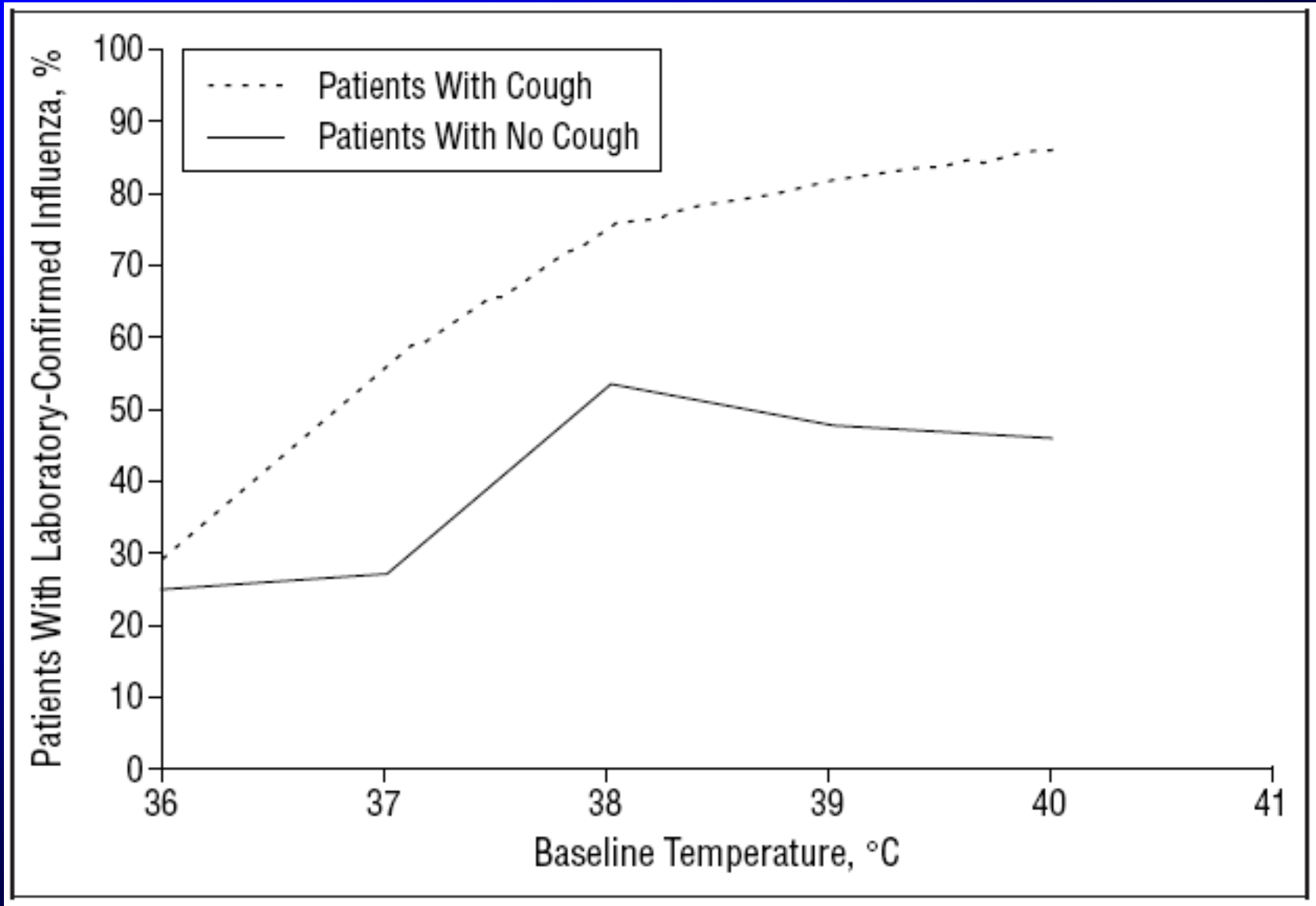
# Percentage of patients with influenza

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# Effect of prevalence on performance of Monto prediction rule: sensitivity of 0.64 specificity of 0.67

| Prevalence | PPV | NPV | LR+ | LR- |
|---|---|---|---|---|
| .1 | 18 | 94 | 1.94 | 0.54 |
| .2 | 33 | 88 | | |
| .3 | 45 | 81 | | |
| .4 | 56 | 74 | | |
| .5 | 66 | 65 | | |
| .6 | 74 | 55 | | |
| .7 | 82 | 44 | | |
| .8 | 89 | 32 | | |
| .9 | 94 | 17 | | |

# Comparison of an optimistic clinical rule with a average rapid test

| Prevalence | Cough and Fever Sens 64% Spec 67% | | Rapid Test Sens 70% Spec 95% | |
|---|---|---|---|---|
| | PPV | NPV | PPV | NPV |
| .2 | 33 | 88 | 78 | 93 |
| .3 | 45 | 81 | 86 | 88 |
| .7 | 82 | 44 | 97 | 58 |

| Source | Study Period | Location | Patients, No. | Age Range, y | Design | Selection Criteria | Level of Evidence | Diagnostic Test | Prevalence of Influenza |
|---|---|---|---|---|---|---|---|---|---|
| Nicholson et al,[25] 1997 | Winters of 1992-1993 and 1993-1994 | Leicestershire, England | 533 | 60-90 | Prospective cohort | Weekly telephone surveillance for symptoms of upper respiratory tract infection; home visit as soon as possible thereafter if symptoms noted | A | 4-Fold increase in hemagglutination inhibition titer | 0.08 |
| Govaert et al,[14] 1998 | Influenza season, 1991-1992 | The Netherlands | 1838 | ≥60 | Randomized controlled trial (of influenza vaccine) | Tested all persons in the study. Persons were originally selected from general practice offices, not "high-risk" groups | B | 4-Fold increase in titer (influenza A) | 0.07 |
| Carrat et al,[12] 1999 | Influenza epidemic, 1995-1996 | France | 610 | Included all ages ≥1 y | Prospective cohort | Sudden onset of ≥1 of the following: influenza-like illness, upper or lower respiratory tract infectious syndrome, and/or temperature of >38°C without any symptoms or signs of other infectious syndromes | A | ELISA, immunofluoresence (influenza A) | 0.28 |
| Monto et al,[20] 2000 | Fall and winters, 1994-1998 | 231 Study centers in North America, Europe, southern hemisphere | 3744 | ≥12 | Retrospective, pooled analysis of clinical trials | Fever or ≥2 symptoms (headache, myalgias, cough, sore throat) | B | Positive culture for influenza A or B or 4-fold increase in titer or PCR or immunofluoresence | 0.66 |
| Hulson et al,[17] 2001 | 3 Consecutive influenza outbreaks, 1999-2000 | Oklahoma | 358 | 10 mo-73 y | Prospective cohort | Any of: fever (temperature >38°C), cough, sore throat, headache, myalgia | A | Positive culture for influenza A or B | 0.67 |
| van Elden et al,[23] 2001 | Influenza season, 1997-1998 | The Netherlands | 81 | Included all ages | Prospective cohort | Fever (temperature >38°C) plus ≥1 constitutional symptom (malaise, headache, myalgia, chills) plus ≥1 respiratory symptom (coryza, sneezing, cough, sore throat, | B | PCR (influenza A) | 0.5 |

Call, S. A. et al. *JAMA* 2005;293:987-997.

# Test Characteristics of Clinical Findings, by Study

| Symptoms, Authors | Sensitivity | Specificity | Positive LR (95% CI)* | Negative LR (95% CI)* | DOR (95% CI)* |
|---|---|---|---|---|---|
| Fever | | | | | |
| No age restriction | | | | | |
| Carrat et al | 0.84 | 0.73 | 3.1 (2.6-3.7) | 0.21 (0.15-0.31) | 14 (8.8-23.0) |
| Monto et al | 0.68 | 0.60 | 1.7 (1.6-1.8) | 0.53 (0.49-0.57) | 3.2 (2.8-3.7) |
| Hulson et al | 0.86 | 0.25 | 1.1 (1.0-1.3) | 0.59 (0.35-0.87) | 1.9 (1.0-3.4) |
| Summary | | | 1.8 (1.1-2.9) | 0.40 (0.25-0.66) | 4.5 (1.8-11.0) |
| Only patients ≥60 y | | | | | |
| Govaert et al | 0.34 | 0.91 | 3.8 (2.8-5.0) | 0.72 (0.64-0.82) | 5.2 (3.4-7.9) |
| Feverishness | | | | | |
| No age restriction | | | | | |
| Monto et al | | | | | 1.1 (0.89-1.4) |
| van Elden et al | 0.88 | 0.15 | 1.0 (0.86-1.2) | 0.70 (0.27-2.5) | 1.3 (0.35-4.6) |
| Summary | | | | | 1.1 (0.88-1.4) |
| Only patients ≥60 y | | | | | |
| Nicholson et al | 0.47 | 0.78 | 2.1 (1.2-3.7) | 0.68 (0.45-1.0) | 3.1 (1.2-8.1) |
| Cough | | | | | |
| No age restriction | | | | | |
| Carrat et al | 0.84 | 0.29 | 1.2 (1.1-1.3) | 0.58 (0.39-0.85) | 2.0 (1.3-3.2) |
| Monto et al | 0.93 | 0.20 | 1.2 (1.1-1.2) | 0.35 (0.29-0.42) | 3.3 (2.7-4.1) |
| Hulson et al | 0.96 | 0.07 | 1.0 (0.95-1.1) | 0.61 (0.25-1.5) | 1.9 (0.71-5.0) |
| van Elden et al | 0.98 | 0.23 | 1.3 (1.1-1.5) | 0.11 (0.01-0.82) | 12 (1.4-97.0) |
| Summary | | | 1.1 (1.1-1.2) | 0.42 (0.31-0.57) | 2.8 (2.1-3.7)† |
| Only patients ≥60 y | | | | | |
| Nicholson et al | 0.53 | 0.56 | 1.2 (0.75-1.9) | 0.85 (0.52-1.4) | 1.4 (0.5-3.7) |
| Govaert et al | 0.66 | 0.77 | 2.9 (2.5-3.4) | 0.44 (0.34-0.56) | 6.7 (4.5-10.0) |
| Summary | | | 2.0 (1.1-3.5) | 0.57 (0.37-0.87) | 3.4 (1.2-9.7) |

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# Test Characteristics of Clinical Findings, by Study

| Symptoms, Authors | Sensitivity | Specificity | Positive LR (95% CI)* | Negative LR (95% CI)* | DOR (95% CI)* |
|---|---|---|---|---|---|
| Fever and cough | | | | | |
| No age restriction | | | | | |
| Monto et al | 0.64 | 0.67 | 1.9 (1.8-2.1) | 0.54 (0.50-0.57) | 3.6 (3.1-4.2) |
| Only patients ≥60 y | | | | | |
| Govaert et al | 0.30 | 0.94 | 5.0 (3.5-6.9) | 0.75 (0.66-0.84) | 6.6 (4.2-10.0) |
| Fever and cough and acute onset | | | | | |
| No age restriction | | | | | |
| Monto et al | 0.63 | 0.68 | 2.0 (1.8-2.1) | 0.54 (0.51-0.58) | 3.6 (3.1-4.1) |
| Only patients ≥60 y | | | | | |
| Govaert et al | 0.27 | 0.95 | 5.4 (3.8-7.7) | 0.77 (0.68-0.85) | 7.1 (4.5-11.0) |

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio; LR, likelihood ratio.
*Positive LR is the LR when the finding is present; negative LR is the LR when the finding is absent; DOR is an indicator of the test's overall accuracy.
†Homogeneous DOR ($P>.05$). When the DOR was heterogeneous, we assessed for homogeneity separately for the positive and negative LRs.

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# Clinical Features of H5N1 in 4 series

| | Thailand 2004 N=14 | Vietnam 2004 N=10 | Indonesia 2005 N=8 | Turkey 2006 N=8 |
|---|---|---|---|---|
| Median age | 19.5 yrs (2-58) | 12.5 yrs (5-24) | 8.5 yrs (1-38) | 10 yrs (5-15) |
| Fever | 100% | 100% | 100% | 100% |
| Cough | 100% | 100% | 100% | 88% |
| Sore Throat | 64% | | 12% | 75% |
| Diarrhea | 36% | 70% | 38% | 38% |
| Vomiting | | | 12% | |
| Pneumonia | 100% | 100% | 62% | 88% |
| ARDS | 71% | 80% | 50% | 50% |

Chotpitayasunodh T et al. *EID* 2005;11:201-9; Ungchusak K et al. *NEJM* 2005;352; Chokephaibulkit K et al. *PIDJ* 2005;24:162-6; Apisarnthanarak A et al. *EID* 2004;10:1321-4. Hien TT et al. *NEJM* 2005;350:1179-88. Kandun IN et al. *NEJM* 2006;355:2186-94; Oner AF et al. *NEJM* 2006;355:2179-85

# How will this play out in a pandemic?

- In a naïve population, symptom frequency will likely be different
- More severe disease might improve function of clinical diagnosis
- Public perception, public health concerns and ethical concerns may lead to pressure to over-diagnose
- A positive predictive value of 50% would require twice as much drug to achieve same goals because of over treatment.

# Conclusions

- Performance of any test depends on prevalence of influenza in population being tested.
- Clinical symptoms and prediction rules for seasonal influenza are limited in adults, especially if pretest prevalence is low
- Current point of care EIA's have limited performance in adults, but still markedly better than clinical prediction, unless prevalence is high
- Better diagnostic approaches are needed.

# Other questions

- What is an acceptable degree of certainty for initiating treatment of an ill patient?
- What is an acceptable degree of certainty for initiating treatment in the family of an ill patient?
- What are the unanticipated consequences of bringing patients to central sites for testing?
- What are the benefits and unanticipated consequences of home testing?