

# Clinical Dx

- ▶ Influenza A infection with shock, caused by either bacterial superinfection or possibly influenza, complicated by rhabdomyolysis, renal failure, and DIC.

# Anatomical Dx

- ▶ Influenza A infection
- ▶ rhabdomyolysis
- ▶ Myoglobinuria
- ▶ viral tracheobronchitis and pneumonia
- ▶ virus-associated cardiac changes and pericardial effusion.
- ▶ DIC
- ▶ Hepatic centrilobular necrosis.
- ▶ Cardiac hypertrophy of unknown cause.

# Diagnosis of seasonal influenza in adults

- ▶ In this case, rapid influenza test was negative...
- ▶ This was a pitfall !
- ▶ No tests with 100% sensitivity and specificity
- ▶ Always have to think about false negative and positive !

# Diagnosis of seasonal influenza in adults

- ▶ There are several kinds of tests.
- ▶ The tests are **highly specific (90–95%)** and help rule in influenza when positive (LR+28.2).
- ▶ But **some of them are not sensitive(55 – 65%)** and cannot rule out influenza (LR–0. 7)
- ▶ Antiviral therapy is effective only within 48 hours, so **time to results is important.**

**Symptom to diagnosis**

# RT-PCR

## Gold Standard

- ▶ Reverse-transcriptase polymerase chain reaction is **the most sensitive and specific** modality for diagnosing influenza infection
- ▶ Can differentiate between influenza types and subtypes.
- ▶ Although RT-PCR takes only 4 to 6 hours to perform, **it often takes longer than this** since it may not be performed in-house and may be batched with other samples

# Rapid influenza test

- ▶ Rapid influenza antigen tests are immunoassays that can identify influenza A and B viral nucleoprotein antigens in respiratory specimens
- ▶ It takes 15 minutes or less, but have much lower sensitivity than RT-PCR and viral culture.

# Rapid influenza test

- ▶ Meta-analysis by Chartrand C et al.(2012) in Ann Intern Med.
  - 159 studies, the pooled **sensitivity was 62.3 percent** (95% CI 57.9–66.6 percent) and the pooled **specificity was 98.2 percent** (95% CI 97.5–98.7 percent).
  - The sensitivity was lower in adults than in children (53.9 versus 66.6 percent), and was higher for influenza A than for influenza B (64.6 versus 52.2 percent).

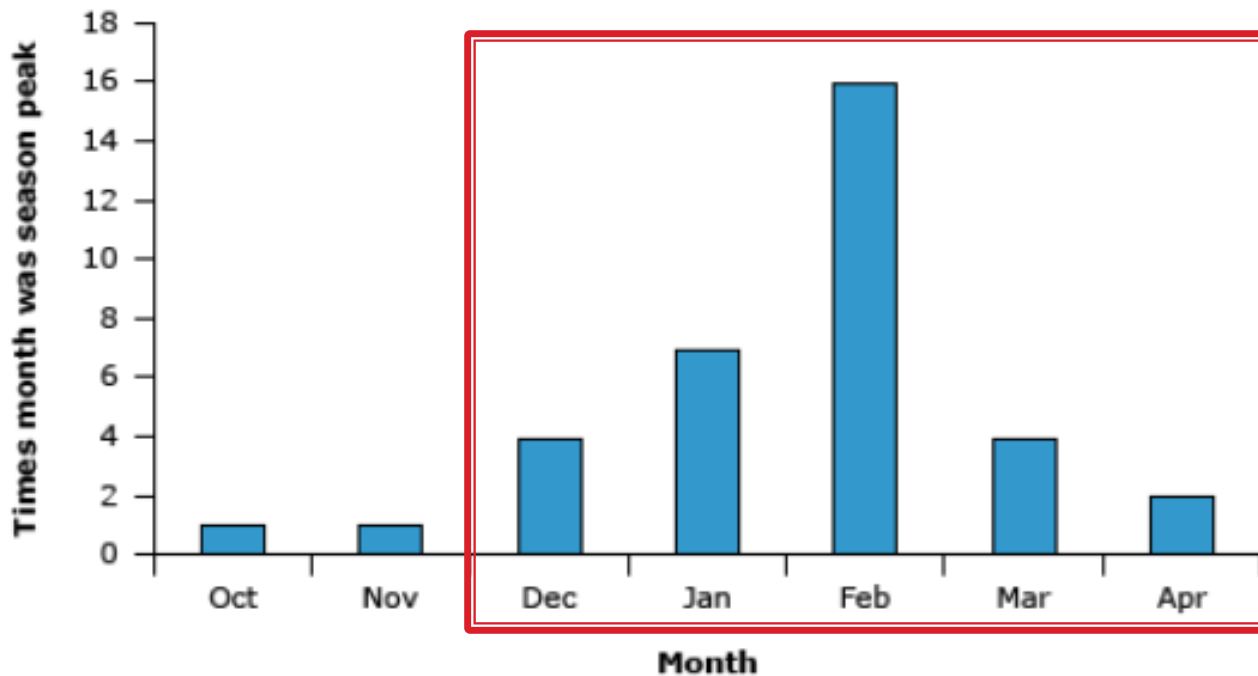
# Diagnosis of seasonal influenza in adults

Test	Time to results	Comments
RT-PCR gold standard	4h	<b>High sensitivity and very high specificity</b> ; can differentiate between influenza types (A or B) and subtypes
Immunofluorescence	2-4 h	<b>Moderately high sensitivity and high specificity</b>
Rapid influenza diagnostic tests	15min	<b>Low to moderate sensitivity</b> and high specificity; recommended; during periods of peak influenza activity, negative rapid antigen tests do not reliably exclude influenza
Viral culture	3 days or more	Moderately high sensitivity and <b>highest specificity</b> Used for epidemiologic purposes.



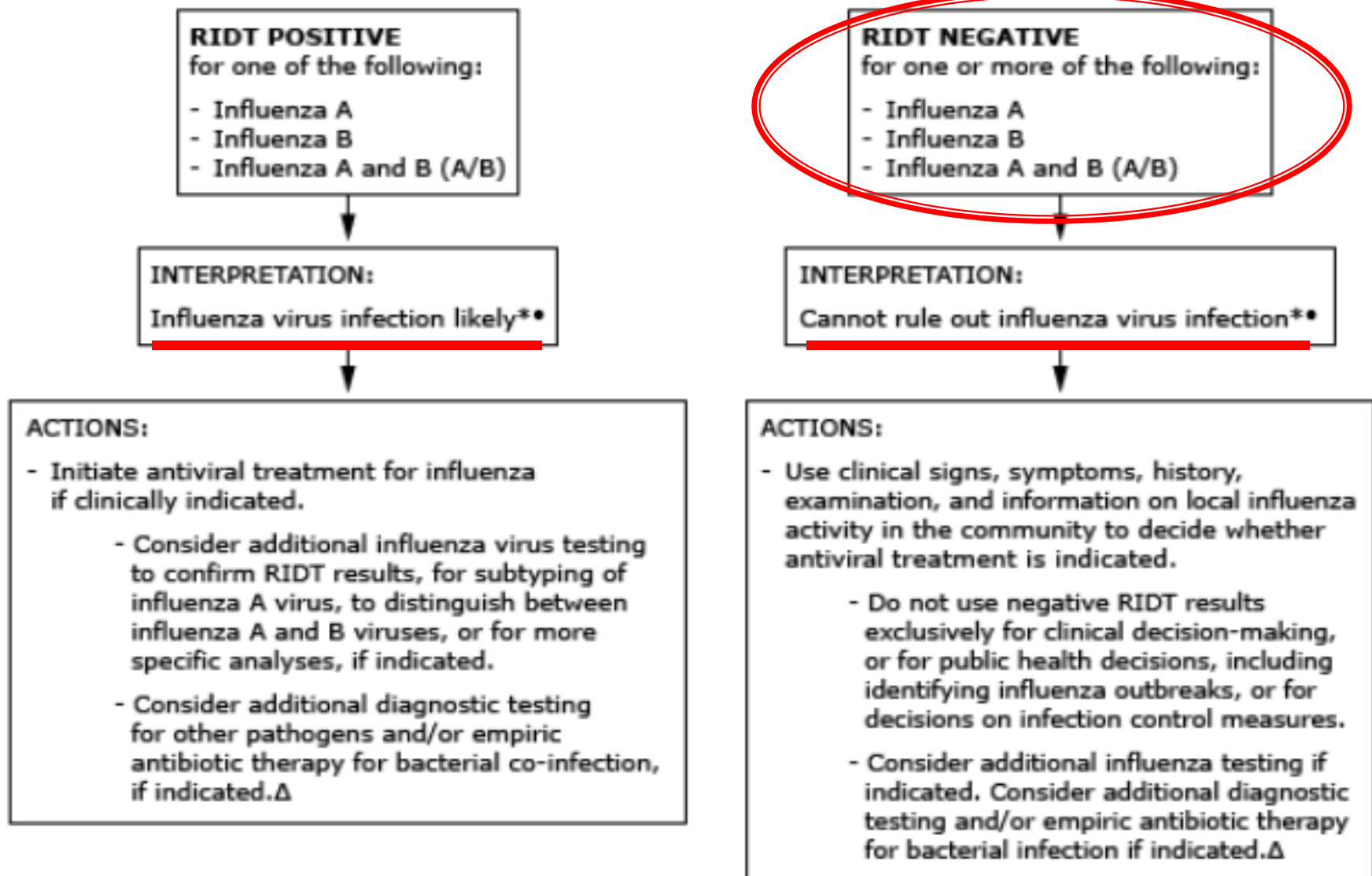
# Seasonal activity of influenza

**Peak influenza activity, by month - United States, 1976-77 through 2010-11**



Centers for Disease Control and Prevention. The flu season. Available at: <http://www.cdc.gov/flu/about/season/flu-season.htm>. Accessed on September 21, 2011.

# Algorithm to assist in the interpretation of rapid influenza diagnostic test (RIDT) results and clinical decision-making during periods when influenza viruses are circulating in the community\*



# Algorithm to assist in the interpretation of rapid influenza diagnostic test (RIDT) results and clinical decision-making during periods when influenza viruses are not circulating or influenza activity is low in the community\*

**RIDT POSITIVE**  
for one of the following:

- Influenza A
- Influenza B
- Influenza A and B (A/B)

**INTERPRETATION:**  
Cannot exclude false positive result\*\*

**ACTIONS:**

- Initiate antiviral treatment for influenza if clinically indicated.
  - Additional influenza virus testing is recommended to confirm RIDT results, for subtyping of influenza A virus, to distinguish between influenza A and B viruses, or for more specific analyses, if indicated.
- Consider additional diagnostic testing for other pathogens and/or empiric antibiotic therapy for bacterial co-infection, if indicated.Δ

**RIDT NEGATIVE**  
for one or more of the following:

- Influenza A
- Influenza B
- Influenza A and B (A/B)

**INTERPRETATION:**  
Influenza virus infection unlikely\*

**ACTIONS:**

- Use clinical signs, symptoms, history, examination, and information on local influenza activity in the community to decide whether antiviral treatment is indicated.
  - Do not use negative RIDT results exclusively for clinical decision-making, or for public health decisions, including identifying influenza outbreaks, or for decisions on infection control measures.
- Consider additional influenza testing if indicated. Consider additional diagnostic testing and/or empiric antibiotic therapy for bacterial infection if indicated.Δ

# Clinical manifestation of influenza

- ▶ **The abrupt onset of fever, headache, myalgia, and malaise** after an incubation period of one to four days (average two days).
- ▶ These symptoms are accompanied by manifestations of **respiratory tract illness**, such as non-productive cough, sore throat, and nasal discharge

# Complications of influenza

- ▶ **Pneumonia**
  - Primary
  - Secondary bacterial
- ▶ **Myositis and rhabdomyolysis**
- ▶ **Cardiac involvement**
  - Especially in people with underlying cardiac disease
- ▶ Toxic shock syndrome
- ▶ CNS(central nervous system)
  - Encephalitis, meningitis or Guillain–Barre

# How to interpret negative results of RIDT in this case

- ▶ This case was in late December, influenza season.
- ▶ **We cannot rule out influenza with RIDT.**
- ▶ Thinking about his symptom, we should start treatment for influenza immediately. And we should consider additional diagnostic test.

# Back to the case again

- ▶ Intravenous vancomycin and ceftriaxone were administered, and levofloxacin was added later.
  - Antibiotics was used because there was a risk for secondary bacterial pneumonia.
- ▶ The microbiology laboratory test confirm the diagnosis of influenza, because viral culture is more sensitive and specific than RIDT.
- ▶ Maybe they should start anti-viral treatment as soon as possible even with negative RIDT results

# Take away points

- ▶ Zebras vs. Horses
- ▶ CC is most important in DDx
- ▶ Season is important to diagnose influenza
- ▶ Sensitivity and Specificity
  - Negative RIDT do **not** reliably exclude influenza
  - RT-PCR is gold standard, but it takes longer than RIDT
- ▶ In Japan, you may not be able to use neuraminidase inhibitor with negative RIDT even though you definitely consider influenza, because of the problem of insurance.



# References

- ▶ N Engl J Med Case 9–2004;350:1236–47
- ▶ Up to date, Diagnosis of seasonal influenza in adults
- ▶ Accuracy of Rapid Influenza Diagnostic Tests  
Caroline Chartrand et al. Ann internal med
- ▶ Symptom to Diagnosis
- ▶ Pocket Medicine 4<sup>th</sup>

# Questions?

