Infectious Diseases Society of America - Influenza Guidelines 2019

A Focus on Diagnostics and Management

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Learning Objectives

- Examine the latest IDSA guidelines for influenza diagnosis
- Discuss the various influenza test methods including immunoassay and molecular
- Review evidence evidence supporting the value of rapid molecular influenza testing
- Discuss the recent experience of evaluation and implementation of rapid molecular influenza testing across an integrated health network

Disclosure

In the last 12m received research and DMSB funding from:

Consultancy:

- Astellas (Antifungals)
- Chimerix (Antivirals)
- Cellerant (Heme/onc)
- PWN Health (ID/IT diagnostics)
- Abbott (ID Diagnostics)

DSMB:

- Visterra (influenza Rx)
- Janssen (influenza Rx, RSV Rx and vaccines)
- Cellerant (neutropenic salvage Rx)
- Merck (CMV Rx)

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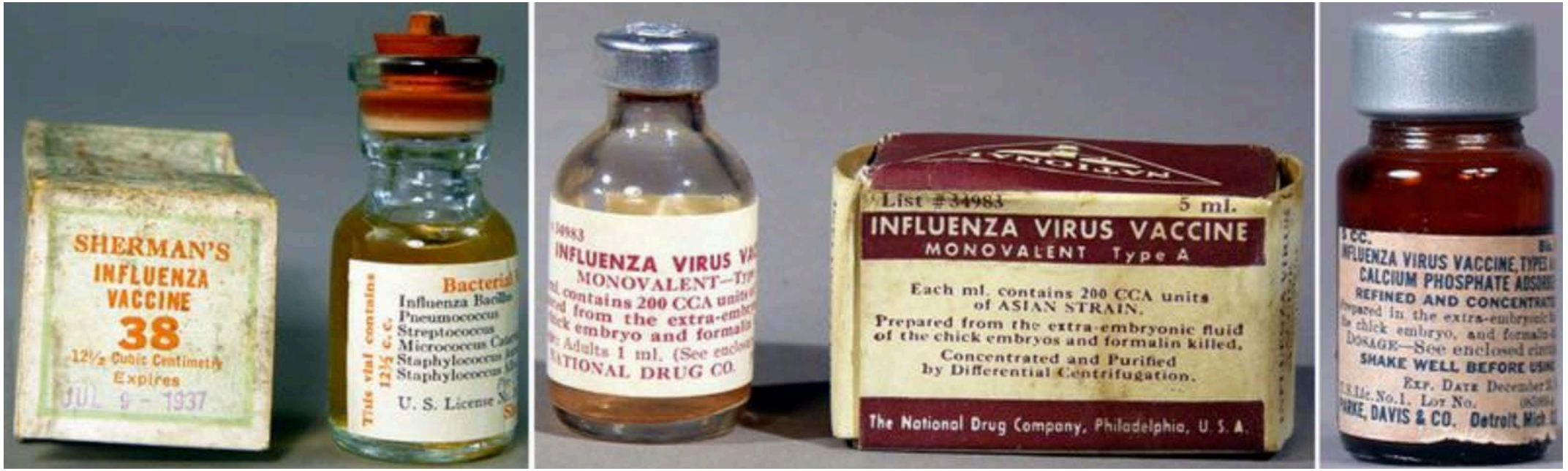
What's New in Flu?



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Outline

- Motivation for New ID Guidelines
  - How are the guidelines constructed, and what questions do they answer?
  - What's new compared to 2009, what's changed?

- Background and Burden
  - How common is influenza, clinical impact?

- Current Clinical Challenges with Testing
  - What are our biggest challenges on the ward?
  - How might the current guidelines drive change in the lab?

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Motivations to Change

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

Timothy M. Uyeki,[1] Henry H. Bernstein,[2] John S. Bradley,[3,4] Janet A. Englund,[5] Thomas M. File Jr,[6] Alicia M. Fry,[1] Stefan Gravenstein,[7] Frederick G. Hayden,[8] Scott A. Harper,[9] Jon Mark Hirshon,[10] Michael G. Ison,[11] B. Lynn Johnston,[12] Shandra L. Knight,[13] Allison McGeer,[14] Laura E. Riley,[15] Cameron R. Wolfe,[16] Paul E. Alexander,[17,18] and Andrew T. Pavia[19]

Clinical Infectious Diseases

IDSA
Infectious Diseases Society of America

- Guideline structure
  - Major sections
  - Major updates since last guideline (e.g., testing – both who, when and with what) and also treatment
  - Subtle changes in when to treat and with what, some new drugs, better understanding of when to use them
  - Ongoing changes occur in vaccination strategies, although these are intentionally not addressed in the guidelines (but specifically, vaccinate more people, more frequently, especially in health care circles where the risk of passing inadvertent flu to at risk folk is greatest)

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Background to Writing the Guidelines

- 4 Major Sections:
  - Diagnosis
    - Who to test, with what specimen?
    - Testing on which platform?
  - Treatment
    - Who to treat, when?
    - Which drug, how long?
    - Hospitalized vs outpatient care
    - Rx when your patient doesn't improve?
    - Experimental strategies
  - Antiviral Chemoprophylaxis
    - Who should receive prophylaxis?
    - If given, with what drug and for how long?
  - Institutional Outbreak Control
    - Focusing on Long-Term Care facilities

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Cost Burden of Four Adult Vaccine-Preventable Diseases in the U.S. (65 yrs and older), 2013

Vaccine-Preventable Disease	Estimated # of CASES	Estimated COSTS (Medical & Indirect) *(in millions)*
Influenza	4,019,759	8,312.8
Pneumococcal	440,187	3,787.1
Zoster	555,989	3,017.4
Pertussis	207,241	212.5
TOTAL	**5,223,176**	**$15,329.8**

226,000 admissions
3-49k deaths, per yr
Typically bimodal:
- very young
- very old or infirm

Direct cost: ~$10.4B
Indirect costs: $87B

~$11 billion more annually if population 50–64 yrs of age included

McLaughlin, JM., Tan, L., et al. 2015 J Prim Prev. 2015 Aug;36(4):259–73.

immunization action coalition
IAC
immunize.org

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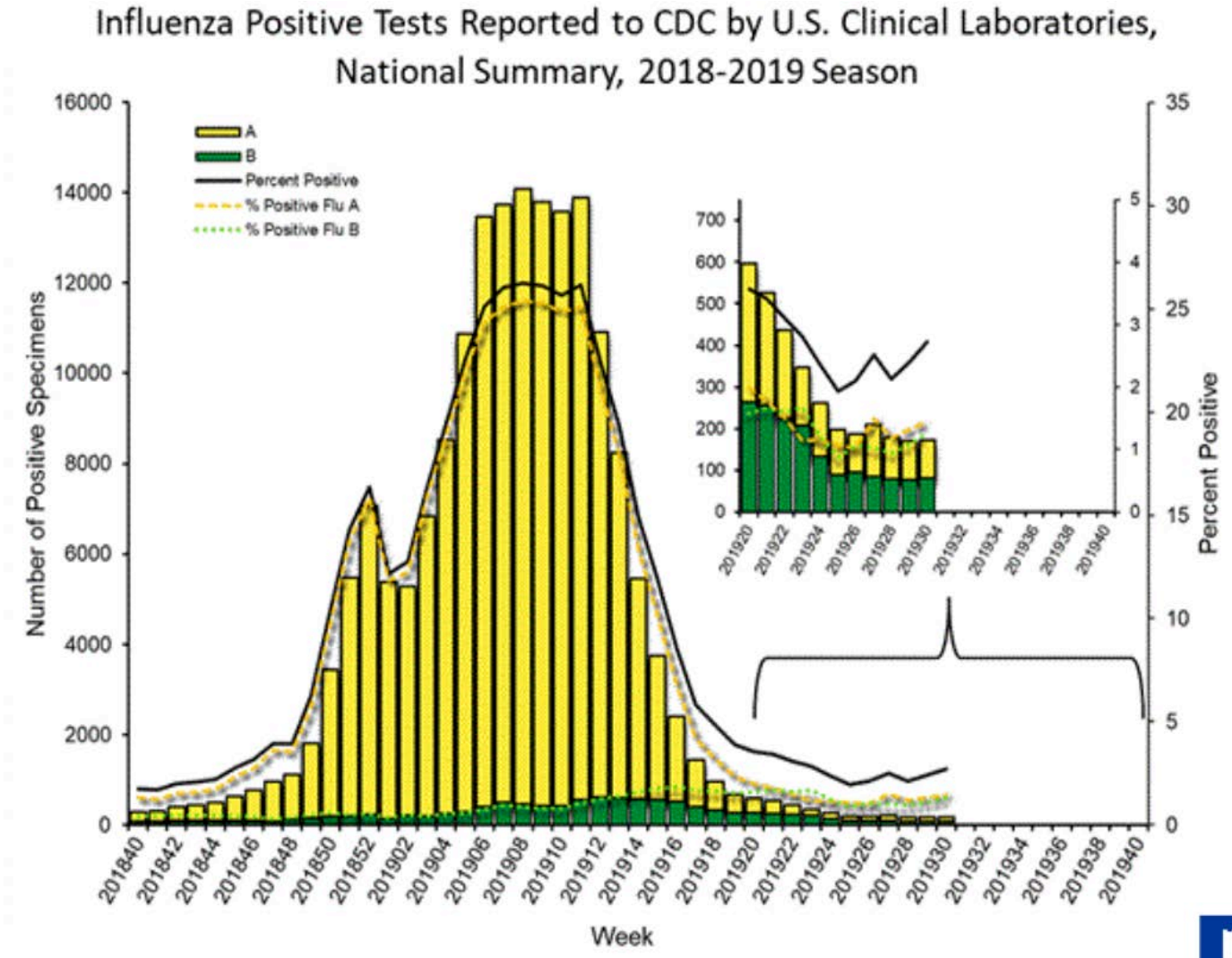
Seasonal Burden of Disease



https://www.cdc.gov/flu/weekly/index.htm (accessed Aug 8, 2019)

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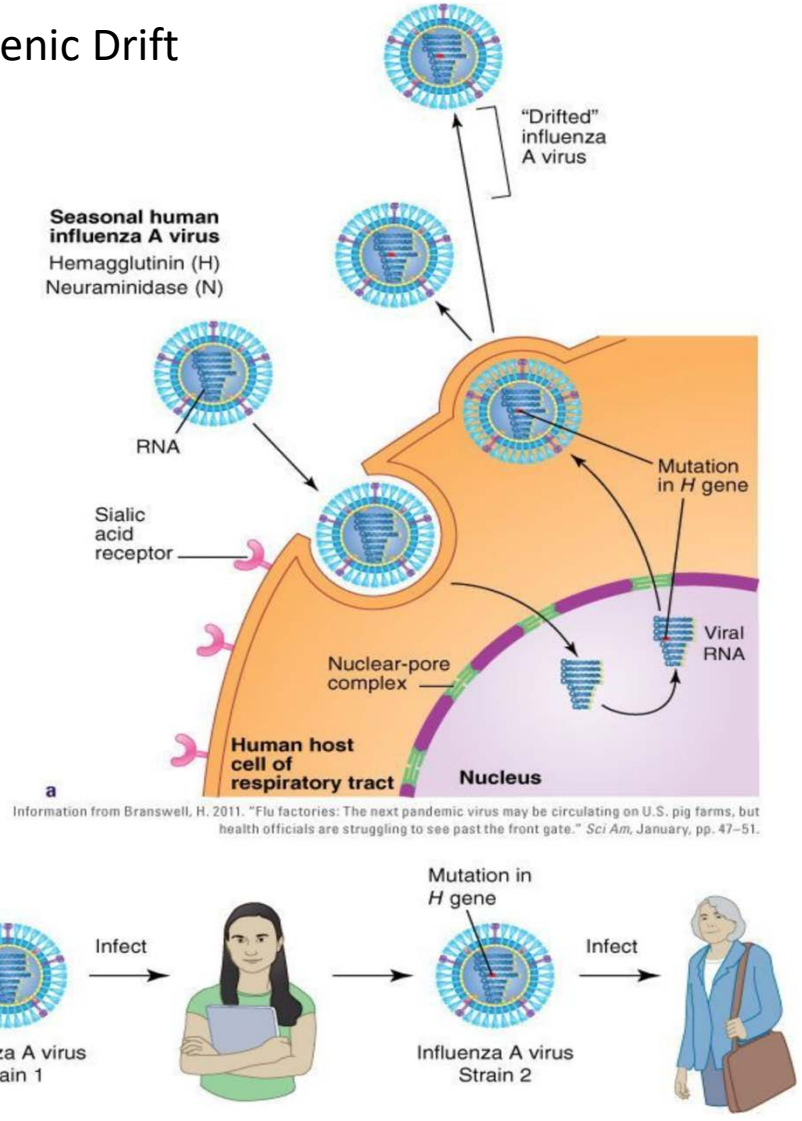
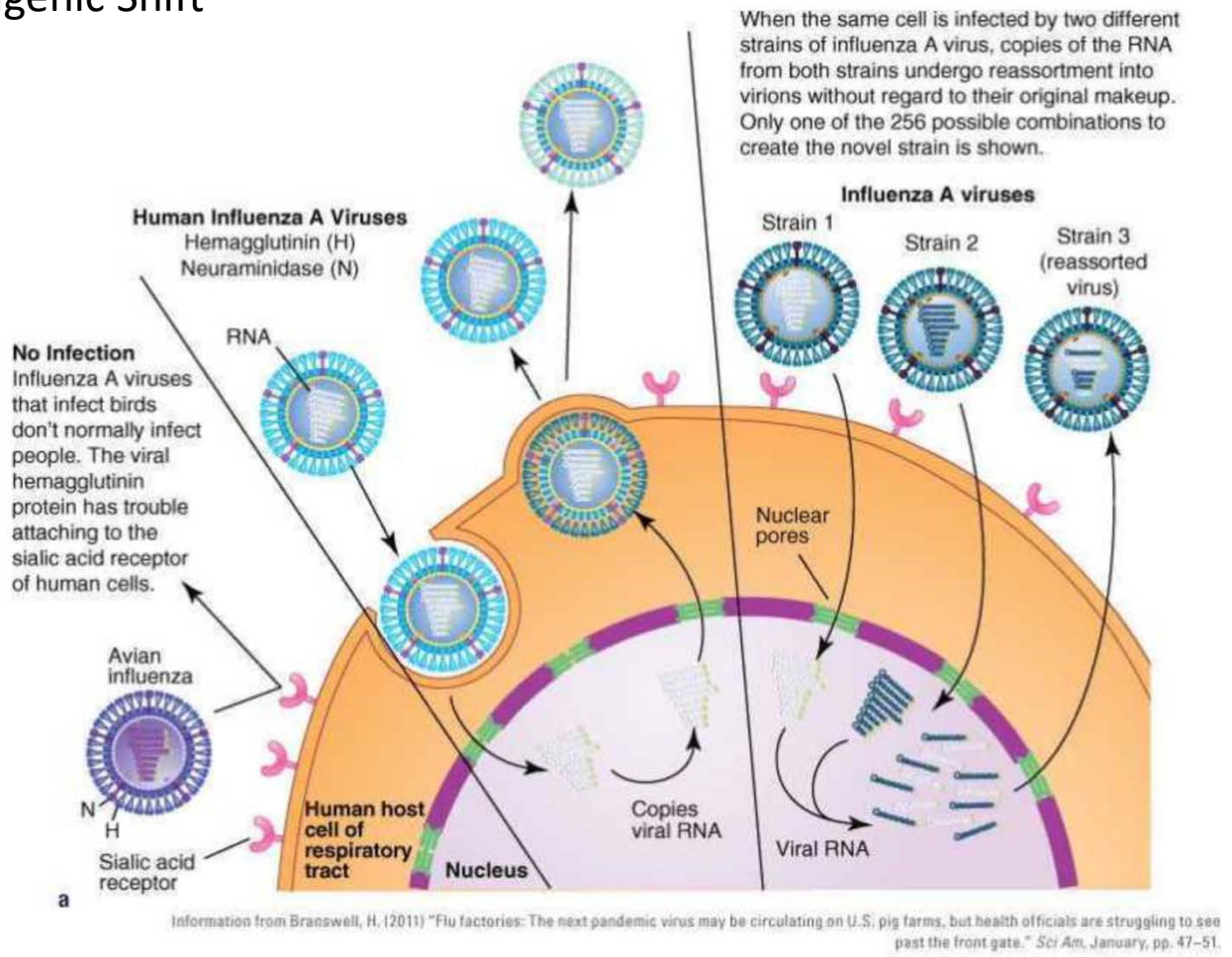
Basic Influenza Virology Review

Antigenic Drift



Antigenic Shift



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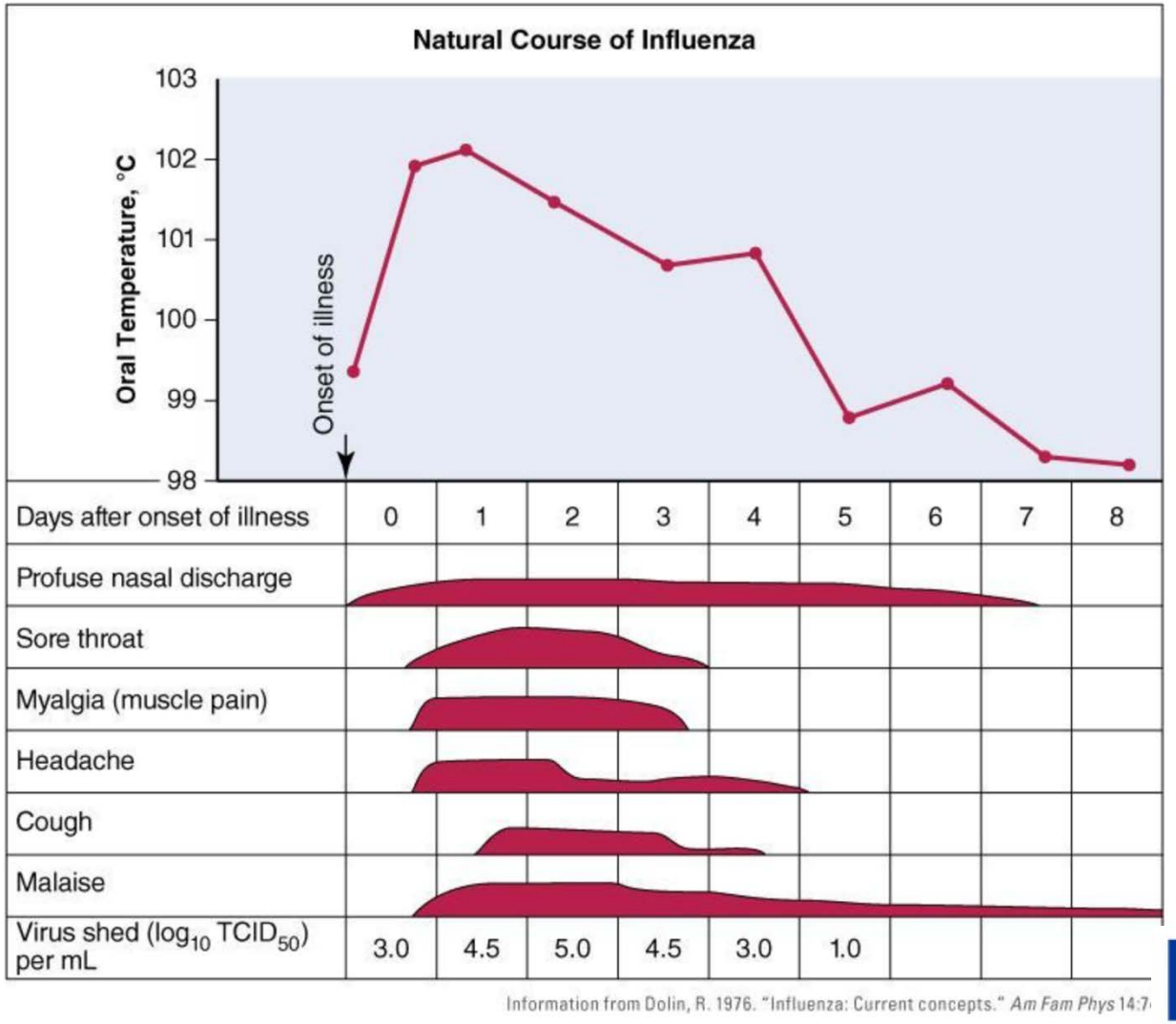
Clinical Syndromes



Information from Dolin, R. 1976. "Influenza: Current concepts." *Am Fam Phys* 14:7

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Breadth & Frequency of Recognized Influenza Complications Has Expanded

Widely recognized:

- Cough
- Sore throat
- Rhinitis
- Fever
- Headache
- Sinusitis / bronchitis
- Myalgias

Less well recognized:

- Neurologic:
  - Febrile convulsions
  - Seizures
  - Encephalitis
  - Guillain-Barre Synd.
- Pulmonary:
  - Pneumonia
  - Exac of COPD
- Cardiac
  - Pericarditis
  - Myocarditis
  - Exac of Ischemic dis
- Pregnancy
  - Inc. fetal loss
  - Inc. maternal mortality
  - Prematurity
  - Small neonatal size

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Background to Writing the Guidelines

- Panel Makeup?
  - Lead by of Infectious Disease Society of America
  - CDC, Emergency Medicine, Obstetrics,
  - Pediatrics, Transplant, Primary Care
- How Constructed?
  - >10,000 manuscripts reviewed from 2009-2017
  - Synthesized data into 'grade level' recommendations to answer directed clinical questions
- Intentionally Does NOT Cover:
  - Vaccination
  - Infection Control Techniques

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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When to test for flu - Outpatients:

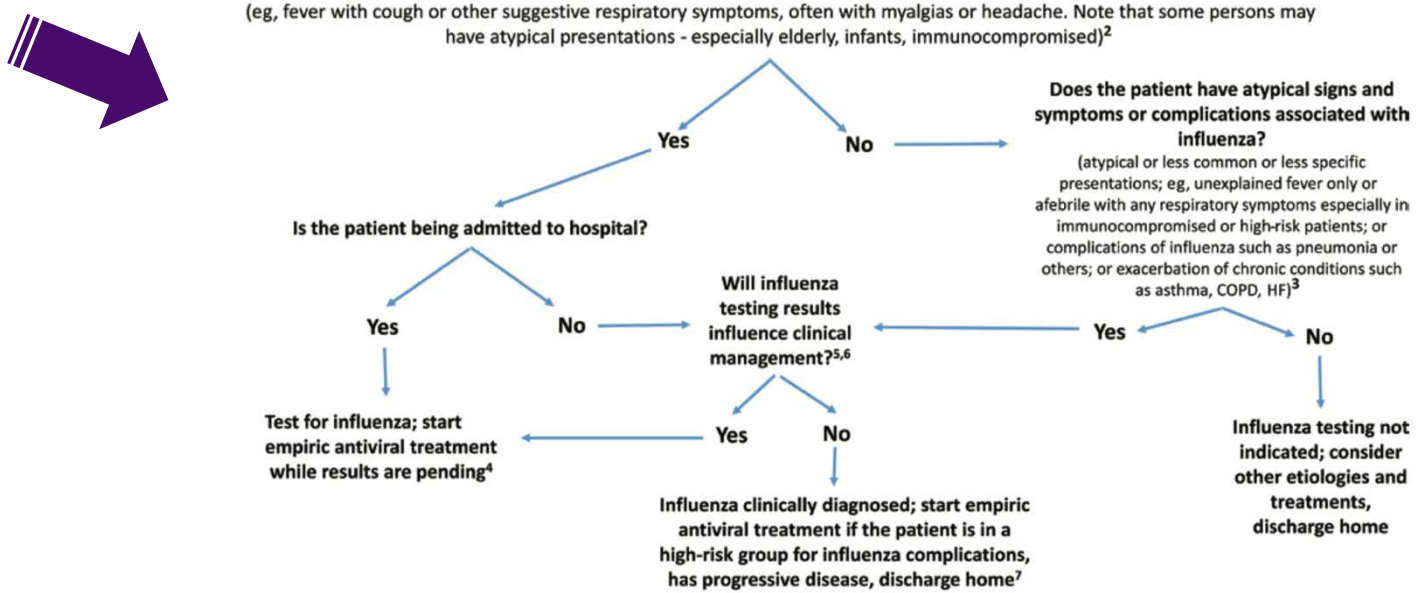
DIAGNOSIS

Which Patients Should Be Tested for Influenza?

Recommendations

Outpatients (including emergency department patients).

1. During influenza activity (defined as the circulation of seasonal influenza A and B viruses among persons in the local community) (see Figure 1):
   - Clinicians should test for influenza in high-risk patients, including immunocompromised persons who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) if the testing result will influence clinical management *(A–III)*.
   - Clinicians should test for influenza in patients who present with acute onset of respiratory symptoms with or without fever, and either exacerbation of chronic medical conditions (eg, asthma, chronic obstructive pulmonary disease [COPD], heart failure) or known complications of influenza (eg, pneumonia) if the testing result will influence clinical management *(A-III)* (see Table 3).
   - Clinicians can consider influenza testing for patients not at high risk for influenza complications who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) and who are likely to be discharged home if the results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 40–42) *(C-III)*.
2. During *low* influenza activity without any link to an influenza outbreak:
   - Clinicians can consider influenza testing in patients with acute onset of respiratory symptoms with or without fever, especially for immunocompromised and high-risk patients *(B-III)*.



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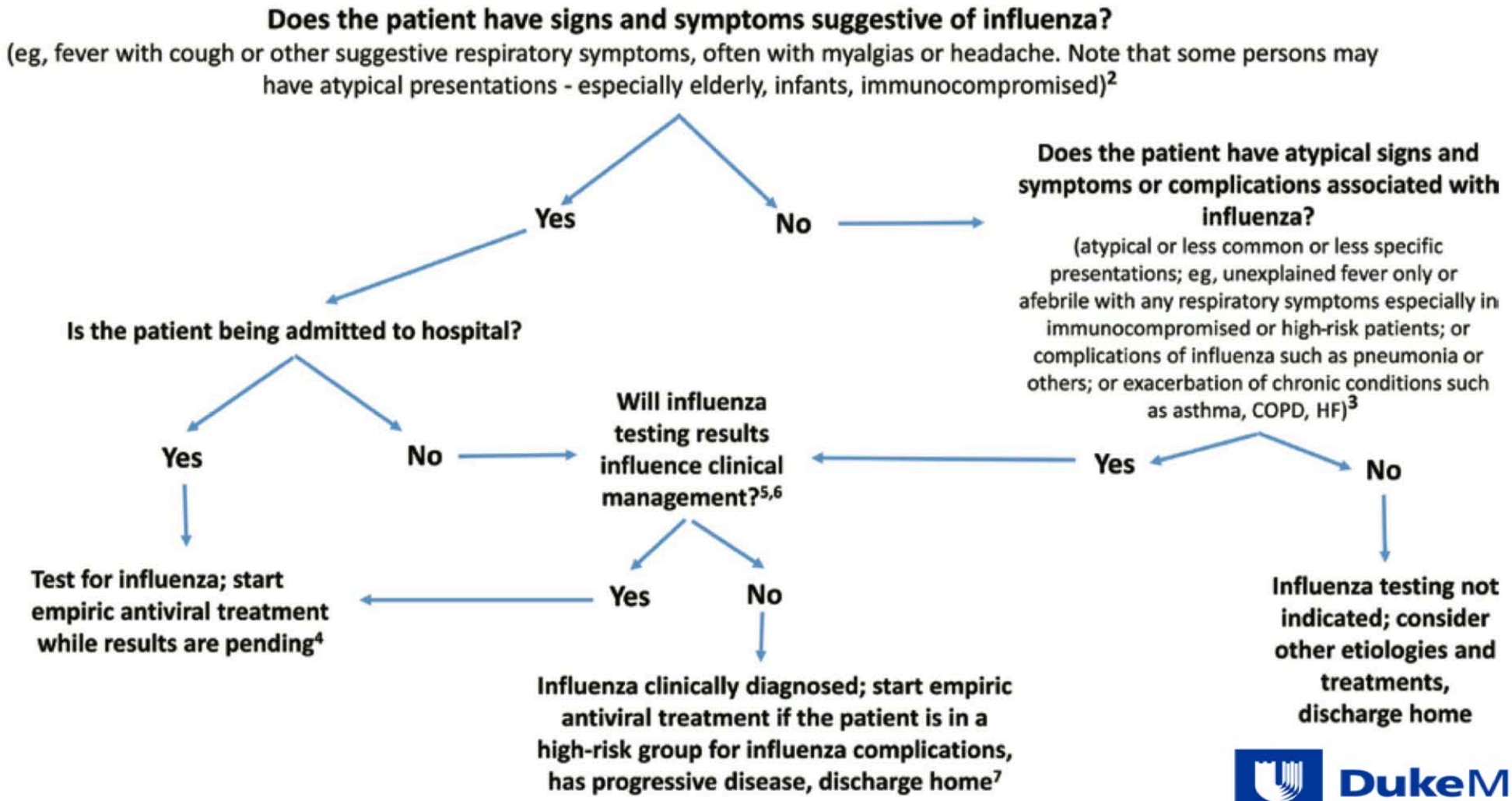

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When to test for flu – Inpatients:

Hospitalized Patients.

3. During influenza activity:
   - Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, including pneumonia, with or without fever *(A-II)*.
   - Clinicians should test for influenza on admission in all patients with acute worsening of chronic cardiopulmonary disease (eg, COPD, asthma, coronary artery disease, or congestive heart failure), as influenza can be associated with exacerbation of underlying conditions *(A-III)*.
   - Clinicians should test for influenza on admission in all patients who are immunocompromised or at high risk of complications and present with acute onset of respiratory symptoms with or without fever, as the manifestations of influenza in such patients are frequently less characteristic than in immunocompetent individuals *(A-III)*.
   - Clinicians should test for influenza in all patients who, while hospitalized, develop acute onset of respiratory symptoms with or without fever, or respiratory distress, without a clear alternative diagnosis *(A-III)*.

4. During periods of low influenza activity:
   - Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, with or without fever, who have an epidemiological link to a person diagnosed with influenza, an influenza outbreak or outbreak of acute febrile respiratory illness of uncertain cause, or who recently traveled from an area with known influenza activity *(A-II)*.
   - Clinicians can consider testing for influenza in patients with acute, febrile respiratory tract illness, especially children and adults who are immunocompromised or at high risk of complications, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 41–43) *(B-III)*.

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Diagnostic Test Recommendations:

What Test(s) Should Be Used to Diagnose Influenza?

Recommendations

10. Clinicians should use rapid molecular assays (ie, nucleic acid amplification tests) over rapid influenza diagnostic tests (RIDTs) in outpatients to improve detection of influenza virus infection *(A-II)* (see Table 6).
11. Clinicians should use reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays over other influenza tests in hospitalized patients to improve detection of influenza virus infection *(A-II)* (see Table 6).
12. Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized immunocompromised patients *(A-III)*.
13. Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who are not immunocompromised if it might influence care (eg, aid in cohorting decisions, reduce testing, or decrease antibiotic use) *(B-III)*.

Increased emphasis on rapid molecular assays, and PCR

Increased emphasis on multiplex platforms for patients who are immunocompromised

14. Clinicians should not use immunofluorescence assays for influenza virus antigen detection in hospitalized patients except when more sensitive molecular assays are not available *(A-II)*, and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative immunofluorescence test results *(A-III)*.
15. Clinicians should not use RIDTs in hospitalized patients except when more sensitive molecular assays are not available *(A-II)*, and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative RIDT results *(A-II)*.
16. Clinicians should not use viral culture for initial or primary diagnosis of influenza because results will not be available in a timely manner to inform clinical management *(A-III)*, but viral culture can be considered to confirm negative test results from RIDTs and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization *(C-II)*.
17. Clinicians should not use serologic testing for diagnosis of influenza because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera 2–3 weeks apart are needed for serological testing *(A-III)*.

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Other tests generally discouraged for clinical practice

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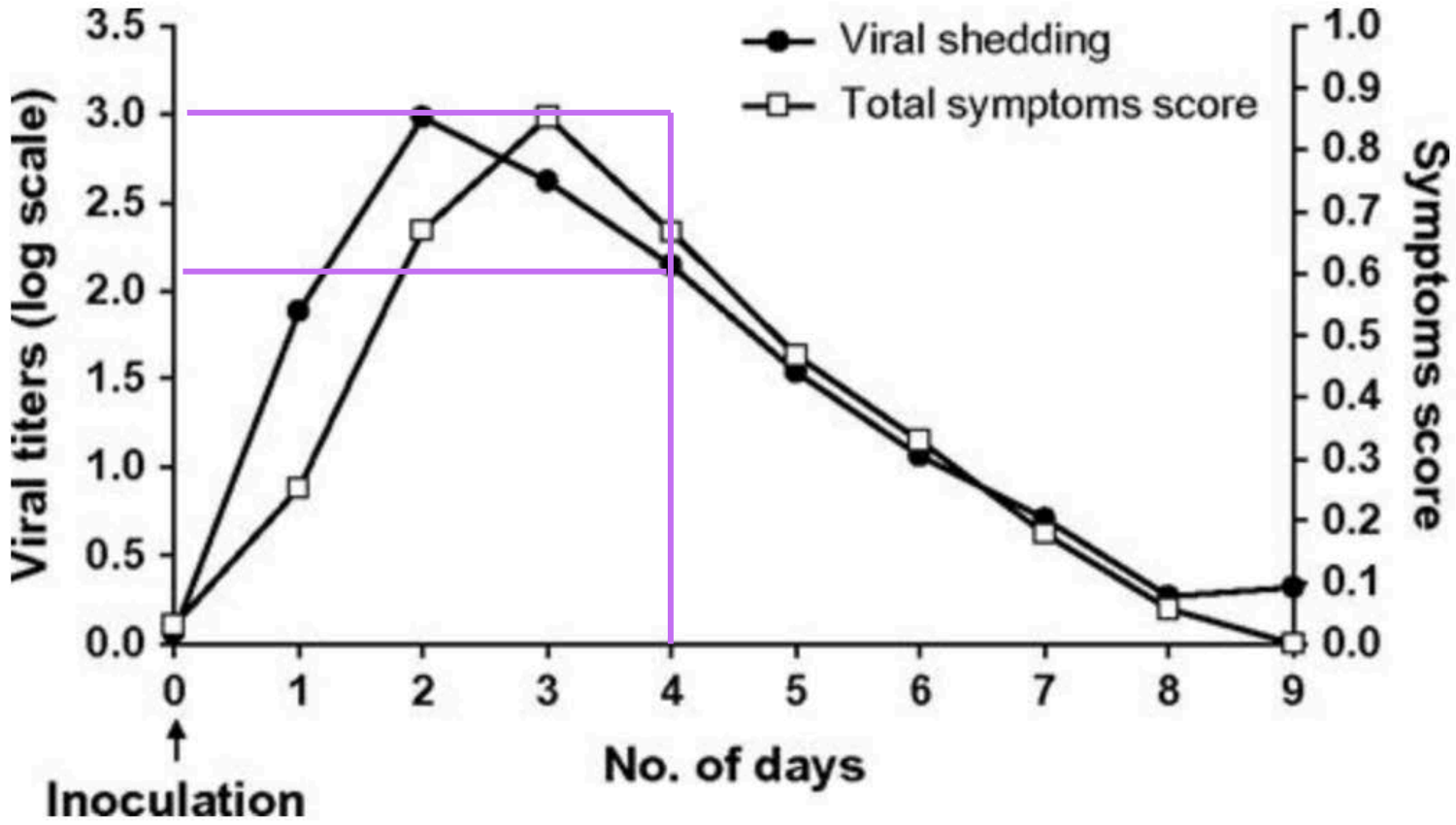
Why the Emphasis on Molecular / PCR Testing?

1. Viral kinetics and social behavior

Already **~33%** reduction in detectable virus



American Journal of Epidemiology, Volume 167, Issue 7, 1 April 2008, Pages 775–785

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Why the Emphasis on Molecular / PCR Testing?

2 Earlier treatment leads to earlier (and more likely) recovery

- Early trials of Oseltamivir demonstrated earlier initiation of drug was more effective
  - Reduced fever and Sx's by 1-2 days if initiated within 36-48hrs of symptoms[1]
  - Reduced symptoms by up to 4 days, if treatment initiated within 6hrs of symptoms[2]

- Pooled meta-analysis of inpatient studies (>29,000 pts) using neuraminidase inhibitors, demonstrated both[3]
  - Survival benefit if NAI Rx given versus placebo, significantly greater if started <2ds after illness onset.
  - Significant survival benefit in pregnant and post-partum women, pts in ICU care

- Other studies[4-7]
  - Reduced lab testing for other etiologies and use of antibiotics
  - Improved effectiveness of infection prevention and control measures
  - Increased appropriate use of antiviral medications
  - Reduced length of stay and risk of mechanical ventilation

NAI, neuraminidase inhibitors

1. Hayden et al, N Engl J Med 1997; 337:874–80. 2. Boivin et al, J Infect Dis 2000; 181:1471–4. 3. Murthuri et al, Lancet Respir Med 2014;2:395–404. 4. Bonner et al, Pediatrics 2003; 112:363–7. 5. Falsey et al. Arch Intern Med 2007; 167:354–60. 6.Coffin et al, Pediatr Infect Dis J 2011; 30:962–6. 7. Eriksson et al, Pediatr Crit Care Med 2012; 13:625–31.

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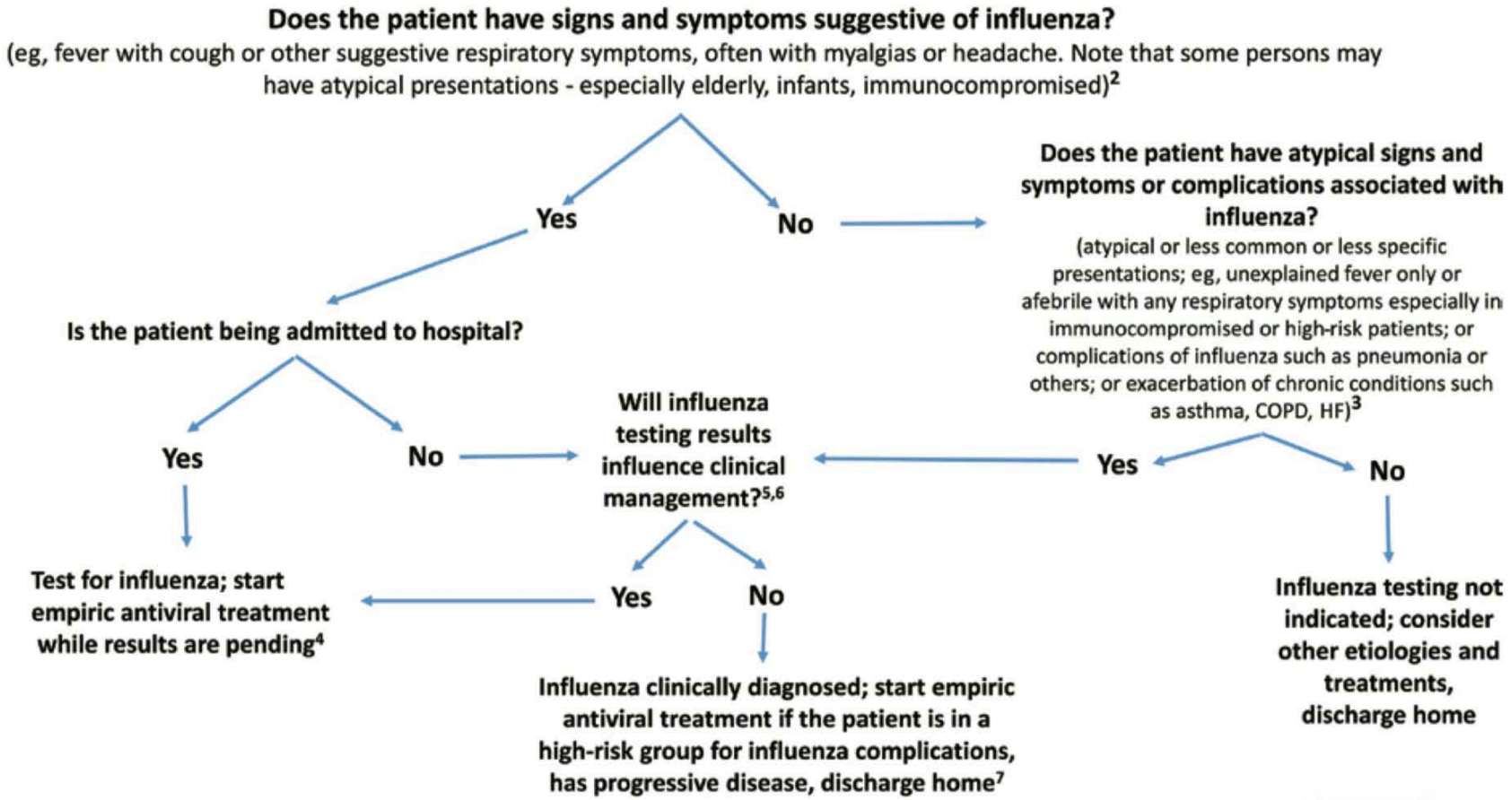
Clinical Implications Derived from Guidelines

- For clinicians:
  - *OUT*-patients
    - Clinicians now pushed to treat if high-risk and only run diagnostic tests on other patients if it would change management.
    - Concentrate on tests that provide actionable results (eg: flu, RSV. ↓ emphasis on multiplex)
      - For ED, UC and the Clinic, this may be operational efficiency and/or benefits with infection control
    - More tests likely to be run if:
      - (a) fast, (b) sensitive and specific, (c) affordable – compared to the risk/cost of a poor outcome
  - *IN*-patients
    - Strong desire to test more frequently, and early in a presentation
    - Recognition that treatment should be early for anyone admitted, so in flu season treatment often given before test result comes back
    - Now that flu recognized as contributing to so many more syndromes, especially in the ICU, proving it's present (given molecular testing & excellent PPV) helps streamline Rx
    - Multiplex viral panels, esp. in the critically ill or immunosuppressed will be encouraged.

Clinical Implications Derived from Guidelines

- For laboratory:
  - Seasonal flexibility critical, especially for molecular platforms, given time sensitivity
  - Anticipate more testing as importance of ruling influenza in (and out) increases. Similarly for multiplex
  - Likely anticipate desire for range of platforms, based on the location of the clinicians (e.g., ICU vs clinic)

When to Test for Influenza – Based on Clinical Grounds?



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Summary

- Flu is probably even more common than we think!
- Clear benefit now recognized for testing and treating influenza early. Guidelines emphasize a broader array of clinical syndromes and clinical settings that should ideally lead to molecular testing, especially in the inpatient setting.
- Understanding your local influenza epidemiology really helps clinicians order and interpret influenza and respiratory viral tests, and treat appropriately when necessary.
- As clinicians are encouraged to think about influenza more frequently, having diagnostic platforms available that allow for rapid, accurate and cost-effective testing will be very helpful, both in the clinic and ward setting.

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