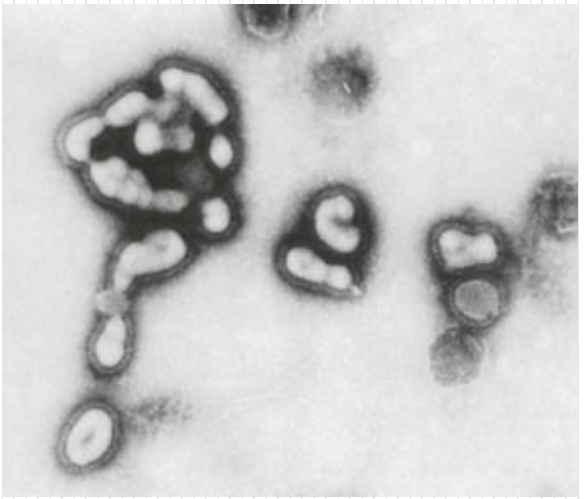
Human Influenza: Diagnosis and Management

Jennifer Hsu, MD FACP

September 24, 2015



Objectives

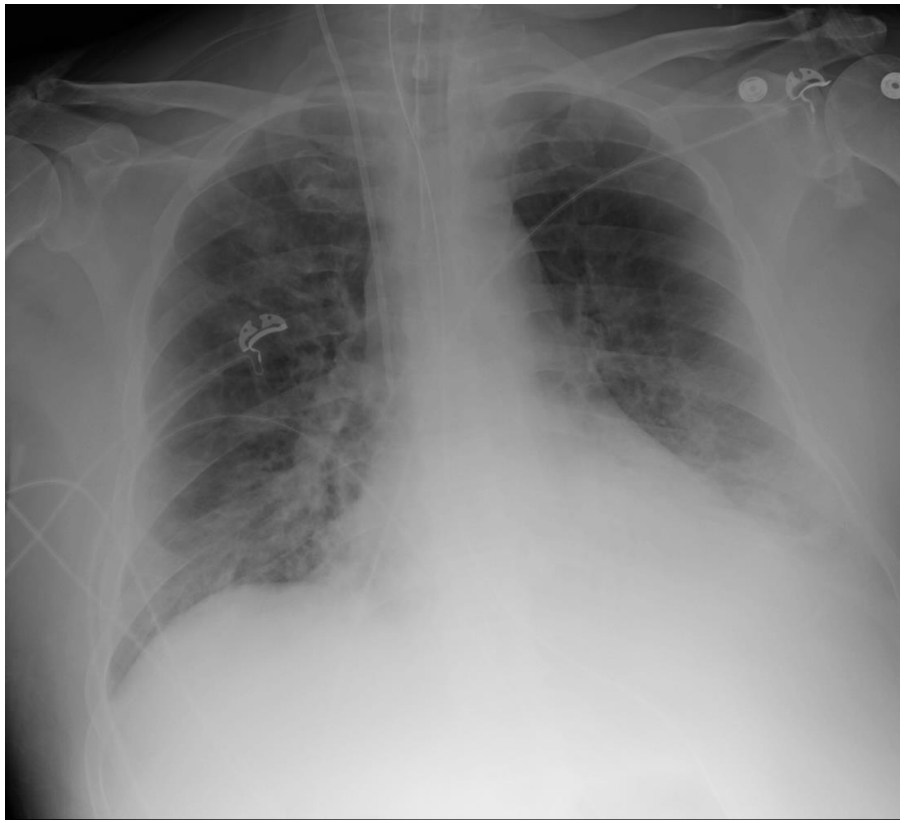
- Review transmission and basic pathogenesis of human influenza
- Discuss clinical and laboratory diagnostic testing
- Survey available treatment modalities

Case 1

- 28 year old male with no past medical history presents to Acute Care in mid-February with fever, non-productive cough, and body aches
- Symptoms developed approximately 4 days prior after his daughter came home ill from school with similar symptoms
- He is maintaining adequate oral intake
- He is mildly ill-appearing with normal vital signs
- Lung exam is notable only for coarse breath sounds
- Rapid influenza test confirms influenza A infection

Case 2

- 58 yo male with diabetes, hypertension, dyslipidemia, CVA, and stage IV CKD
- Presented to ED in late December with 3-4 days of dry cough, dyspnea, and weakness
- In respiratory distress with O2 saturation 38%
- Failed non-invasive ventilation and required intubation

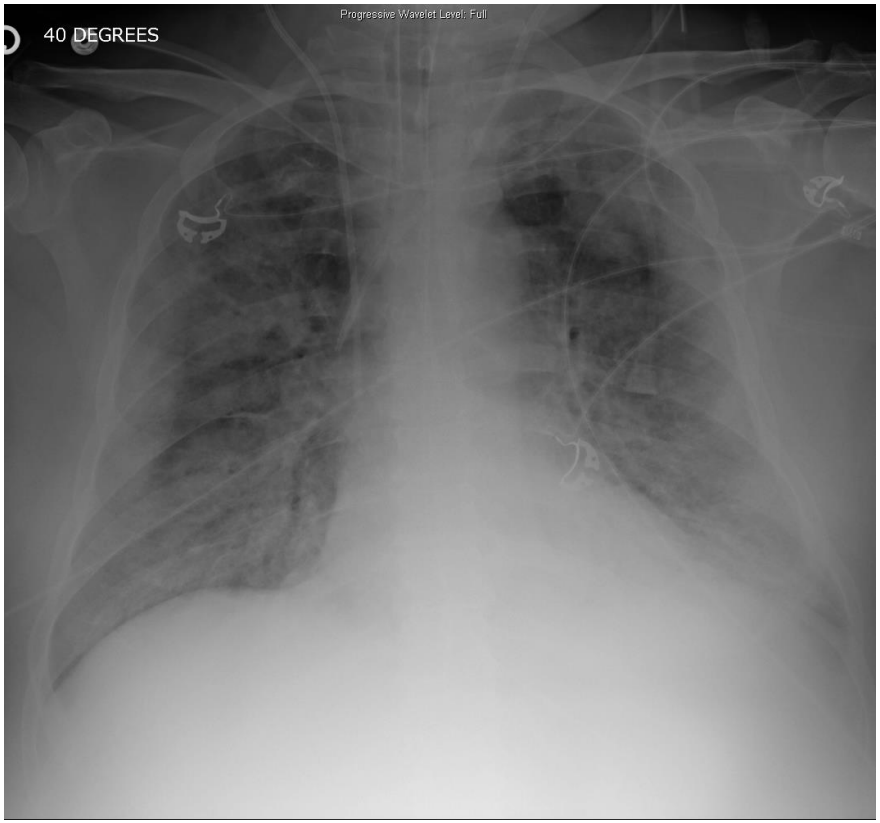


Case 2 (cont.)

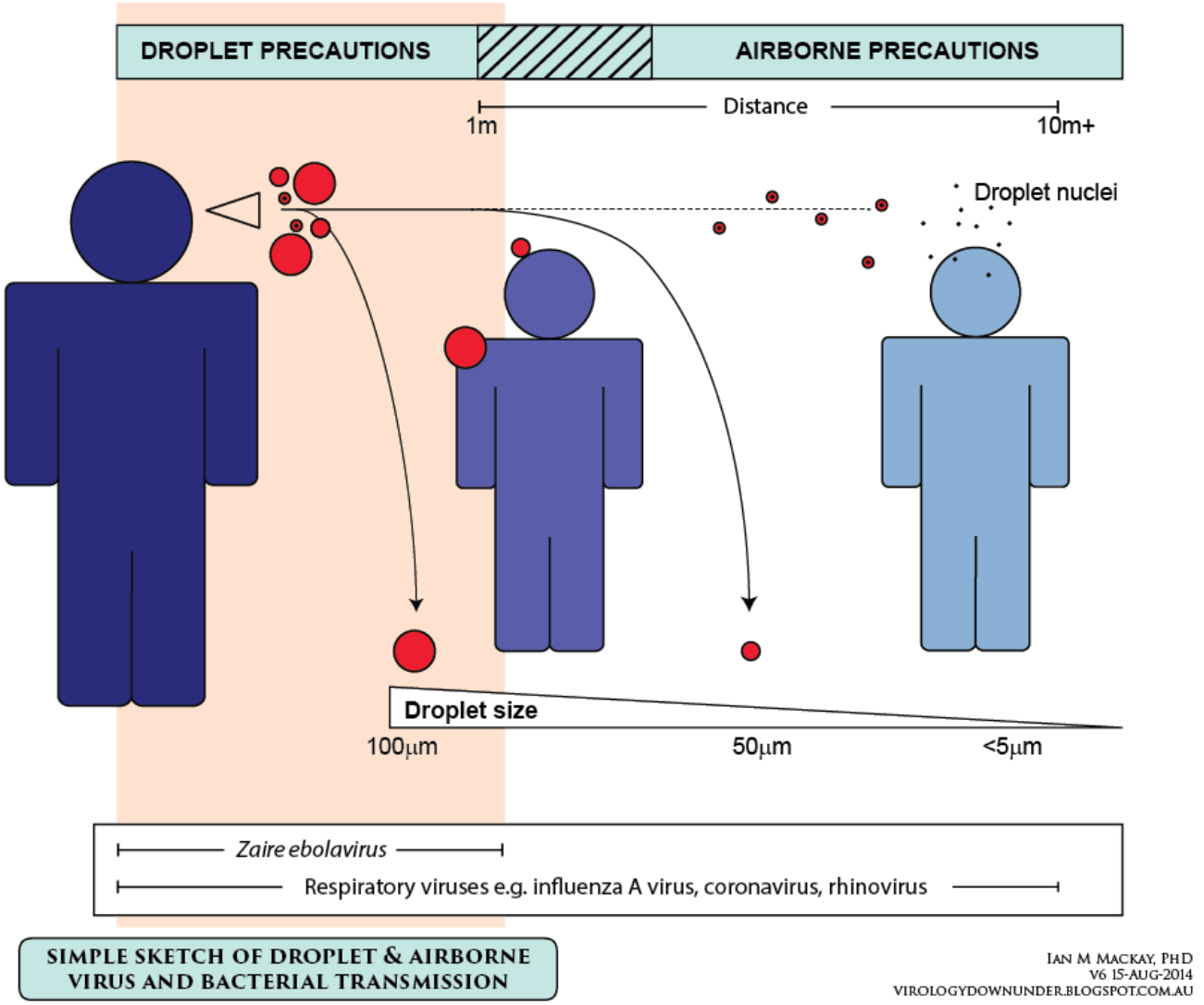
- Started on broad-spectrum anti-bacterial agents for presumed community-acquired pneumonia
- Initial diagnostic testing:
  - Mycoplasma IgM, pneumococcal urine Ag, influenza A and B DFA all negative
  - Sputum culture with MSSA; blood cultures negative
- Required CRRT and vasopressors
- No response when sedation weaned

Case 2 (cont.)

- Progressive bilateral pulmonary infiltrates and hypoxemia
- Required switch to HFOV
- Additional testing:
  - HIV negative
  - Legionella Ag negative
  - Influenza A PCR positive

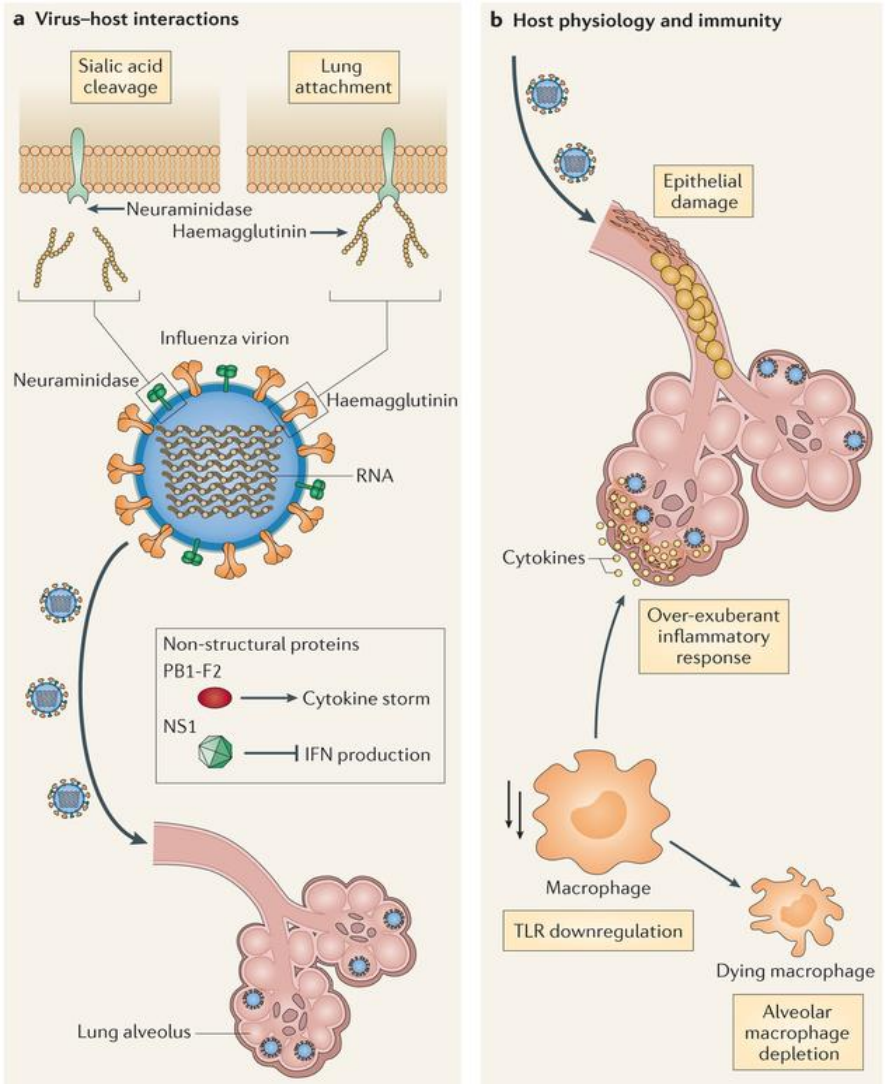


Human-To-Human Transmission



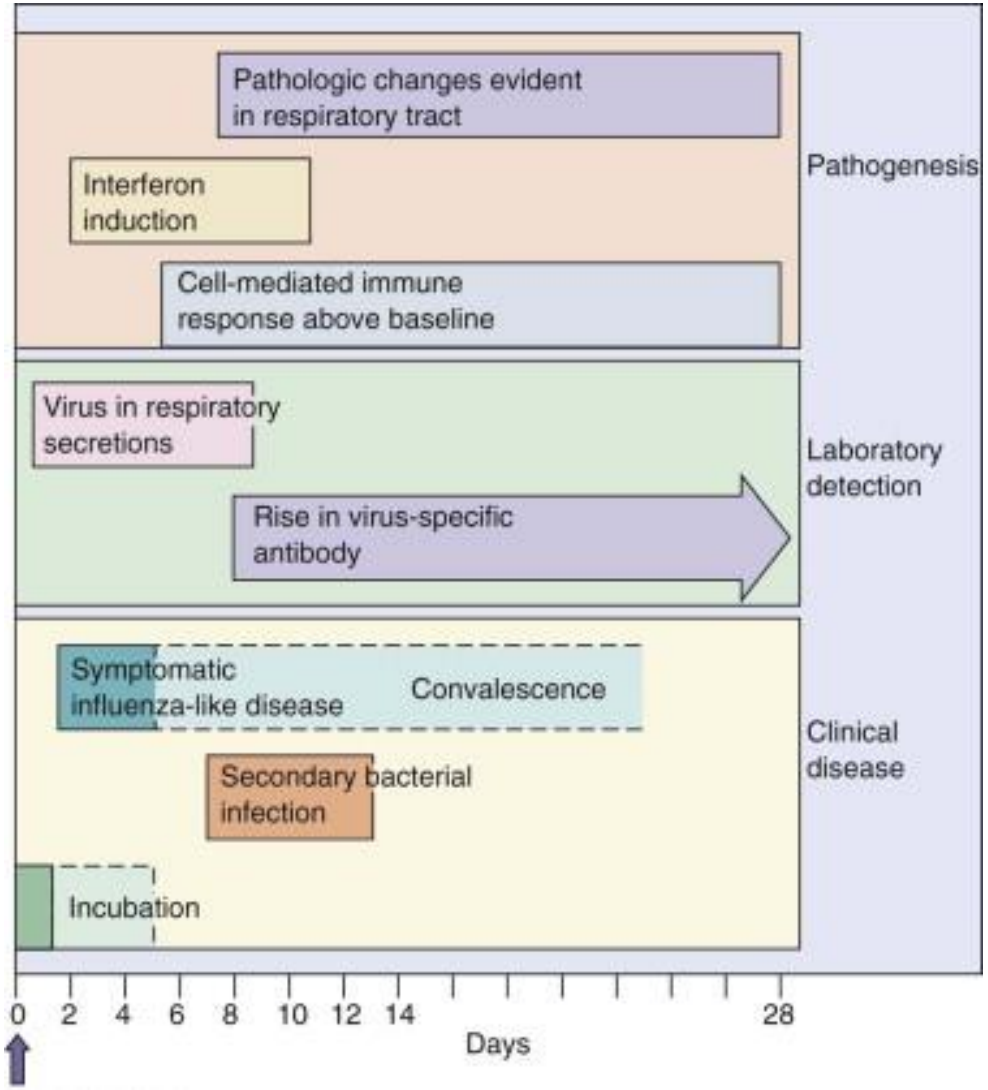
Simplified Pathogenesis

1. Hemagglutinin mediates attachment.
2. Nonstructural proteins made in infected cells:
    1. PB1-F2 causes cytotoxicity and inflammatory response to co-pathogens
    2. NS1 modulates innate pathways, including interferon signaling
3. Virus-mediated effects change the physical property of the lungs and compromise innate immunity.
4. Dysfunctional and over-exuberant inflammatory response (PMN influx and cytokine storm) furthers acute lung injury started by the virus.



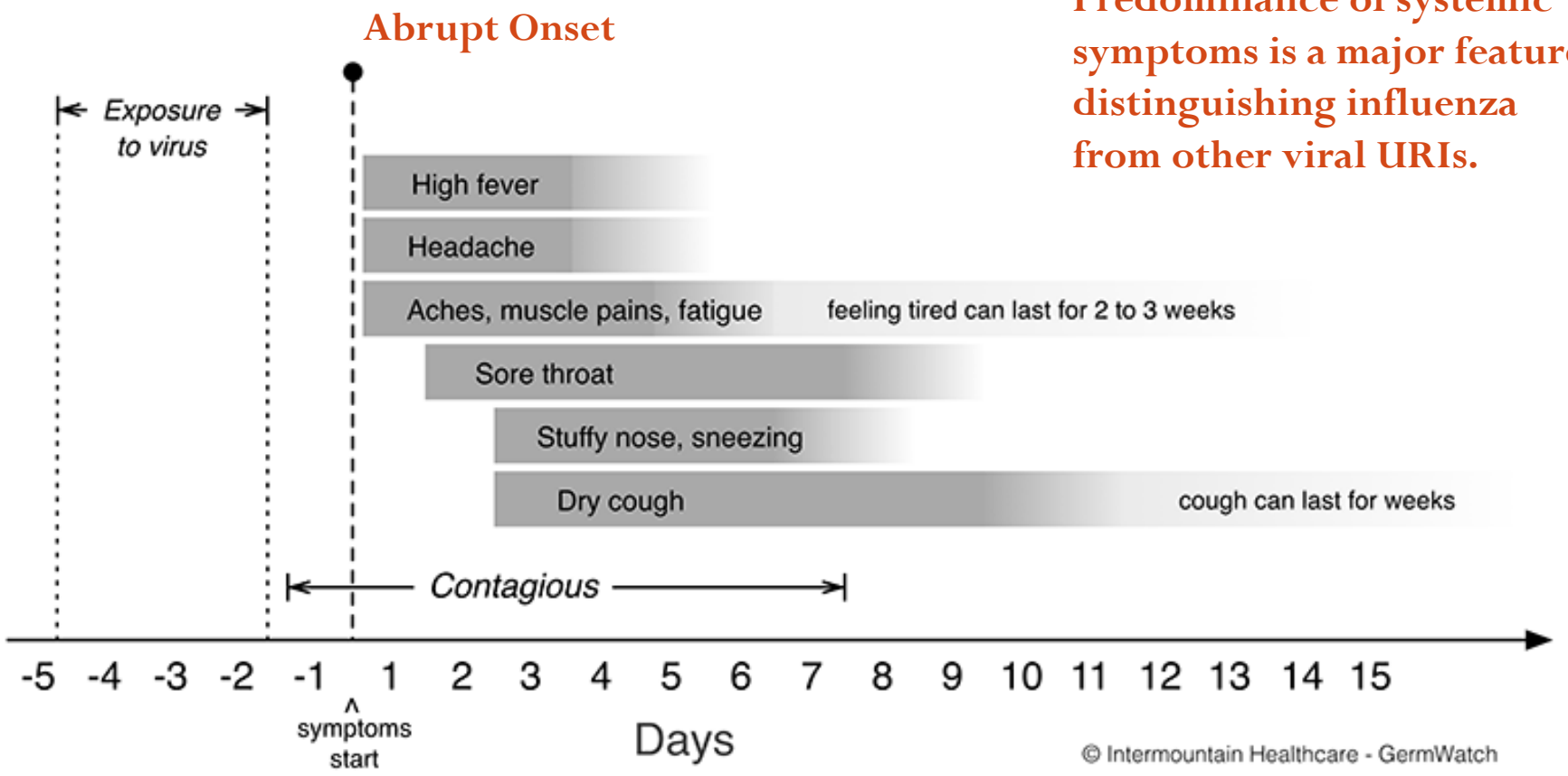
Culler JA. *Nat Rev Microbiol* 2014;12:252-262.

Pathogenesis vs. Illness



Murray P, Rosenthal K, Pfaller M. *Murray: Medical Microbiology* 57, 524-532.

Symptom Time Course



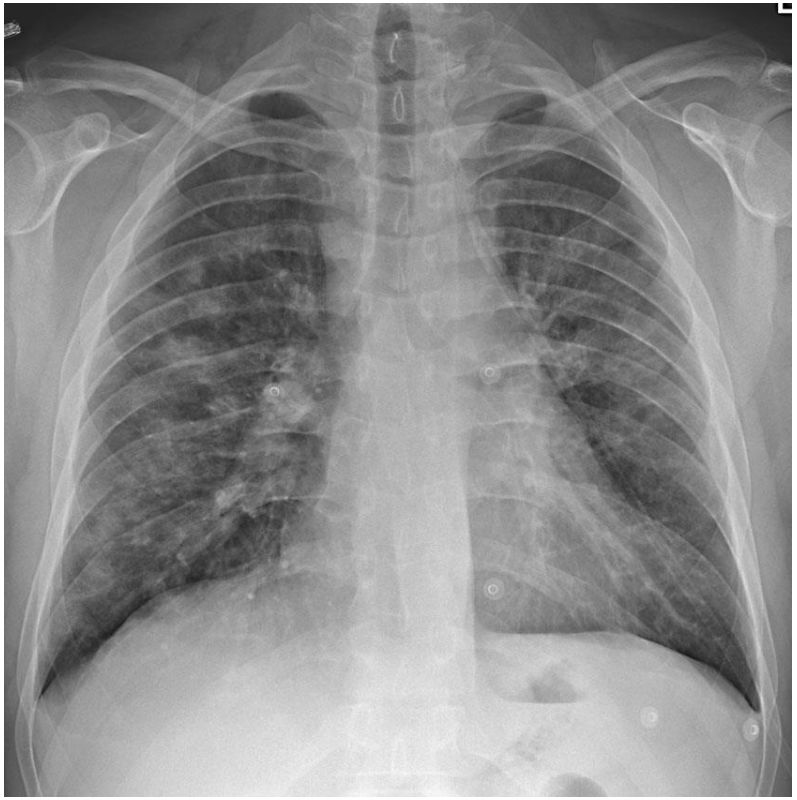
Predominance of systemic symptoms is a major feature distinguishing influenza from other viral URIs.

Risk of Complications

- Age <5 years and ≥ 65 years
- Pregnancy and immediate post-partum
- American Indians and Alaskan Natives
- Residents of long-term care facilities
- Co-Morbidities: asthma, chronic lung disease, neurological / neurodevelopmental disorders, heart disease, sickle cell anemia, diabetes mellitus, kidney disease, liver disease, metabolic disorders, immunosuppression, <19 years of age on chronic ASA therapy, morbid obesity

www.cdc.gov/flu/about/disease/high_risk.htm, Accessed 9/21/15.

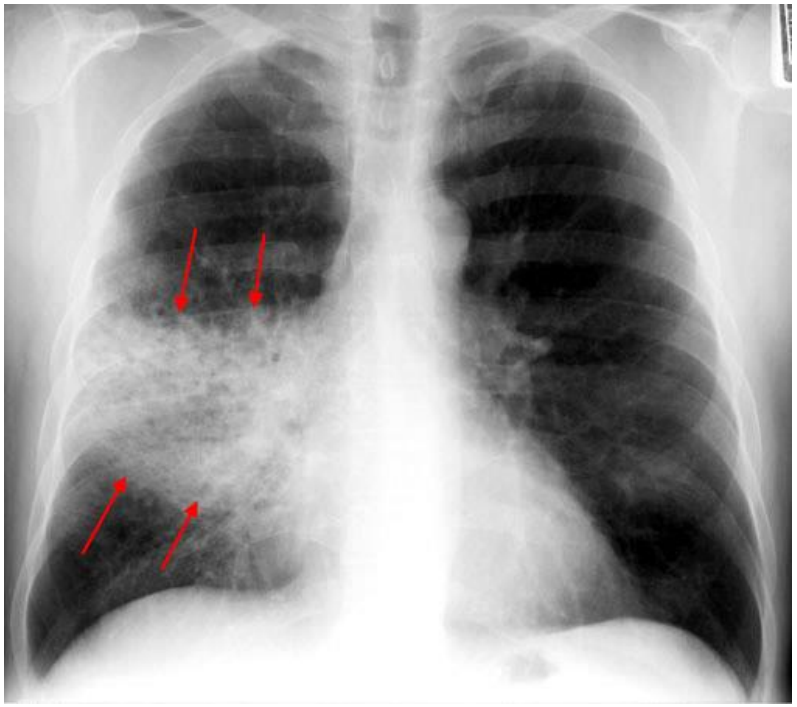
Complications: Viral Pneumonia



- Relentless progression from 3-day influenza
- Marked hypoxia
- Bilateral infiltrate on CXR
- Reduced/normal bacterial flora on sputum culture
- Lack of response to antibiotics
- High mortality

radiology.casereports.net, Accessed 9/21/15.

Complications: Bacterial Pneumonia



- Improvement, then worsening after 3-day influenza
- Consolidation on CXR
- Sputum culture: *S. pneumo*, *S. aureus*, *H. influenzae*
- May detect influenza
- Response to antibiotics
- Mortality variable

www.med-ed.virginia.edu/courses/rad/cxr/pathology3chest.html, Accessed 9/21/15.

Complications: Non-Pulmonary

- Myositis – pain and CK elevation, more common in kids
- Myocarditis & pericarditis – rare
- Toxic shock syndrome – altered staphylococcal colonization
- CNS syndromes – GBS, transverse myelitis, encephalitis
- Reye syndrome – with concomitant ASA use

Clinical Diagnosis: Healthy Adults

- Difficult to clinically distinguish from other respiratory pathogens
- Sensitivity and positive predictive value of clinical definitions vary widely depending on prevalence of other viral respiratory pathogens and level of influenza activity
- If confirmed circulation of influenza, positive predictive value of acute onset of cough and fever for lab-confirmed influenza is approximately 80-90%

Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2008 Aug 8;57(RR-7):1-60.

Clinical Diagnosis: Other Groups

- Young children less likely to report typical symptoms:
  - PPV of acute fever/cough in 5-12 year olds: 70-80%
  - PPV of acute fever/cough in <5 year olds: 64%
- Older adults less likely to report typical symptoms:
  - PPV of acute fever/cough in non-hospitalized, ≥60 years: 30%
  - PPV of acute fever/cough in hospitalized adults aged ≥65 years with chronic cardiopulmonary disease and illness of <7 days: 53%

Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2008 Aug 8;57(RR-7):1-60.

Considerations for Testing

- Individual patient
  - How long have symptoms been present
  - Will it change management?
- Public health
  - Is there an outbreak of respiratory infection in a closed setting?
  - What is the community epidemiology?
  - Is there a need for characterization of the circulating strains?

Testing Methods

Method	Types Detected	Acceptable Specimens	Test Time
Viral cell culture	A and B	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days
Rapid cell culture	A and B	As above	1-3 days
Immunofluorescence	A and B	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours
RT-PCR	A and B	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Variable (1-6 hours)
Rapid influenza diagnostic tests, RIDT (antigen)	A and B	NP swab, (throat swab), nasal wash, nasal aspirate	<30 minutes

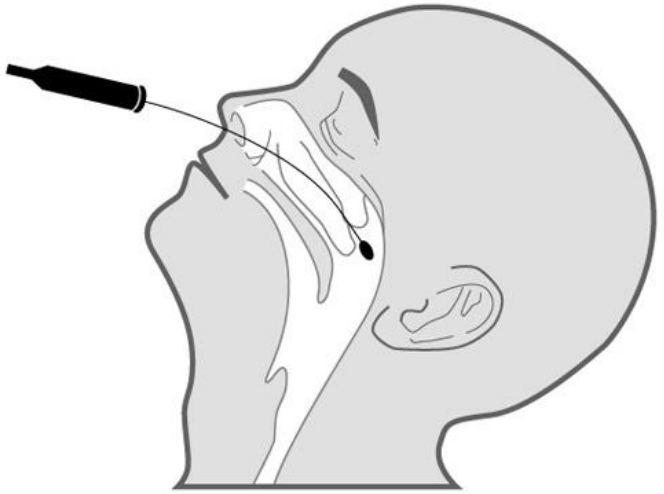
www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table, Accessed 9/21/15.

Specimen Collection

NP Swab

NEJM Procedure Video, Accessed 9/21/15.

NP Aspirate



www.stanfordlab.com/esoteric/Virology.html, Accessed 9/21/15.

Rapid Test Methods

- 16 different assays available with differing characteristics
- When compared to viral culture or RT-PCR, sensitivity 20-70% and specificity 90-95%
- Low community prevalence → false positives
- High community prevalence → false negatives
- Reducing test error:
  - Test early with high sensitivity kit
  - Consider confirmatory culture or RT-PCR

www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table, Accessed 9/21/15.

Molecular Assays (RT-PCR)

- Detect influenza viral RNA – viable virus?
- High sensitivity and specificity; short turnaround time
- Can distinguish between A and B, as well as influenza A subtypes (depending on the specific assay)
- Specimen types may be limited to upper respiratory tract
- Uses:
  - Hospitalized patients in which management will be affected
  - Institutional outbreak investigation
  - Detection of novel influenza A subtypes
- False positive with recent LAIV administration

www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm, Accessed 9/21/15.

Back to the cases…

- Case 1: Healthy 28 yo male with influenza A presenting on day 4 of illness with typical symptoms
- Case 2: 58 yo male with multiple co-morbidities, including diabetes and chronic kidney disease, diagnosed with influenza A on day 10 of illness with course complicated by multi-organ failure

Principles of Treatment

- Bulk of viral replication occurs early in healthy hosts
- Most healthy persons with uncomplicated influenza will recover without therapy
- Resistance to antiviral agents has been observed frequently with almost all influenza antivirals

Treanor J. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 167, 2000-2024.

General Treatment Recommendations

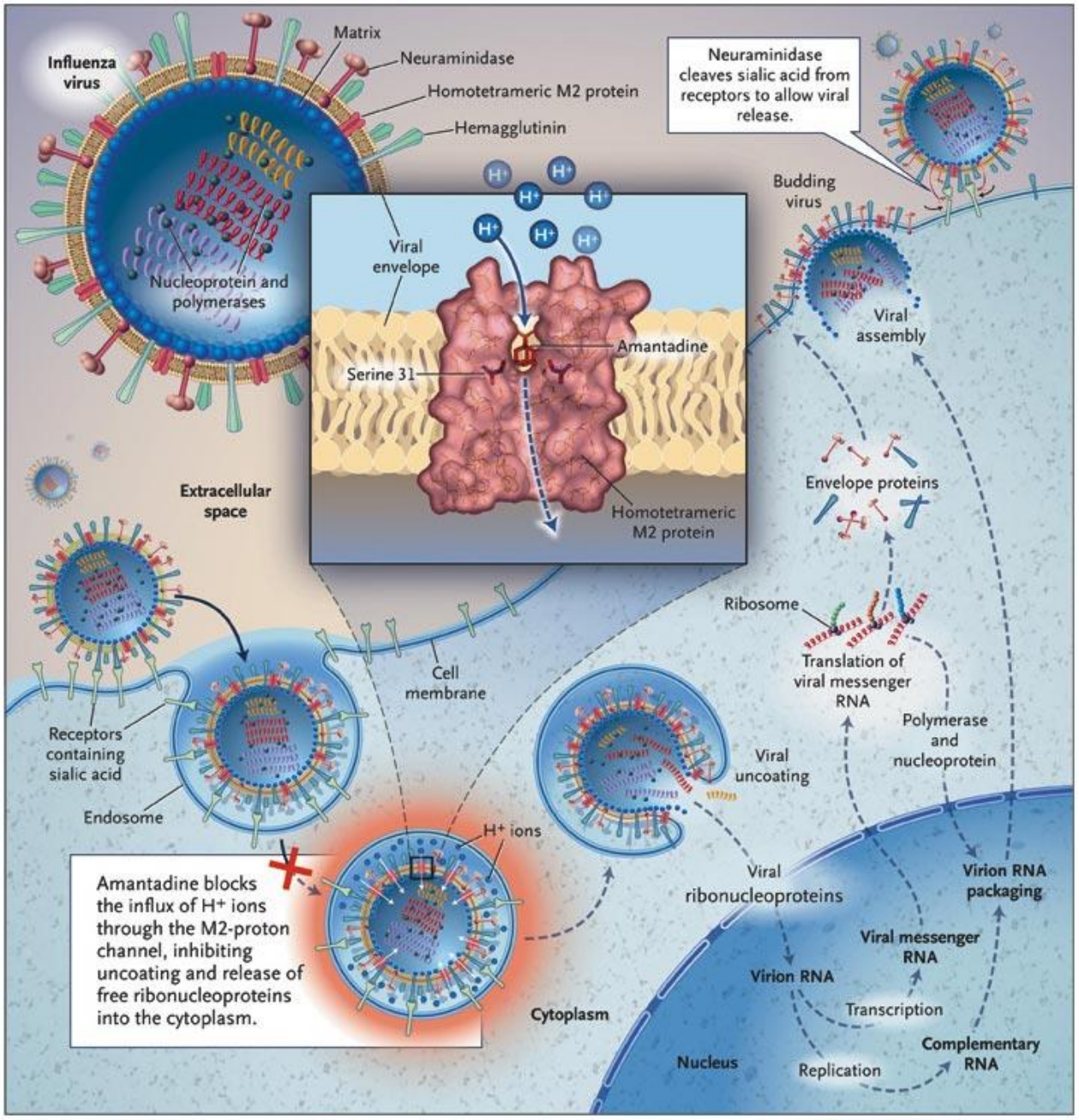
- Treatment can:
  - Shorten the duration of illness
  - Reduce the risk of complications from influenza
  - Reduce mortality risk in hospitalized patients
  - Shorten duration of hospitalization in children
- Clinical benefit is greatest with early therapy (<48 h of illness)
- Antiviral treatment is recommended for any patient with confirmed or suspected influenza who:
  - is hospitalized
  - has severe, complicated, or progressive illness
  - is at higher risk for influenza complications

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, Accessed 9/21/15.

Special Populations

- Pregnant women should be treated
- Hospitalized patients may benefit from therapy even if started later in the course of illness
- Critically ill patients may benefit from a longer course of therapy due prolonged viral replication

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, Accessed 9/21/15.

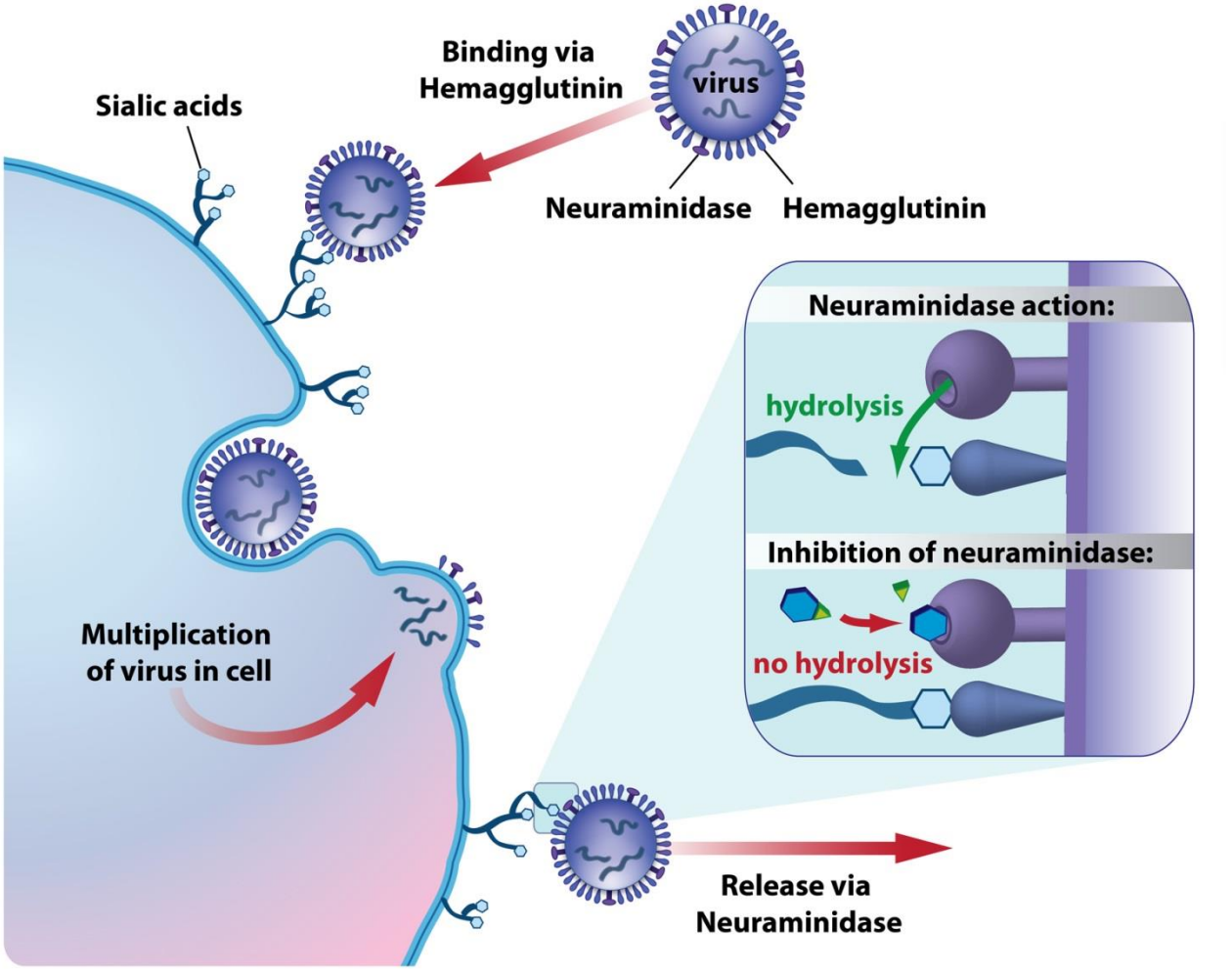


www.ufrgs.br/imunovet/molecular_immunology/antimicrobialsviruses.html, Accessed 9/21/15.

Adamantanes

- Inhibit H^+ influx through M2 ion channels
- Prevent viral uncoating and ultimately, viral replication
- Two drugs: amantadine (1966), rimantadine (1993)
- Approved for treatment and chemoprophylaxis of influenza A
- High levels of resistance (>99%) in recent years (H3N2 and 2009 H1N1)
- NOT RECOMMENDED for treatment or prophylaxis

Neuraminidase Inhibitors



Oseltamivir, zanamivir, peramivir

medicalxpress.com/news/2013-02-flu-drug-virus-tracks.html, Accessed 9/23/15.

Oseltamivir (Tamiflu©)

- FDA-approved in 1999 for treatment and prevention in 2000
- Prodrug rapidly absorbed and converted by hepatic esterases to the active metabolite, oseltamivir carboxylate
- Only available as enteric formulation
- Approved dosing dose of 75 mg po bid x 5 days in adults
- Dosing in critically ill and renal failure less clear
  - Need for higher dose – some use 150 mg po bid
  - Longer course in critically ill
- GI side effects and reports of neuropsychiatric side effects

Efficacy of Oseltamivir

- Evaluation of 9 trials with 4328 participants randomized to oseltamivir (75 mg po bid) vs. placebo
- Shorter time to symptom alleviation with oseltamivir (97.5 hours vs. 122.7 hours)
- Fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomization (4.9% oseltamivir vs. 8.7% placebo)
- Fewer admittances to hospital for any cause (0.6% oseltamivir vs. 1.7% placebo)
- Increased rates of nausea and vomiting with oseltamivir

Dobson J, Whitley RJ, Pocock S, Monto AS. *Lancet* 2015; 385: 1729–37.

Zanamivir (Relenza©)

- FDA-approved in 1999 for treatment and 2006 for prevention
- Administered topically via inhaler
- IV zanamivir is available through an ongoing phase III trial or EIND request

dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=10425, Accessed 9/21/15.

Peramivir (Rapivab©)

- FDA-approved in 2014 for treatment of adults
- IV formulation only
- RCT showed that a single dose given IM or IV shortened duration of symptoms by 1 day (similar to oseltamivir and zanamivir)
- Option for patients with GI symptoms who cannot tolerate oral oseltamivir and/or patients who cannot tolerate inhalation of zanamivir

Choosing a Drug

- Current CDC guidelines do not express a preference between the 3 NAIs for treatment of acute uncomplicated influenza in adults
- Oseltamivir recommended for pregnant women
- Development of resistance to oseltamivir or peramivir is possible (most commonly with influenza A H1N1)
- Need to consider this in setting of progressive disease despite treatment

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, Accessed 9/21/15.

Back to the cases…

- Case 1: Healthy 28 yo male with influenza A presenting on day 4 of illness with typical symptoms --> I would not treat
- Case 2: 58 yo male with multiple co-morbidities, including diabetes and chronic kidney disease, diagnosed with influenza A on day 10 of illness with course complicated by multi-organ failure → Treated with IV zanamivir via EIND. Course complicated by prolonged respiratory failure, renal failure, recurrent paralytic ileus, and critical illness polyneuropathy / myopathy. Required 7-week hospitalization and 5-week rehab course.

Prevention of Influenza

- VACCINATION IS BEST!!
- Widespread chemoprophylaxis risks increased resistance
- Special situations where PEP should be considered:
  - Persons at high risk of influenza complications during the first two weeks following vaccination
  - Persons with severe immune deficiencies who might not respond to influenza vaccination
  - Persons at high risk influenza complications who cannot receive influenza vaccine
  - Prevention of influenza among residents of institutions during influenza outbreaks in the institution.

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, Accessed 9/21/15.


STAR TRIBUNE
SACK
THE FIRST TIME ONE OF THEM SNEEZES, CUT THE ROPE....

Thank You