Boonshoft School of Medicine
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Sepsis associated with influenza and flu-related complications

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Epidemiology

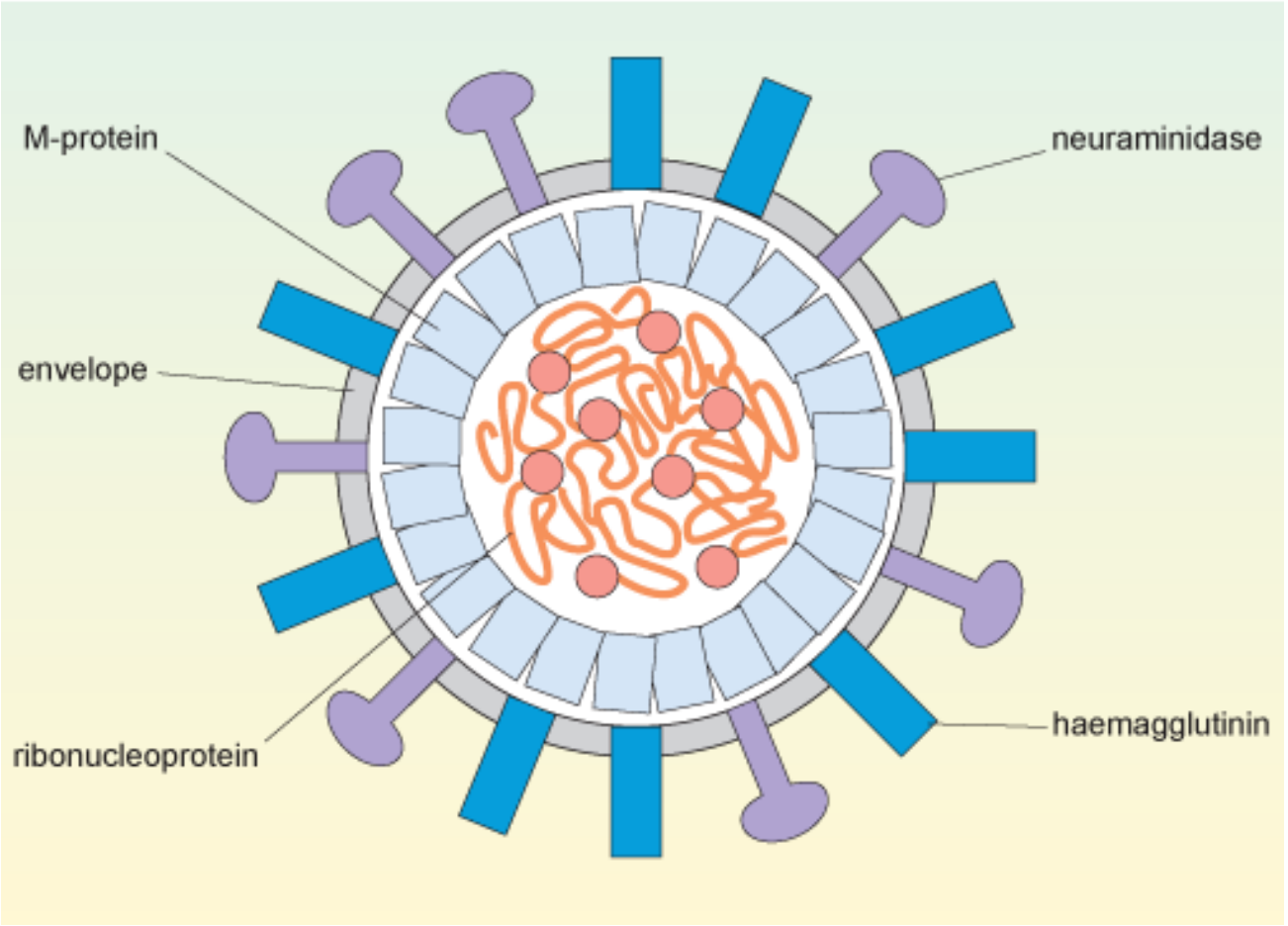
- 2017-2018 influenza season
  - 80,000 deaths in the United States
  - 1 million laboratory-confirmed cases of people with influenza who were admitted to the hospital
    - Most had influenza A
  - Will never know the true number of people who contracted the flu though, because so many become ill but do not see a doctor.

General Epidemiology

- 44 million days of lost productivity
- Average year 200,000 hospital admissions
  - 36,000 deaths annually
- 31 million doctors visits
- 3.1 million hospital days
- For every 100 school aged kids
  - Flu will cause 63 days of missed school
  - 20 missed work days by parents

https://www.flumistquadrivalent.com/hcp/influenza-resources/burden-of-influenza.html

Influenza virus

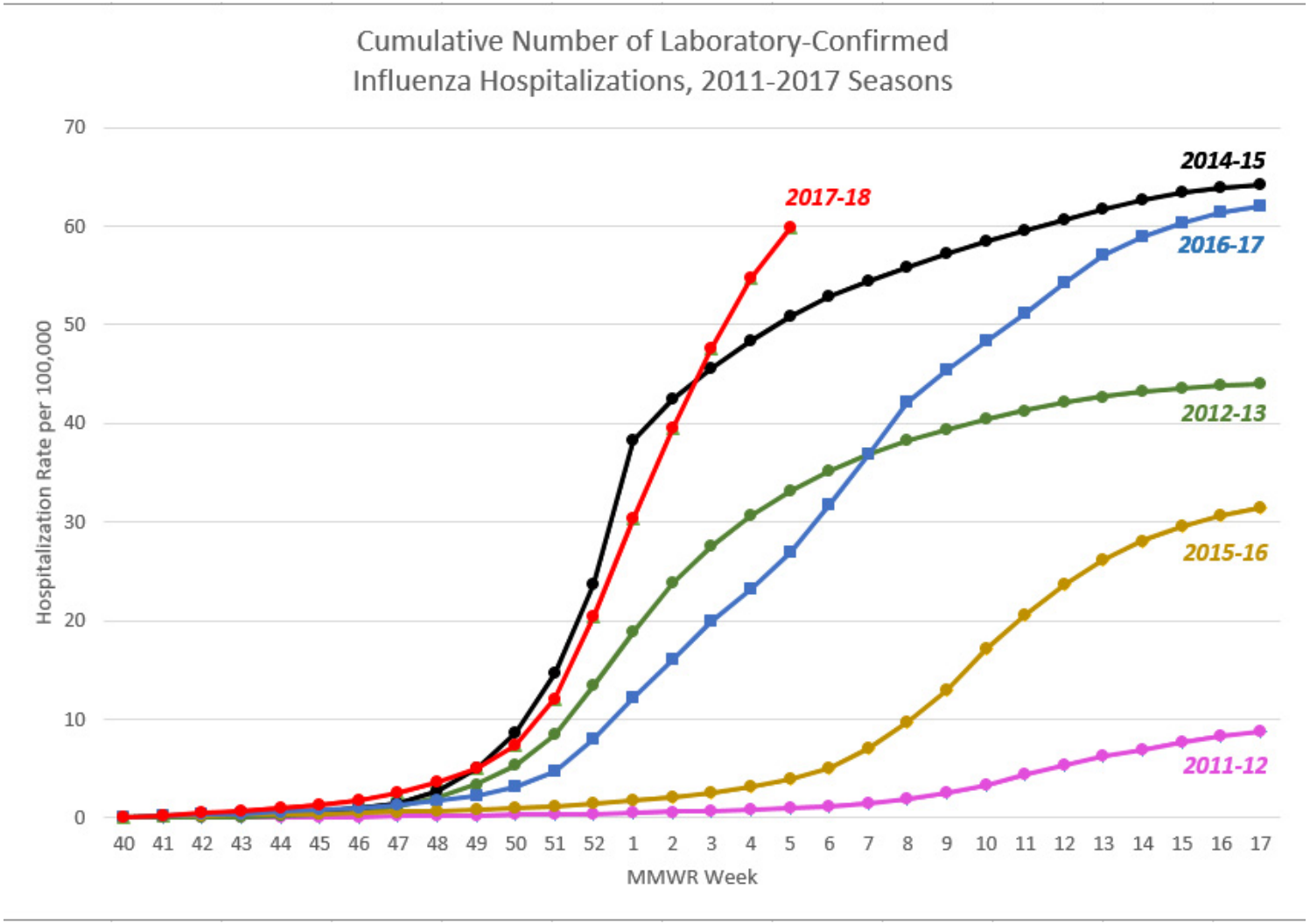


https://www.open.edu/openlearn/science-maths-technology/science/biology/influenza-case-study/content-section-2.1

Contagiousness

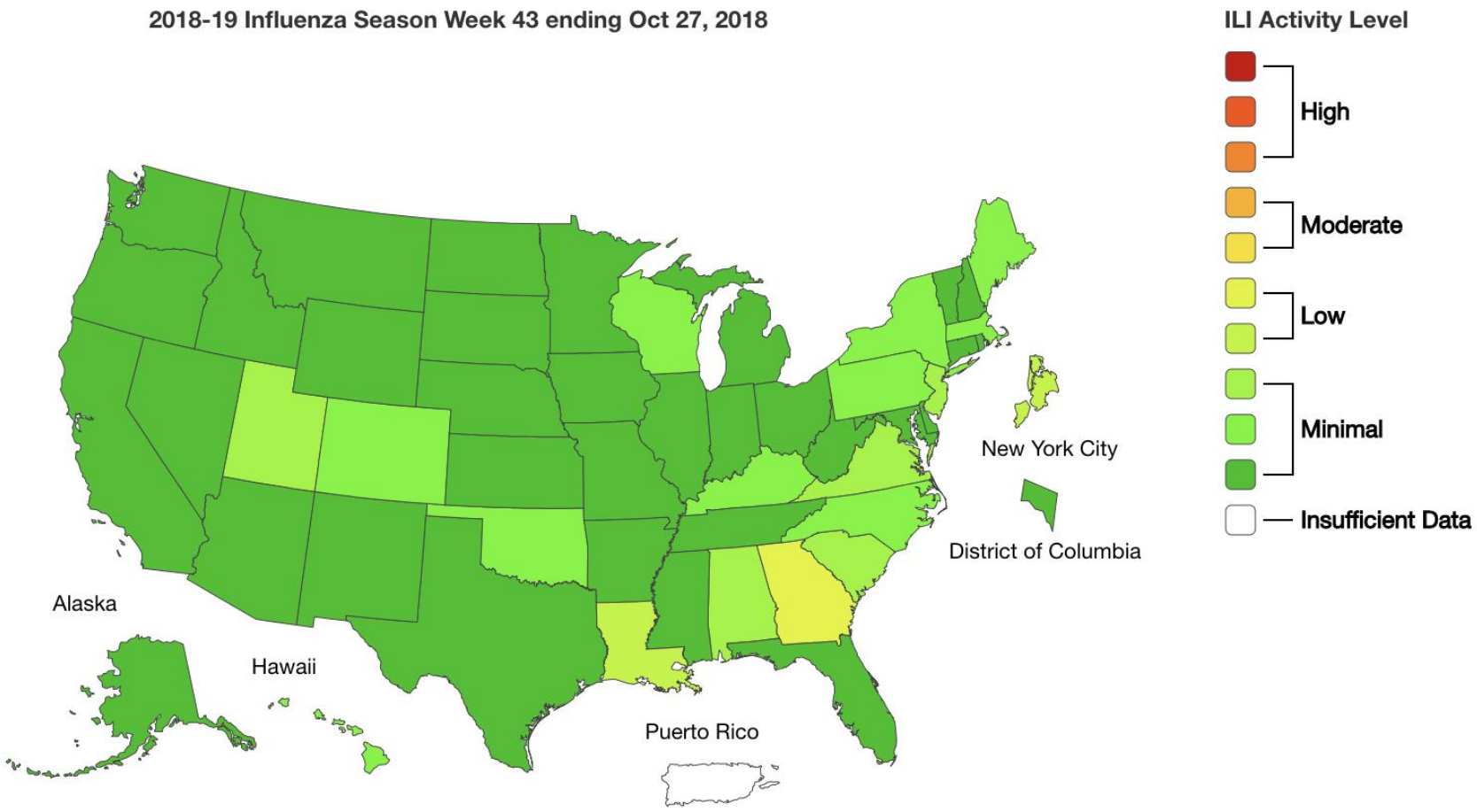
- Highly contagious
- Acquired when the virus comes in contact with the mucus membranes in your nose
  - Contamination of the air (someone next to you sneezing)
  - By touch
    - Someone who has the flu touches his nose or mouth and then touches an object, which you then pick up.
- If you don't wash your hands, at some point if you touch your mouth or nose, you have brought the virus close enough to infect yourself

Influenza 2017-2018



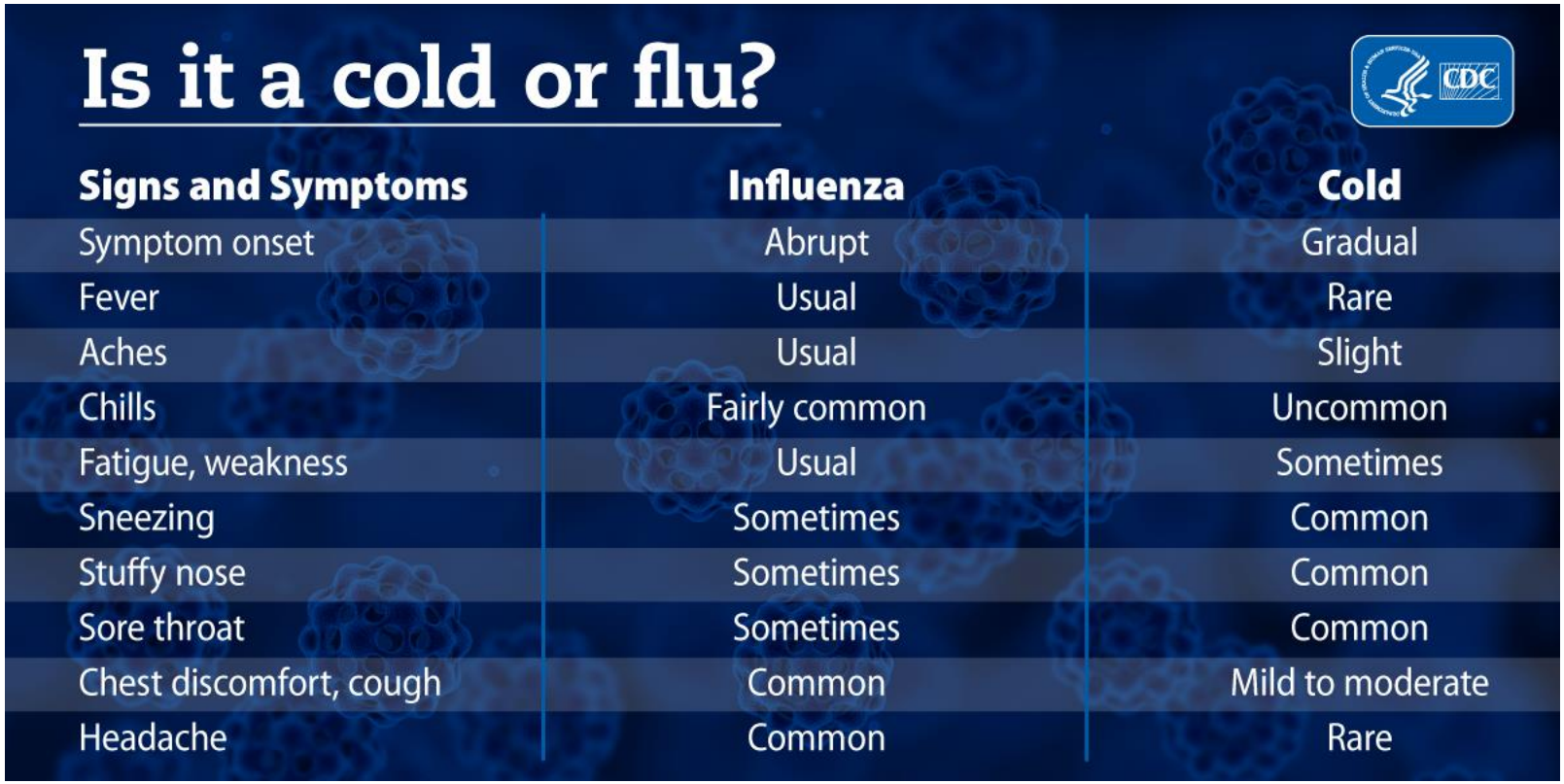
https://www.cdc.gov/media/releases/2018/t0209-flu-update-activity.html

2018-2019 Current Data



Signs and Symptoms

- Sudden onset
  - Many folks can tell you the minute they get sick
  - Muscle aches and arthralgias
- Usually respiratory manifestations
  - Cough
  - Sore throat
- GI symptoms vary by year and age group
- Many will meet the SIRS criteria for sepsis
  - Discussion of the sepsis measure to occur at end of lecture



Signs and Symptoms	Influenza	Cold
Symptom onset	Abrupt	Gradual
Fever	Usual	Rare
Aches	Usual	Slight
Chills	Fairly common	Uncommon
Fatigue, weakness	Usual	Sometimes
Sneezing	Sometimes	Common
Stuffy nose	Sometimes	Common
Sore throat	Sometimes	Common
Chest discomfort, cough	Common	Mild to moderate
Headache	Common	Rare

**Influenza patients typically will meet the SIRS criteria, patients with a cold will not

Severe influenza

- Influenza with a severe symptom or syndrome such as:
  - respiratory distress
  - deceased consciousness
  - or accompanying a severe complication such as encephalopathy or renal failure
- Requires hospital admission in most cases
  - ICU treatment in some cases
- Elderly, infants, and chronic disease patients are known to be at high risk because they may have accompanying complications such as exacerbation of an underlying disease, development of pneumonia, and another organ dysfunction
  - death

Severe Influenza definition

- Influenza corresponding to the definition of influenza-like illness (ILI; sudden onset of fever and cough or sore throat) and presenting at least one of the following clinical presentations:
  - Dyspnea, tachypnea, or hypoxia
  - Radiological signs of lower respiratory tract disease
  - Central nervous system involvement (e.g., encephalopathy, encephalitis)
  - Severe dehydration
  - Acute renal failure
  - Septic shock
  - Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal insufficiency, diabetes mellitus, or other cardiovascular conditions
  - Any other influenza-related condition or clinical presentation requiring hospital admission

Severe Influenza

- Inflammatory response triggered by a severe influenza infection is a double-edged sword.
- It can effectively eliminate the infection
  - prolonged and excessive inflammatory response may result in poor outcomes
- Influenza virus, like other viruses, displays significant interaction with the immune system
  - directly lead to severe sepsis or to a secondary bacterial infection

Diagnostic Testing

- Rapid tests
  - Office and ED based
- Direct fluorescent antibody (DFA)
- Molecular diagnostics
  - Influenza
  - Respiratory panels
  - Some ED's do offer rapid molecular testing

Diagnostic Testing

- Rapid influenza diagnostic tests (RIDTs) are screening tests for influenza virus infection.
  - Sensitivity ~50%
  - Specificity ~95%
- False-positive results are more likely to occur when disease prevalence is low
  - Beginning and end of the influenza season.
- False-negative results are more likely to occur when disease prevalence is high

Diagnosis – NP!!!

Table 1: Influenza Virus Testing Methods

Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Rapid Influenza Diagnostic Tests[4] (antigen detection)	A and B	NP[5] swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	<15 min.	Yes/No
Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, nasal swab	15-30 minutes[6]	Yes/No[6]
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining [antigen detection]	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[7] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (1 to 8 hours, varies by the assay)	No
Rapid cell culture (shell vials; cell mixtures; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum; (specimens placed in VTM[8])	1-3 days	No
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in VTM8)	3-10 days	No

https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm


Nasopharynx

Diagnostic Testing Sensitivity

- Rapid antigen – antibody assays – 50% at best
  - Negative test does NOT rule out influenza
- Direct fluorescent antibody testing – 70% at best
  - Negative test does NOT rule out influenza
- Molecular diagnostic assays – 96%

- But must be a NP swab

Clinical challenge

- Influenza?
- Bacterial pneumonia?
- Influenza + bacterial pneumonia?
- Post-influenza bacterial pneumonia?

- Later 3 especially with severe influenza

- Most common causes of post-influenza pneumonia
  - *Streptococcus pneumoniae*
  - MSSA
  - MRSA
  - Group A Streptococcus

Influenza and bacterial pneumonia

- Incidence of influenza A H1N1 infection in CAP during the pandemic period was 19%
  - No non-influenza PNA still occurs during influenza outbreaks
- 128 patients; 42(33%) had bacterial co-infection.
  - *Streptococcus pneumoniae* (26, 62%) and *Pseudomonas aeruginosa* (6, 14%) most common
    - MRSA, MSSA and GAS have been shown in other studies
- Predictors for bacterial co-infection were COPD and increased platelets
- Although patients with bacterial co-infection presented with higher PSI risk class, hospital mortality was similar to patients without bacterial co-infection (7% *vs.* 11%, respectively, $p = 0.54$).

Cilloniz et al. J of Infection. 2012

Bacterial complications

- 5–6% of invasive pneumococcal pneumonia and 6–10% of all invasive pneumococcal diseases can be attributed to influenza infections.
- Several studies demonstrated that viral replication denudes the respiratory epithelium
  - exposing basement membrane to which bacteria can adhere.
- At the same time, pro-inflammatory cytokines, might upregulate platelet-activating factor receptor (PAFr), providing a receptor for pneumococcal adherence and invasion.
- Influenza **impairs** antibacterial defense mechanisms by:
  - increasing neutrophil apoptosis
  - neutrophil, and monocyte dysfunction
  - depressing chemotaxis
  - suppressing phagocytosis

Virulence 5:1, 137–142; January 1, 2014; © 2014 Landes Bioscience

The Burden of Viruses in Pneumonia Associated With Acute Respiratory Failure

An Underappreciated Issue

Andrew F. Shorr, MD, MPH; Kristen Fisher, MD; Scott T. Micek, PharmD; and Marin H. Kollef, MD

BACKGROUND: Pneumonia associated with mechanical ventilation (MV) results in substantial mortality and represents a leading reason for the use of antibiotics. The role of viruses in this setting is unclear. Identifying a viral cause in such instances could facilitate antibiotic stewardship.

METHODS: We performed a secondary analysis of a prospective cohort with pneumonia requiring MV. We included both cases occurring in the community and hospital-onset cases and classified patients according to the cause of the pneumonia. The prevalence of viral pathogens represented the primary end point. We identified variables independently associated with isolation of a viral organism as the sole pathogen.

RESULTS: The cohort included 364 patients, and a virus was the sole pathogen in 79 cases (21.7%). The most common viruses included rhinovirus/enterovirus (n = 20), influenza A (n = 12), and respiratory syncytial virus (n = 11). The rate of in-hospital death was high (37.2%) and did not differ from that seen in other patients (36.5%). The duration of MV, hospital length of stay, and 30-day readmission rates also did not differ based on the cause of pneumonia. Two variables were independently associated with recovery of a virus: an Acute Physiology and Health Evaluation II score of < 26 (adjusted odds ratio [AOR], 0.51; 95% CI, 0.28-0.93; $P = .027$) and stem cell transplantation (SCT) (AOR, 4.39; 95% CI, 2.03-9.50; $P = .001$). A sensitivity analysis excluding patients who underwent SCT did not substantially alter our observations.

CONCLUSIONS: Viruses represent a major cause of pneumonia in critically ill patients requiring MV. Identifying such subjects presents an opportunity for discontinuing antibiotics. Clinicians should consider systematically evaluating patients with pneumonia requiring MV for viral pathogens.

CHEST 2017; ■(■):■-■

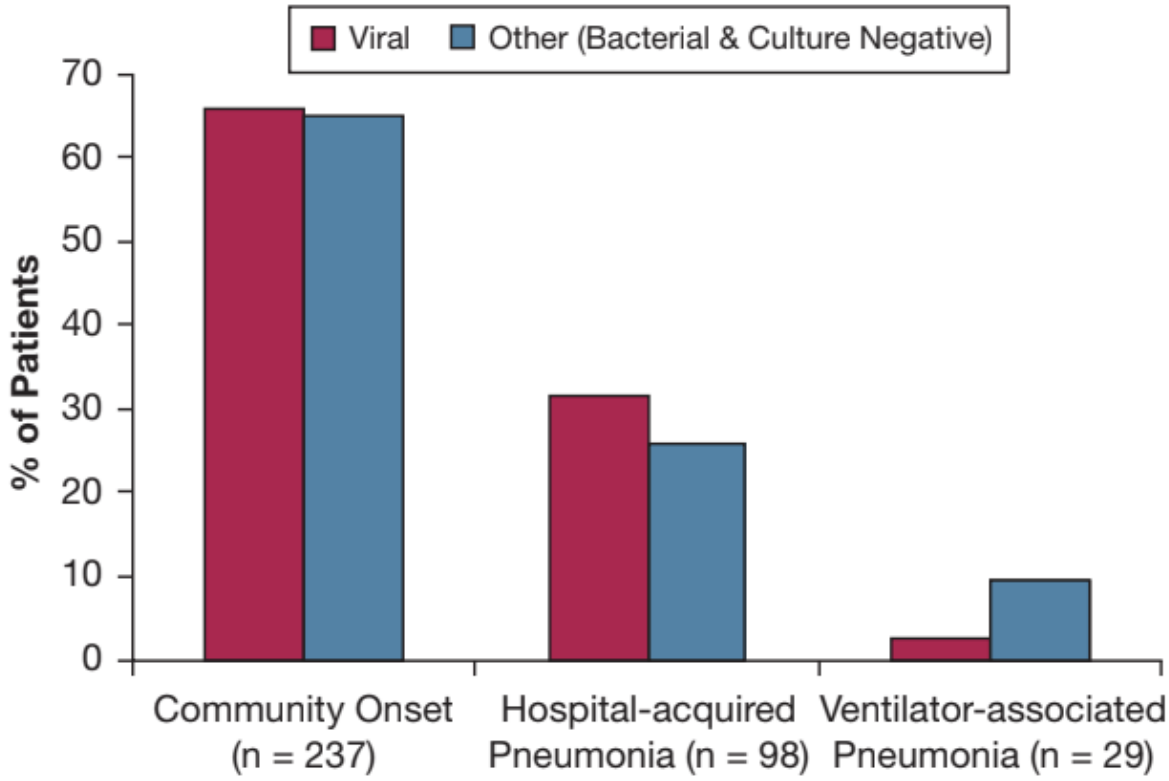


Figure 1 – *Viral etiology based on pneumonia type. Although no statistical difference in the overall distribution of pneumonia types between the population (P = .357), ventilator-associated pneumonia was less frequent amont viral cases (P < .05).*

Positive Viral Panel Results, Procalcitonin and Antibiotic Utilization

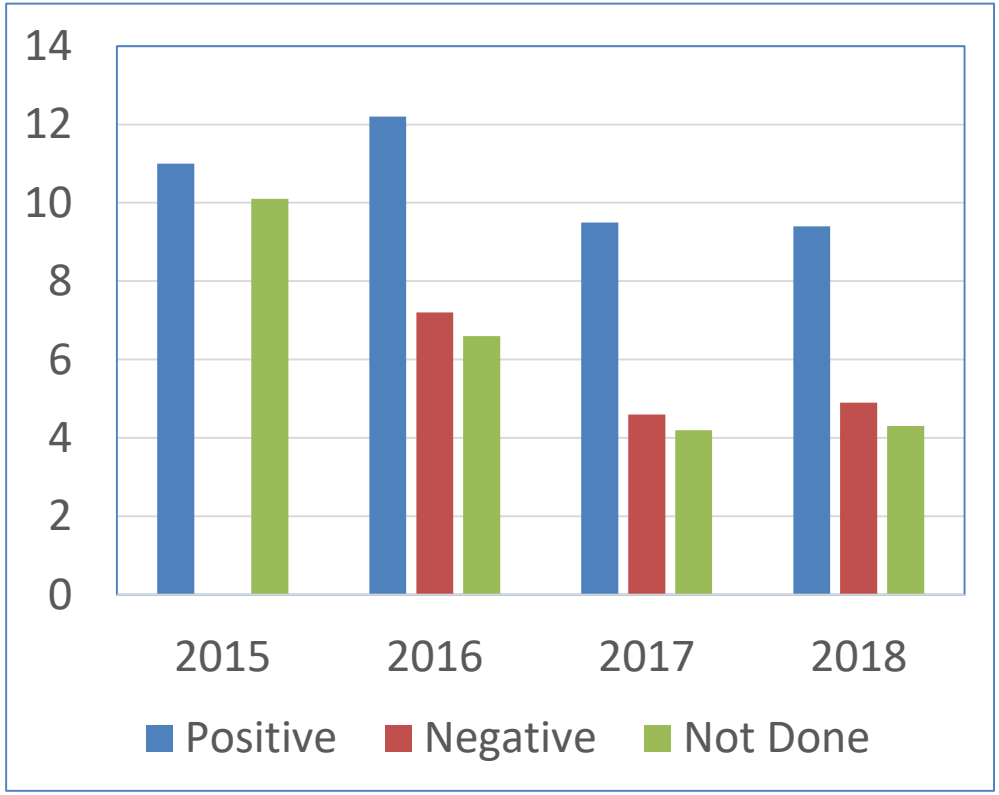
MVH specific data from our antimicrobial stewardship program

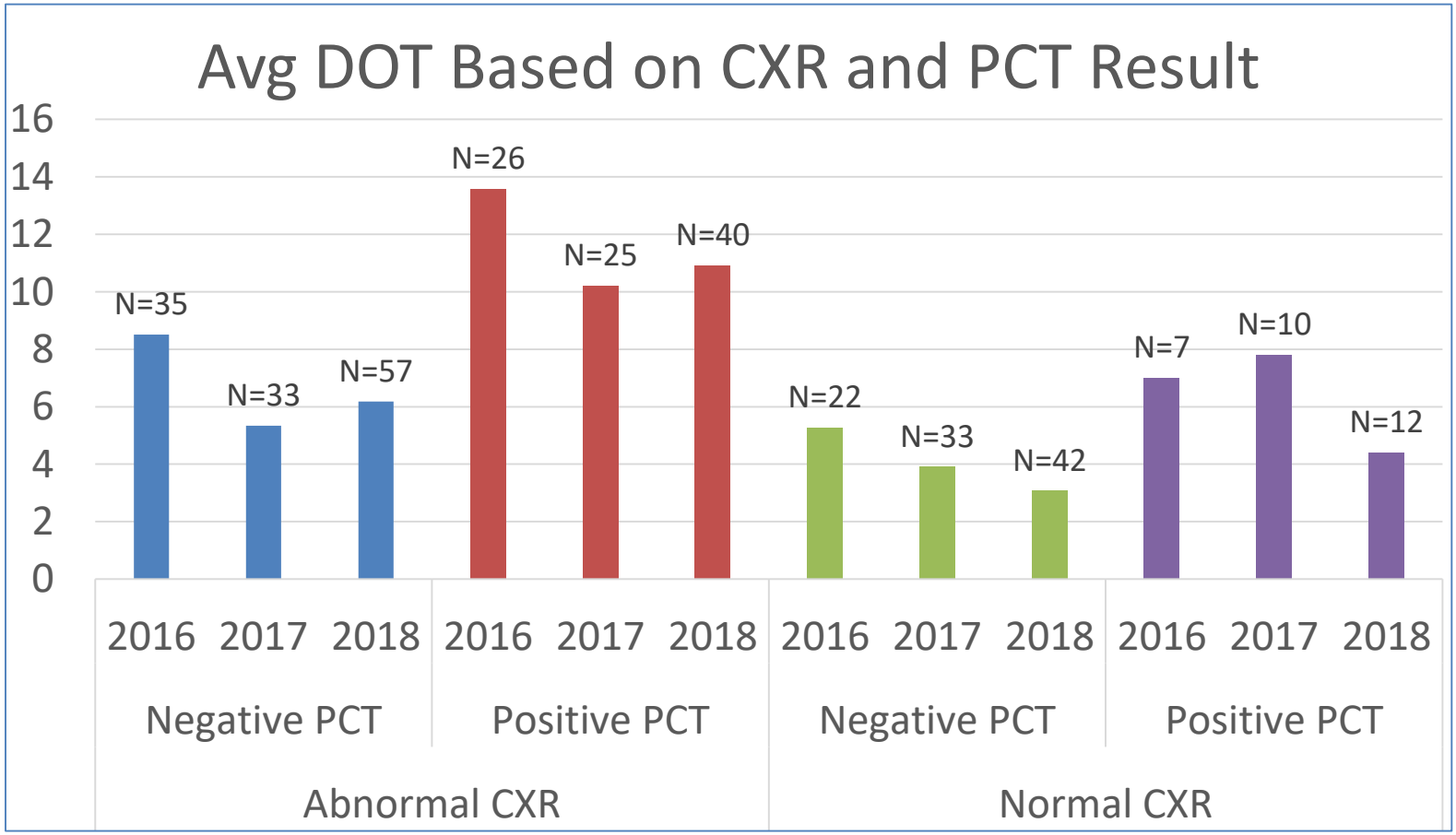
Procalcitonin

- Blood test that helps to differentiate viral from bacterial infections
  - Elevated by renal failure, trauma, ischemia, surgery
- Takes 6-8 hours to elevate after the onset of symptoms
- When used properly can help determine when it is "just" a viral infection or when there is a bacterial infection as well

Average Days of Therapy Based on PCT

Average DOT Based on Procalcitonin (n)			
	Positive	Negative	Not Done
2015	11 (1)	0	10.1 (65)
2016	12.2 (33)	7.2 (58)	6.6 (145)
2017	9.5 (35)	4.6 (69)	4.2 (128)
2018	9.4 (52)	4.9 (103)	4.3 (111)




Avg DOT Based on CXR and PCT Result
16
14
12
10
8
6
4
2
0
N=35
N=33
N=57
N=26
N=25
N=40
N=22
N=33
N=42
N=7
N=10
N=12
2016 2017 2018 2016 2017 2018 2016 2017 2018 2016 2017 2018
Negative PCT
Positive PCT
Negative PCT
Positive PCT
Abnormal CXR
Normal CXR

Treatment

- Antiviral therapies can reduce the duration and complications of influenza when administered within 2 days of illness onset.
- Zanamivir and oseltamivir can reduce the duration of influenza A and B illness by 1-2 days when started early in an outpatient setting
  - patients treated with zanamivir can return to normal activities 3 days earlier
  - Data less impressive for hospitalized patients
- Recommended duration of treatment with antiviral drugs is 5 days

TABLE 3. Antiviral treatment options for influenza

Antiviral agents	Activity against	Treatment age recommendation	Contraindications	Adverse events
Oseltamivir	Influenza A and B	Any age	Kidney failure (dosage adjustment recommended for renal insufficiency)	Nausea, vomiting, serious and sporadic skin reaction, transient neuropsychiatric event
Zanamivir	Influenza A and B	≥7 y	Milk allergy; underlying respiratory condition	Diarrhea, nausea, sinusitis, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections; allergic reaction: oropharyngeal or facial edema
Peramivir	Influenza A and B	≥18 y	None	Diarrhea, serious and sporadic skin reaction, transient neuropsychiatric event

Adapted from Centers for Disease Control and Prevention[28]

https://www.clinicaladvisor.com/features/influenza-a-review-of-the-pathogenesis-and-disease/article/452733/2/

New therapy: baloxavir

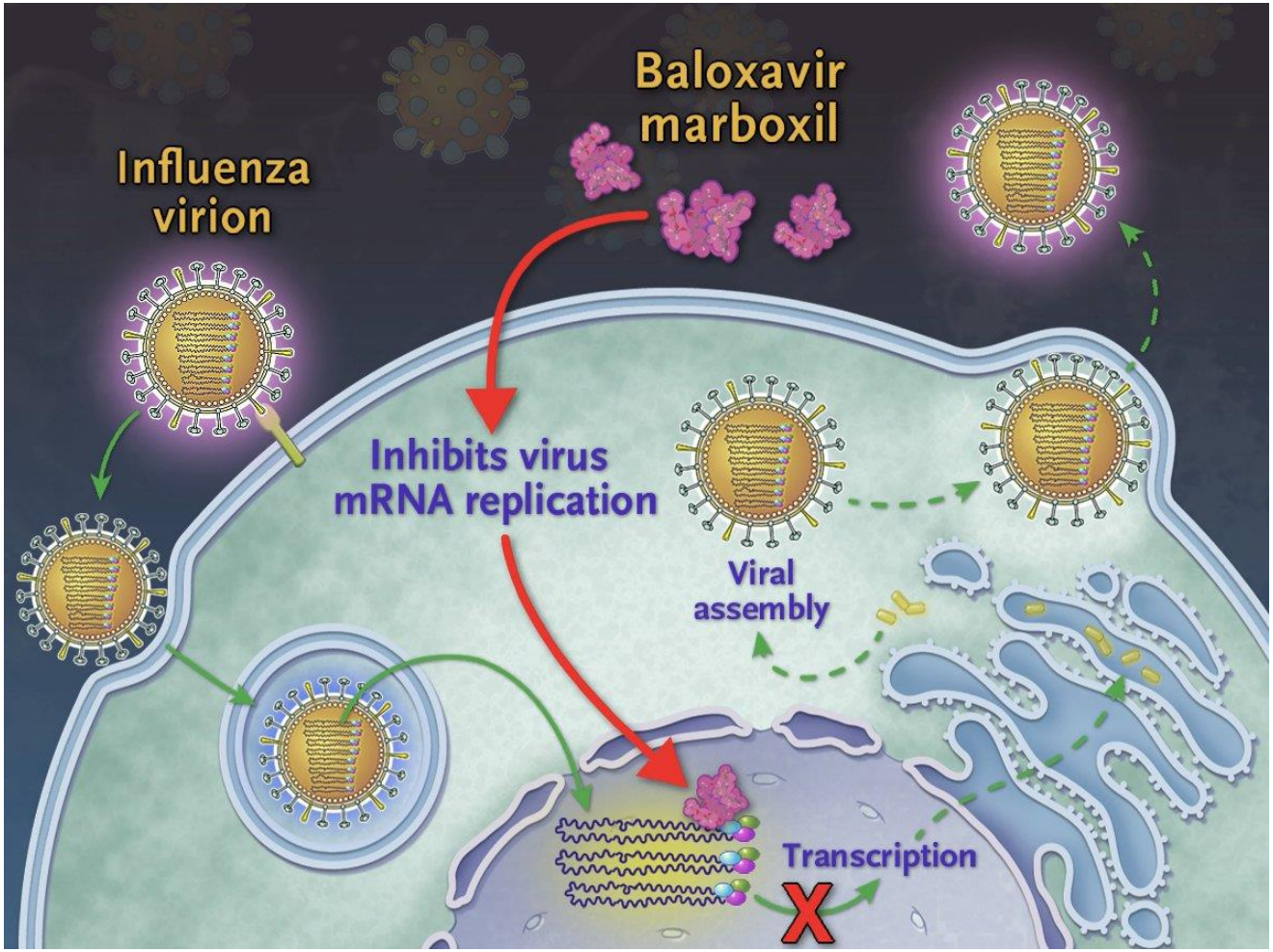


Table 2. Adverse Events during the Phase 3 Trial (Safety Population).*

Event	Baloxavir (N=610)		Placebo (N=309)		Oseltamivir (N=513)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	126 (20.7)	6 (1.0)	76 (24.6)	4 (1.3)	127 (24.8)	1 (0.2)
Adverse events reported in ≥1% of patients in any group						
Diarrhea	18 (3.0)	1 (0.2)	14 (4.5)	1 (0.3)	11 (2.1)	0
Bronchitis	16 (2.6)	0	17 (5.5)	1 (0.3)	18 (3.5)	0
Nasopharyngitis	9 (1.5)	0	2 (0.6)	0	4 (0.8)	0
Nausea	8 (1.3)	1 (0.2)	4 (1.3)	1 (0.3)	16 (3.1)	0
Sinusitis	7 (1.1)	0	8 (2.6)	1 (0.3)	5 (1.0)	0
Increase in ALT level	6 (1.0)	0	4 (1.3)	0	7 (1.4)	0
Headache	5 (0.8)	1 (0.2)	3 (1.0)	0	4 (0.8)	0
Vomiting	5 (0.8)	1 (0.2)	2 (0.6)	0	6 (1.2)	0
Dizziness	3 (0.5)	0	4 (1.3)	0	1 (0.2)	0
Leukopenia	0	0	3 (1.0)	0	1 (0.2)	0
Constipation	0	0	3 (1.0)	0	0	0
Adverse event considered to be related to the trial regimen	27 (4.4)	2 (0.3)	12 (3.9)	1 (0.3)	43 (8.4)†	0
Adverse events considered to be related to the trial regimen and reported in ≥1% of patients in any group						
Diarrhea	11 (1.8)	1 (0.2)	4 (1.3)	0	7 (1.4)	0
Nausea	2 (0.3)	1 (0.2)	2 (0.6)	1 (0.3)	8 (1.6)	0
Serious adverse event	2 (0.3)	2 (0.3)	0	0	0	0
Adverse event leading to discontinuation of the trial regimen‡	2 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.4)	0

* The severity of an event was categorized by the investigators according to definitions based on the Common Terminology Criteria for Adverse Events, version 4.0. ALT denotes alanine aminotransferase.

† No significant differences were noted between the groups except for the prespecified comparison of adverse events that were considered to be related to the trial regimen, which were more common in the oseltamivir group than in the baloxavir group (P=0.009).

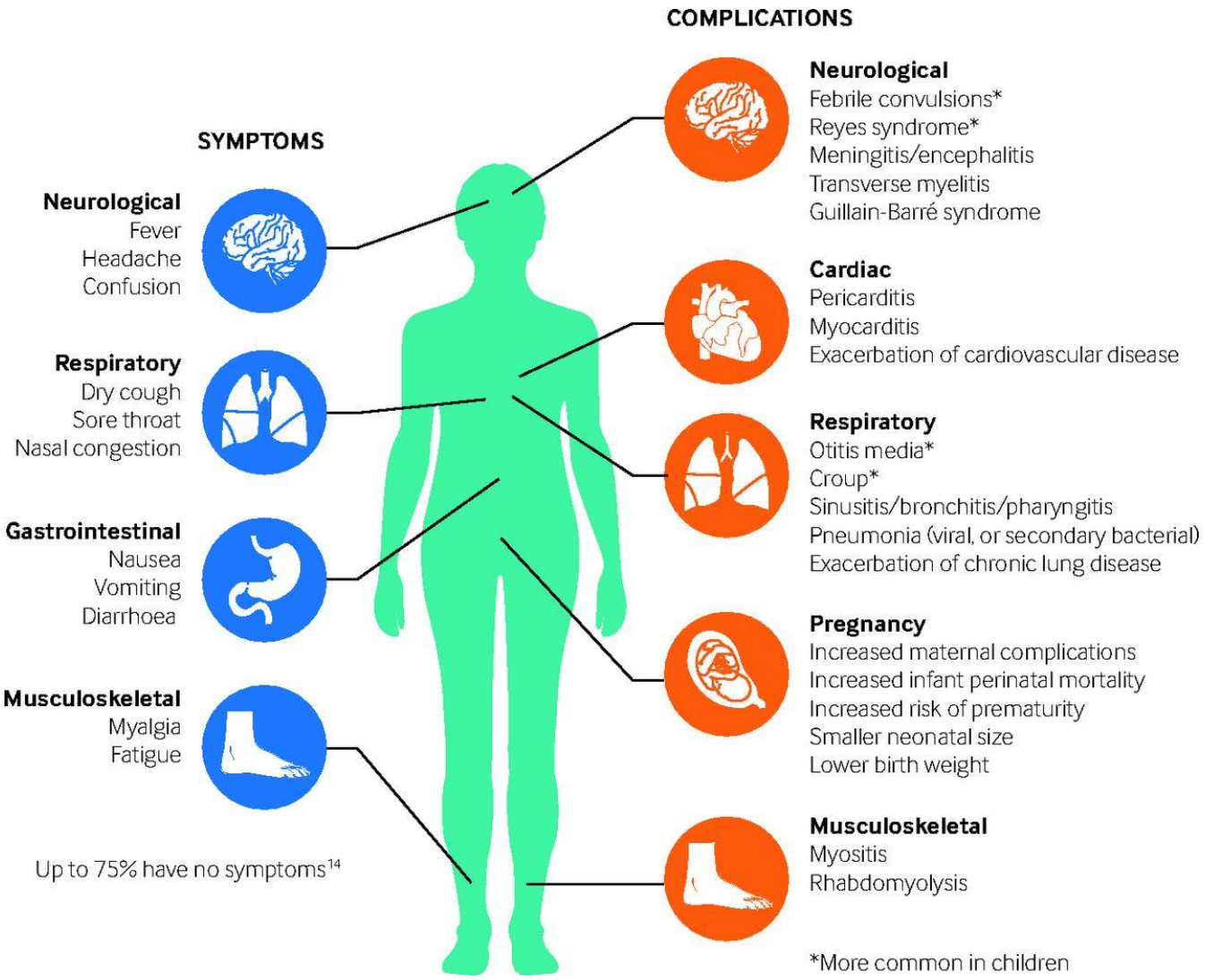
‡ Adverse events leading to discontinuation of the trial regimen occurred in two patients who received baloxavir (bronchitis and pneumonia in one patient and acute bronchitis in one patient), in one patient who received placebo (nausea, hip pain, low back pain, and jaw pain), and in two patients who received oseltamivir (nausea in one patient and pneumonia in one patient).

NEJM September 6th, 2018

Influenza Complications

- Increased risk of complication from seasonal influenza are the very young (age <1 year), the elderly (age >65 years), pregnant women, and individuals with certain chronic medical conditions.
  - Pulmonary complications, such as bronchitis and pneumonia, secondary to influenza virus infection
- Neuromuscular and cardiac complication
  - rare
- Other minor complications include sinusitis and acute otitis media.

Influenza Complications



Influenza Vaccination

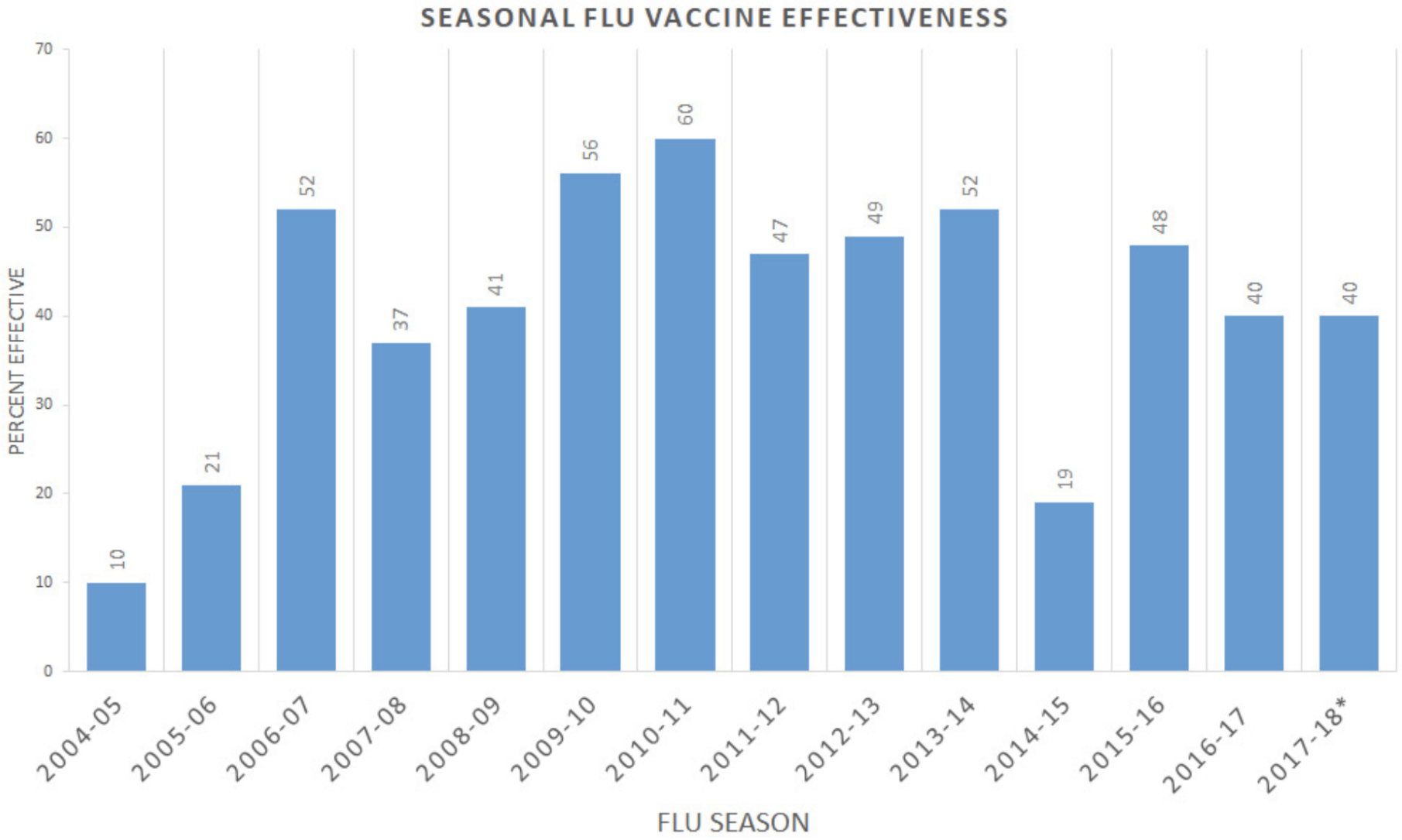
- 2018-19 influenza vaccines will contain hemagglutinin (HA) derived from influenza viruses antigenically similar to those recommended by FDA.
- Trivalent vaccines will contain
  - an A/Michigan/45/2015 (H1N1)pdm09–like virus,
  - an A/Singapore/INFIMH-16-0019/2016 (H3N2)–like virus; and
  - a B/Colorado/06/2017–like virus (Victoria lineage).
- Quadrivalent vaccines will contain the same three HA antigens as trivalent vaccines, plus a B/Phuket/3073/2013–like virus (Yamagata lineage)

Influenza vaccination and egg allergies

- Able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be egg-allergic.
- Experienced only hives after exposure to egg should receive any licensed, recommended, age-appropriate influenza vaccine
- Symptoms other than hives after exposure to egg (such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention) may also receive any licensed and recommended influenza vaccine that is otherwise appropriate.
  - inpatient or outpatient medical setting and supervised by a health care provider

Influenza Vaccination

- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of causing the reaction, is a contraindication to future receipt of the vaccine
- Even when match is poor, data and personal experience clearly demonstrates less complications and a more rapid recovery from influenza


SEASONAL FLU VACCINE EFFECTIVENESS
PERCENT EFFECTIVE
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30
40
50
60
70
10
21
52
37
41
56
60
47
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52
19
48
40
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2004-05
2005-06
2006-07
2007-08
2008-09
2009-10
2010-11
2011-12
2012-13
2013-14
2014-15
2015-16
2016-17
2017-18*
FLU SEASON

Advocate!

- If HCW will advocate for vaccination (pneumococcal, influenza, etc) over 70% of patients will accept the vaccine
- Do not take “NO” at face value!
  - Ask why not
  - Try and alleviate fears or questions

Sepsis and the CMS Core Measure

- For purposes of the SEP-1 measure, only severe sepsis due to bacterial infections are abstracted.
  - Severe sepsis can be caused by fungal, viral, and parasitic infections.
  - The measure specifications are designed and intended to only address severe sepsis cases caused by a bacterial infection
  - For Severe Sepsis Present criteria A (infection), if the infection is documented as due to a viral, fungal, or parasitic infection, the condition would not be used for criteria A (infection).
- If the pneumonia was not documented as due to the influenza, the pneumonia could still be used for the suspected infection criteria.
  - Thus testing is important

Sepsis Core Measure

Hospital Inpatient Quality Reporting (IQR) Program

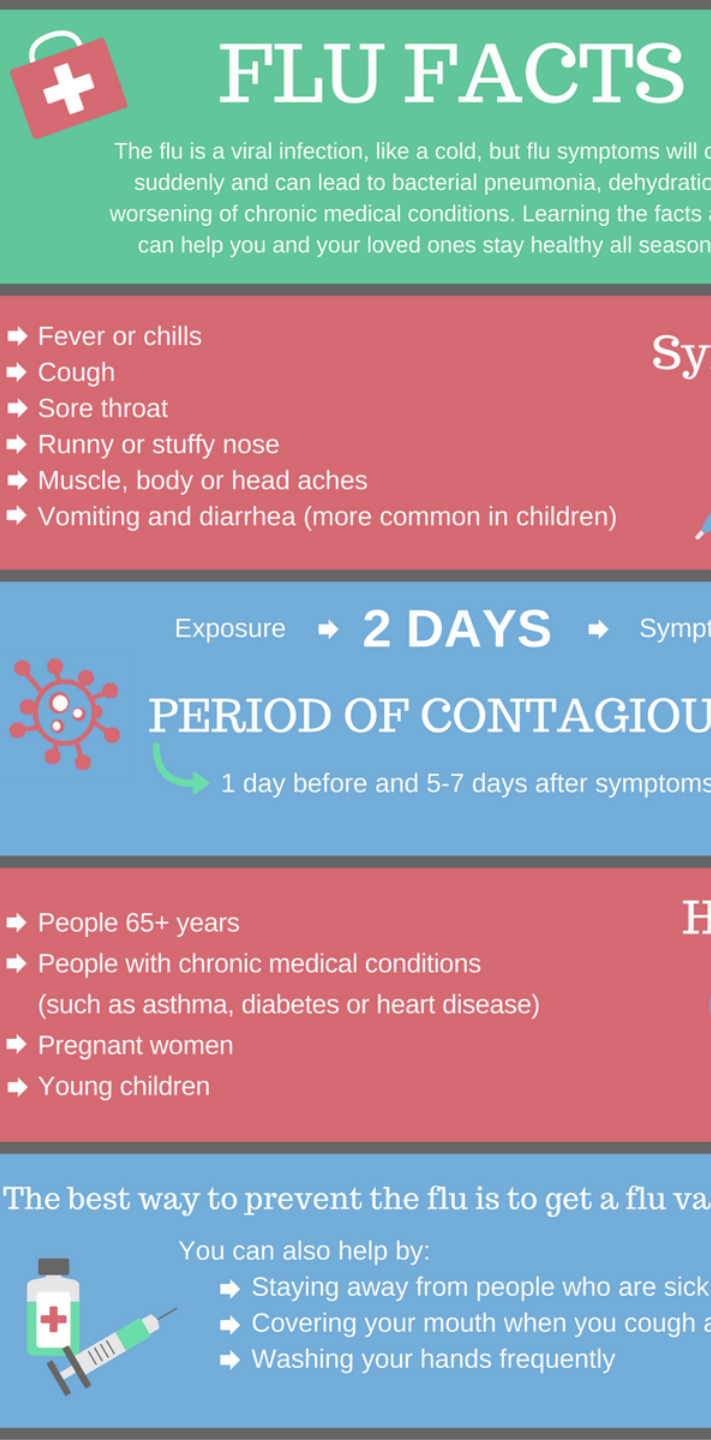
Support Contractor

Question 189: **In the admitting note, the physician documents "1) severe sepsis 2) influenza. Medication: Tamiflu." There were no antibiotics ordered. Would this case be excluded?**

Since there is no documentation indication that severe sepsis is due to the viral infection, selecting Value "1" (Yes) for *Severe Sepsis Present* would be appropriate.

Conclusion

- Get your flu shot, influenza sucks!
- Thanks!



Questions?