Viruses in the ICU: Are they prime time?

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Disclosures

- I have no financial interests or other relationship with commercial concerns related directly or indirectly to this presentation.

Learning Objectives

- Identify and evaluate patients at risk for development of a viral infection
- Review the pathogenic viruses seen in the critically ill population
  - Influenza
  - CMV
  - RSV

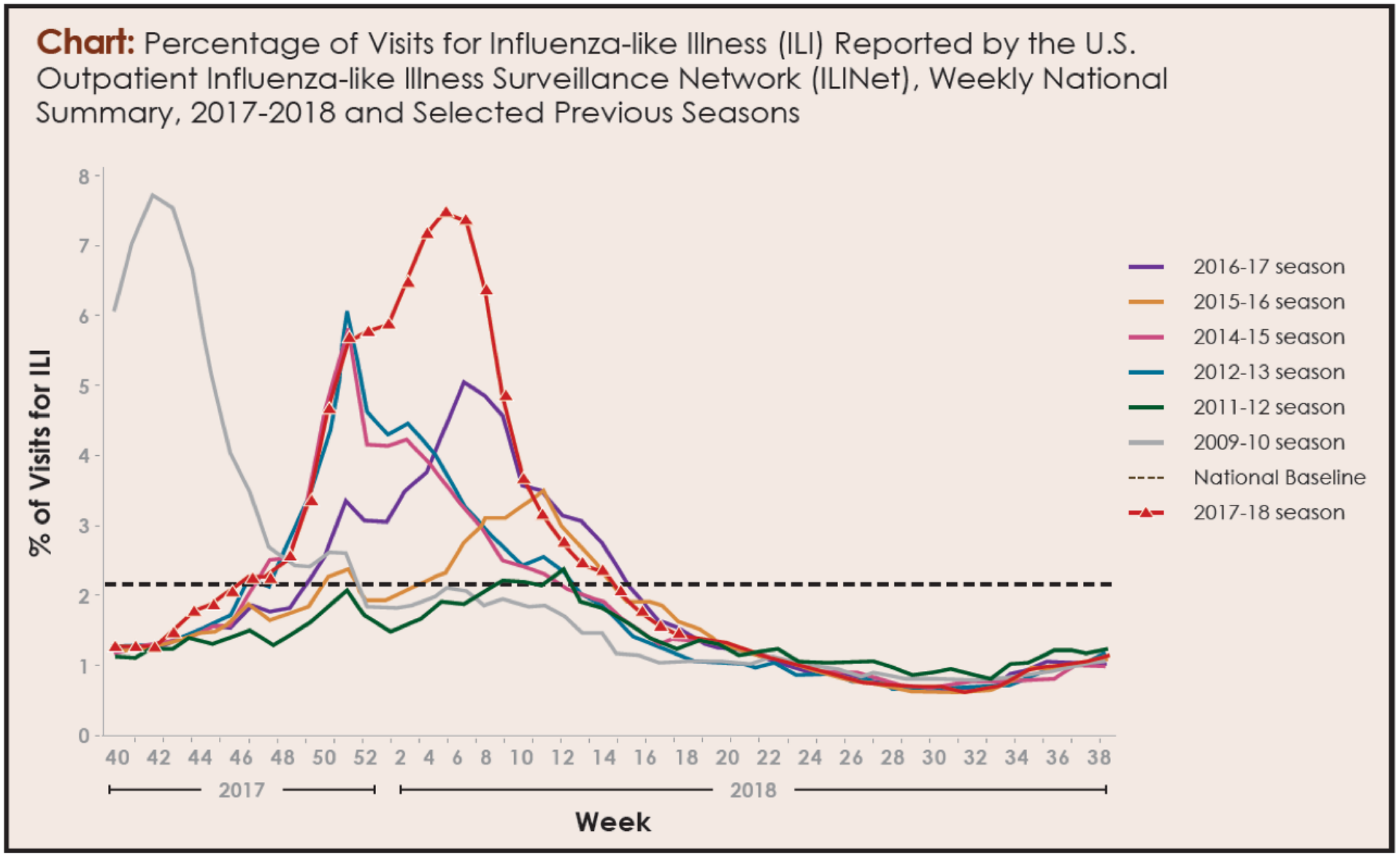
Influenza

Influenza – 100th anniversary of the 1918 pandemic

- ~500 million people became infected
  - 1/3 of the world's population
- At least 50 million deaths worldwide
  - ~675,000 in the United States
- Life expectancy fell by about 12 years
  - 36 years for men and 42 years for women
- Disproportionately affected younger adults

Centers for Disease Control and Prevention. History of 1918 Flu Pandemic. https://www.cdc.gov/flu/pandemic-resources/1918-commemoration/1918-pandemic-history.htm

2017-2018 Seasonal Flu



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Centers for Disease Control and Prevention. Summary of the 2017-2018 Influenza Season. https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm

2017-2018 Seasonal Flu

- H3N2 predominated

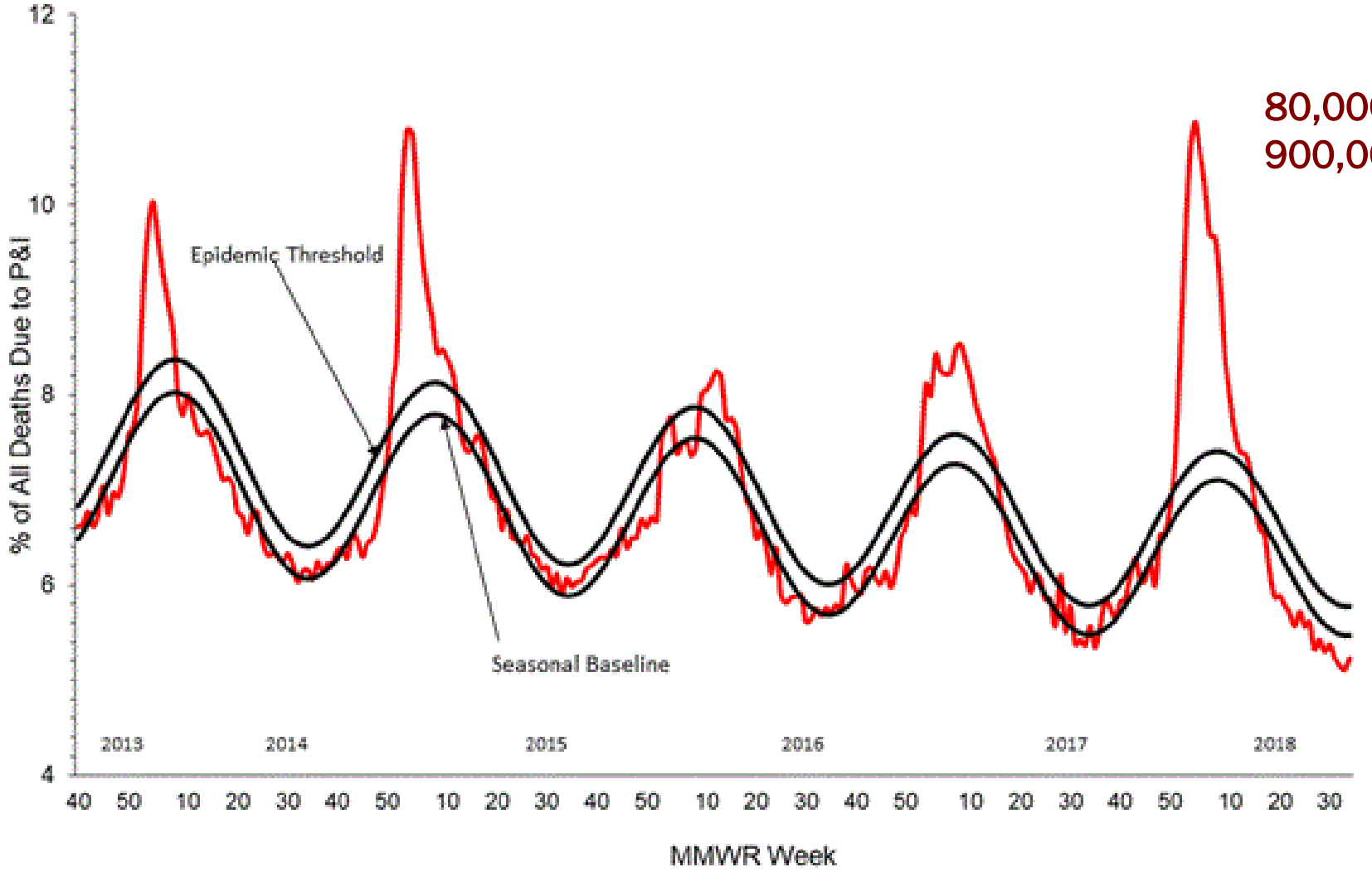
Vaccine Effectiveness

- Overall 36%
- H3N2 25%
- H1N1 67%
- Flu B 42%

Centers for Disease Control and Prevention. Summary of the 2017-2018 Influenza Season. https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending August 25, 2018, as of September 13, 2018



80,000 deaths
900,000 hospitalizations

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Centers for Disease Control and Prevention. Summary of the 2017-2018 Influenza Season. https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm

Influenza

- Acute respiratory illness, caused by influenza A, B, and C viruses
- Occurs in local outbreaks or seasonal epidemics
- Short incubation period
- Presentation ranges from asymptomatic to fulminant
- Influenza A
  - Host - Birds, swine, humans
  - Evolves rapidly, more virulent
  - Classified into subclasses based on hemagglutinin and neuraminidase antigens
- Influenza B
  - Hosts - Humans
  - Less genetically diverse

Lancet. 2017 Aug 12;390(10095):697-708.

Influenza Clinical Presentation

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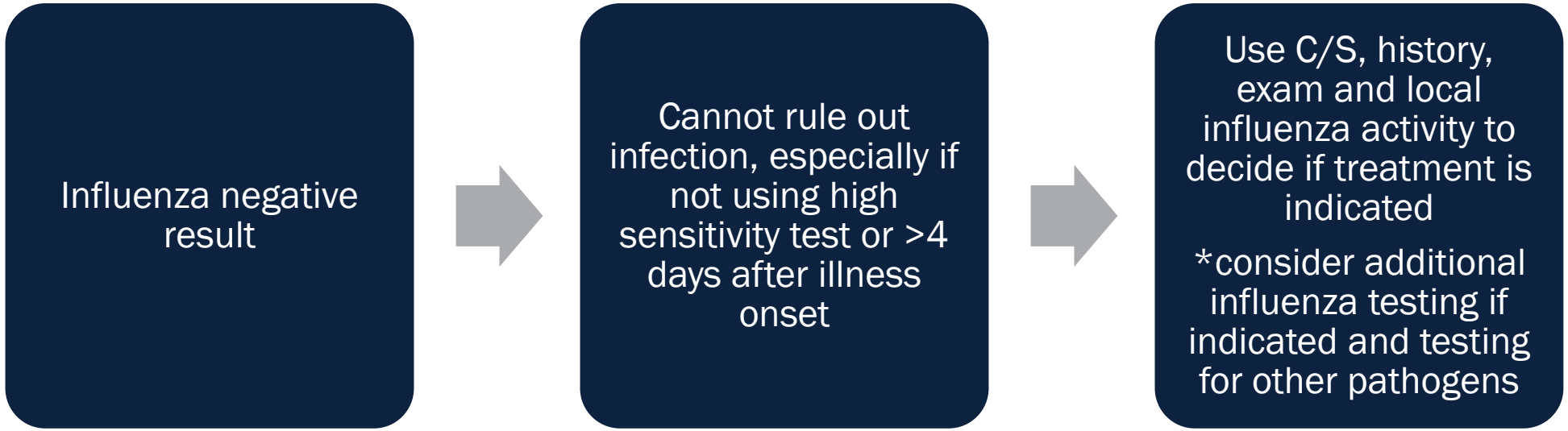
Lancet. 2017 Aug 12;390(10095):697-708.

Diagnosis and Interpretation of Testing

- PCR Based Methods
- Rapid, non-PCR methods false-negatives



Centers for Disease Control and Prevention.2018-2019Information for Health Professionals. https://www.cdc.gov/flu/about/season/health-care-professionals.htm

Antiviral Therapy

Antiviral Agent	Dose	Comments
Oseltamivir (Tamiflu®)	75mg PO BID x5 days	• Initiate as promptly as possible • Longer duration and high-dose can be considered in certain patients
	150mg PO BID	
Zanamivir (Relenza®)	10mg INHALED BID x5 days	• Not recommended for severe disease
Peramivir (Rapivab®)	600mg IV as a single dose	• Uncomplicated
	600mg IV daily x5 days	• Hospitalized patients • If clinically unstable on day 4, continue for 10 days total

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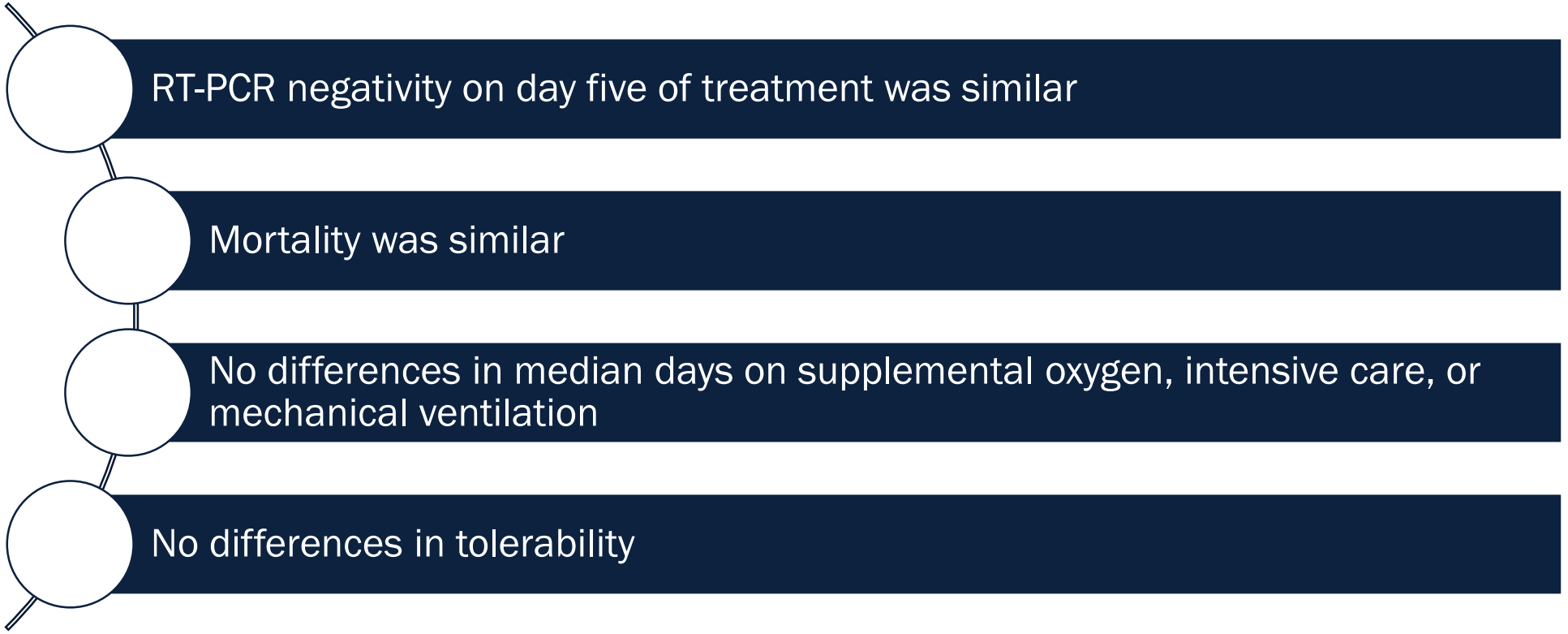
Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

High-dose Oseltamivir

- Optimal dose and duration unknown for severe cases
- Doubling the dose of oseltamivir has been suggested
  - Severely ill patients with H5N1 avian influenza
  - Certain severely ill patients (eg, immunocompromised hosts) during the 2009 to 2010 H1N1 influenza pandemic

High-dose Oseltamivir

- Randomized trial of hospitalized patients with severe influenza
  - 165 and 161 patients randomized to double or standard dose oseltamivir



Extended Duration Antivirals

- Optimal duration for severe cases uncertain
- Clinical judgment and virologic testing of lower respiratory tract specimens by RT-PCR should be used to help guide decisions to treat longer for severe and prolonged illness or immunosuppressed patients
- Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia
  - *S. pneumoniae*, *S. aureus* (including MRSA), and *S. pyogenes*

Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Prevention

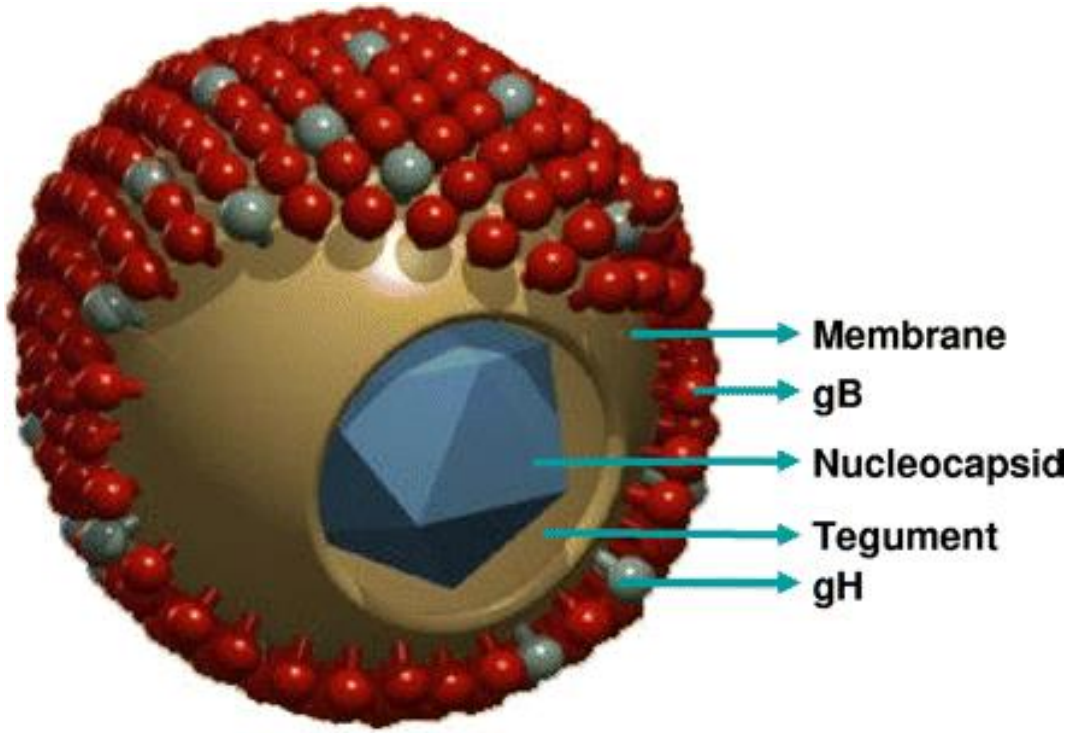
- 2017-2018 Influenza Vaccine
  - 38.5% of adults vaccinated last season
  - 58% of children vaccinated
- Everyone ≥6 months of age should get a flu vaccine every season
- Vaccines include:
  - Inactivated influenza vaccine
  - Recombinant influenza vaccine
  - Live attenuated influenza vaccine
- No vaccine preference given

Centers for Disease Control and Prevention. Seasonal Influenza Vaccination Resources for Health Professionals. https://www.cdc.gov/flu/professionals/vaccination/index.htm

CMV

CMV

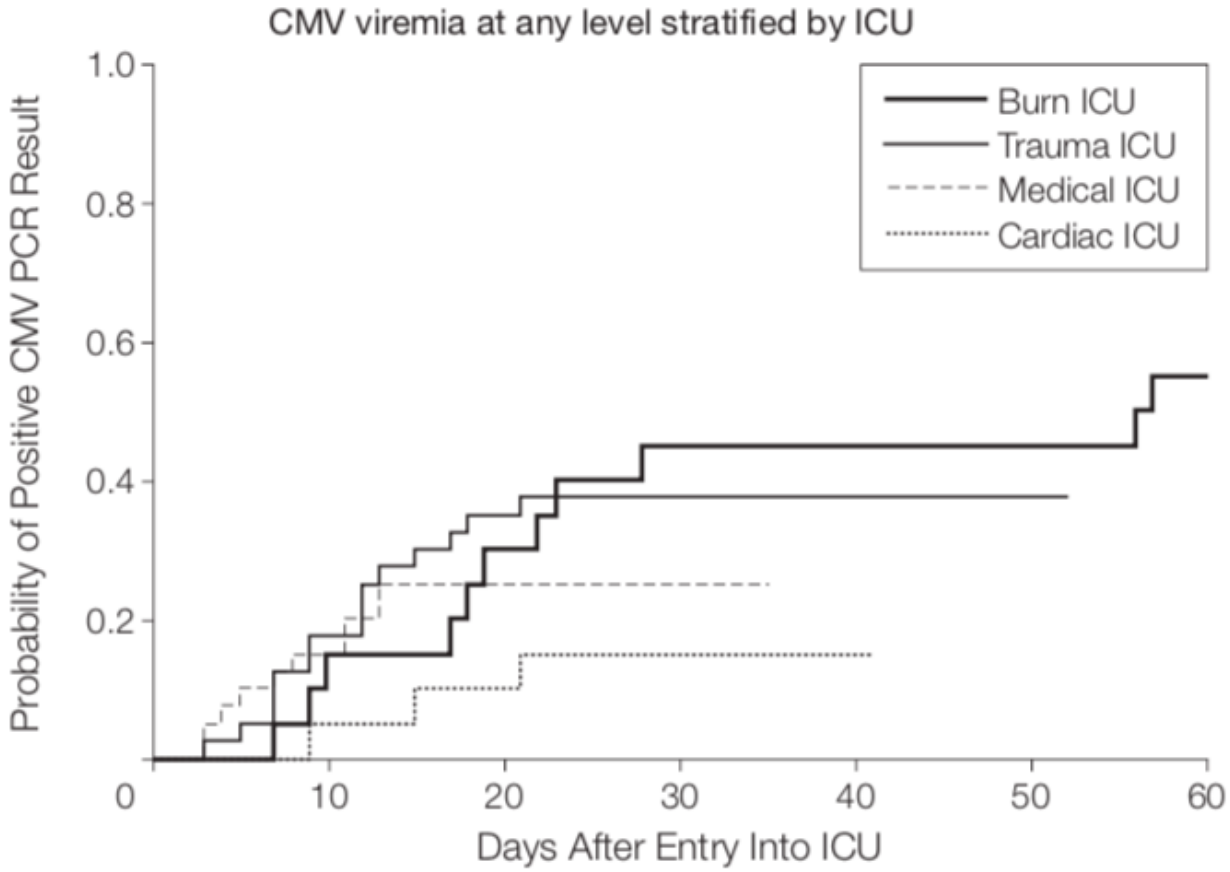
- Cytomegalovirus (CMV) is member of the herpes virus family
- Infects people of all ages – most asymptomatic
  - 1/3 children are already infected by age 5
  - 1/2 infected by the age of 40
- Establishes latent phase mainly within leukocytes
- Past exposure diagnosed with a positive anti-CMV IgG serology



JAMA. 2008 Jul 23; 300(4): 413–422.

CMV Reaction in ICU Patients

- Reactivation of CMV occurs frequently in critically ill immunocompetent patients
- Cumulative incidence at any level was 33%
- Associated with prolonged hospitalization or death



No. at risk							
Burn ICU	20	17	12	8	5	4	1
Trauma ICU	40	27	8	3	1	1	0
Medical ICU	40	21	5	2	0	0	0
Cardiac ICU	20	7	2	1	1	0	0

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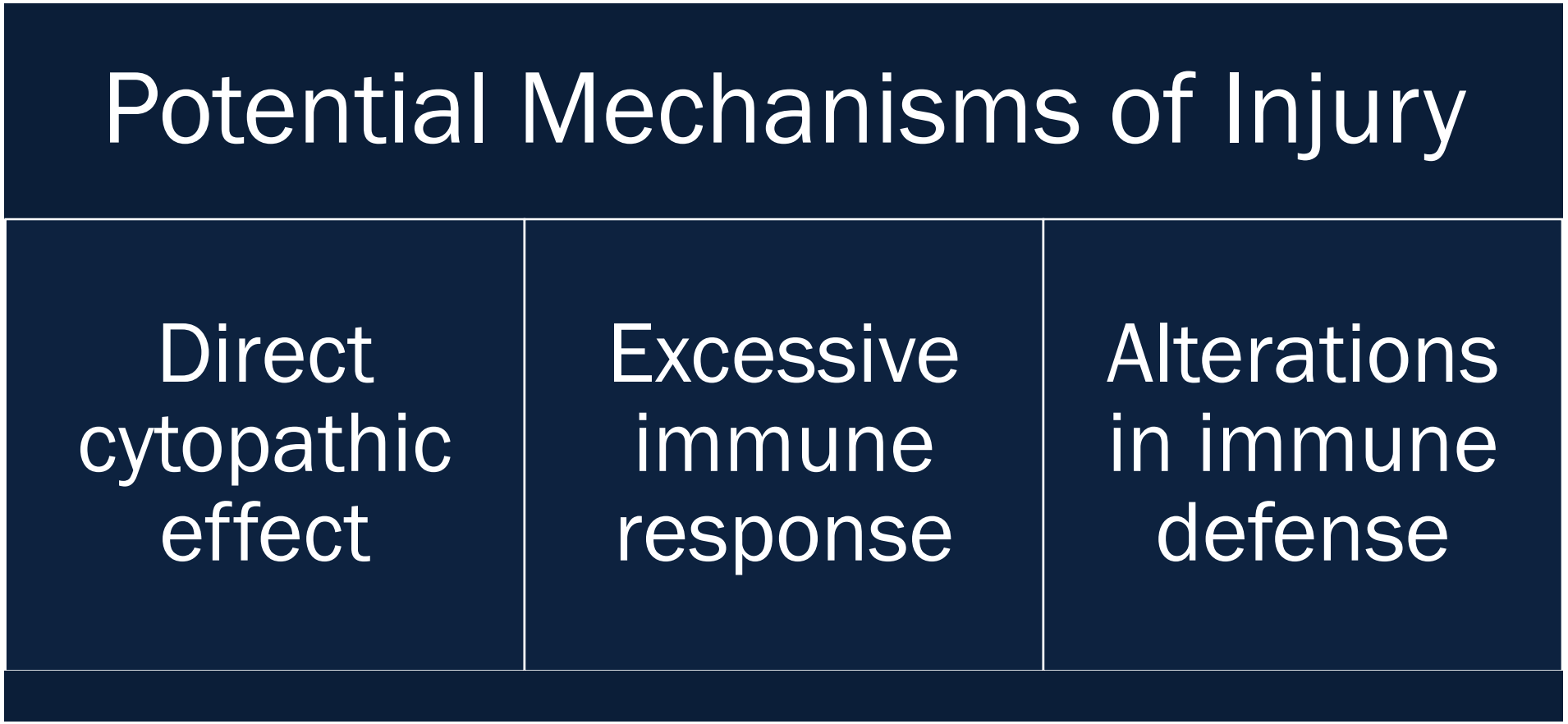
JAMA. 2008 Jul 23; 300(4): 413–422.

CMV Reactivation



JAMA. 2008 Jul 23; 300(4): 413–422.

Associated Effects of CMV on Outcomes

- Prolonged mechanical ventilation
- Prolonged duration of ICU stay
- Organ system failure
- Nosocomial infections
- Higher mortality rates

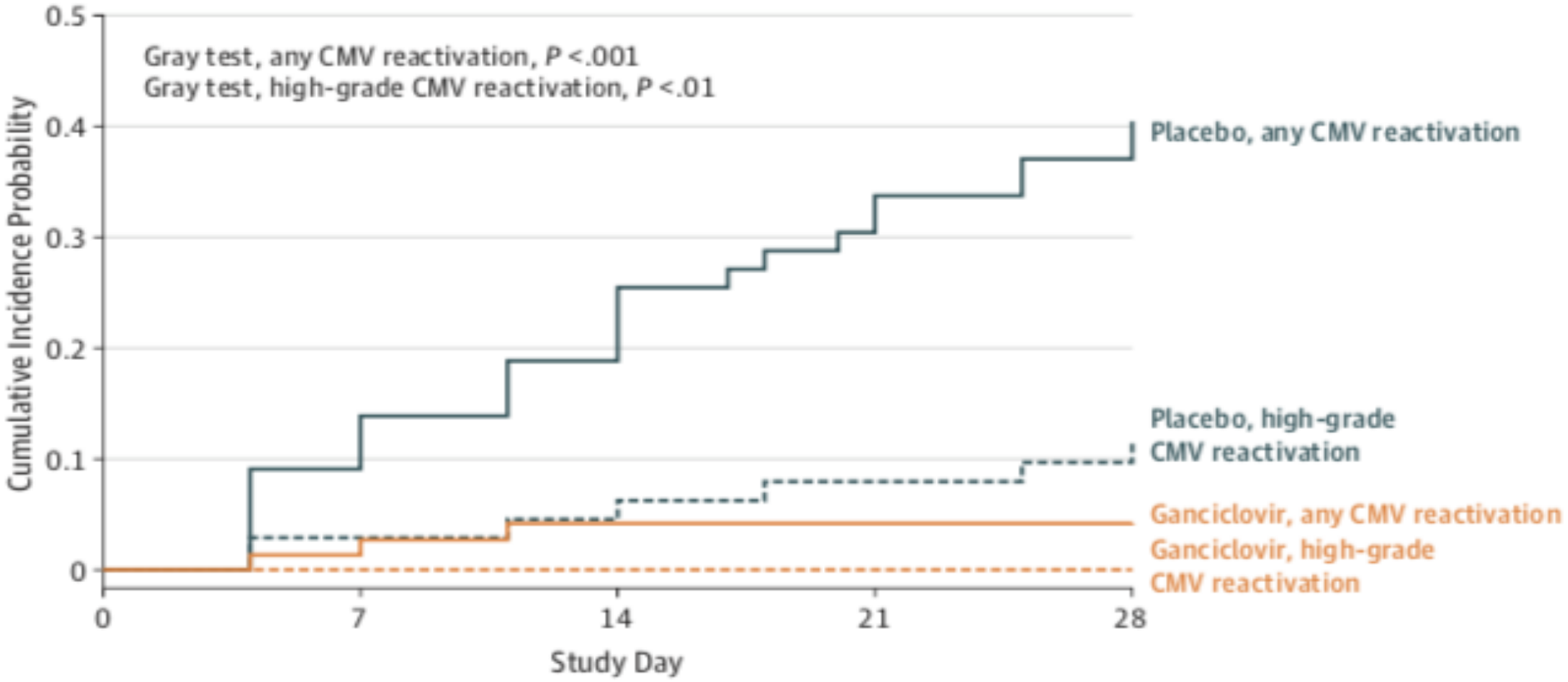
JAMA. 2008 Jul 23; 300(4): 413–422.

Prevention of CMV Reaction

- A Randomized Double-Blind Placebo-Controlled Trial of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (The GRAIL Study)
- 160 non-immunocompromised patients with sepsis or trauma respiratory failure
- Experimental Arm: 5mg/kg IV twice daily for 5 days, then followed by either IV ganciclovir or oral valganciclovir once daily until hospital discharge
- Primary endpoint: IL-6 levels from day 1-14

JAMA. 2017 Aug 22;318(8):731-740

Cumulative Incidence of Any CMV Reactivation and High-Grade CMV Reactivation



No. of participants					
Any CMV reactivation					
Ganciclovir	77	72	62	60	60
Placebo	69	57	49	42	37
CMV reactivation >1000 IU/mL (high-grade reactivation)					
Ganciclovir	83	79	70	68	67
Placebo	72	62	56	54	51

JAMA. 2017 Aug 22;318(8):731-740

Effect of Ganciclovir on IL-6 Levels Among CMV + Critically Ill Adults

	Intention-to-Treat Group (n = 156)				Sepsis Subgroup (n = 137)			
	Placebo Group (n = 72)	Ganciclovir Group (n = 84)	Absolute Difference (95% CI)	*P* Value	Placebo Group (n = 66)	Ganciclovir Group (n = 71)	Absolute Difference (95% CI)	*P* Value
Primary Outcome at Day 14								
Difference in plasma IL-6 level, mean, $\log_{10}$ units	−0.79 (−2.14 to 0.56)	−0.79 (2.06 to 0.48)	0 (−0.3 to 0.2)	>.99	−0.88 (−2.23 to 0.47)	−0.81 (−2.20 to 0.58)	0.1 (−0.2 to 0.2)	.83
Secondary Outcomes at Day 28								
Cumulative incidence of any plasma CMV reactivation, No. (%)	28 (39)	10 (12)	−27 (−40 to −14)	<.001	26 (39)	10 (14)	−25 (−40 to −11)	<.001
Mechanical ventilation duration, median (IQR), d[a]	6 (3 to 12)	5 (3 to 9)	−1 (−3 to −1)[b]	.16	6 (3 to 11)	5 (3 to 8)	−1 (−4 to 0)	.06
Ventilator-free duration, median (IQR), d[a]	20 (8 to 24)	23 (16 to 25)	3 (0 to 6)	.05	20 (9 to 24)	23 (16 to 25)	3 (0 to 4)	.03
ICU length of stay, median (IQR), d[a]	8 (5 to 15)	8 (4 to 14)	0 (−4 to 2)	.76	8 (5 to 14)	7 (4 to 12)	−1 (−4 to 1)[b]	.36
Hospital length of stay, median (IQR), d[a]	13 (8 to 23)	14 (8 to 22)	1 (−1 to 1)	.92	13 (8 to 22)	13 (8 to 20)	0 (−1 to 1)	.76
Secondary bacteremia or fungemia, No. (%)	11 (15)	13 (15)	0 (−10 to 10)	.97	9 (14)	10 (14)	0 (−10 to 10)	.96
Mortality, No. (%)	11 (15)	10 (12)	−3 (−14 to 7)	.54	10 (15)	9 (13)	−2 (−14 to 9)	.68
Composite end point of mortality and >7 d of mechanical ventilation or >50% increase in IL-6 level, No. (%)	49 (68)	42 (50)	−18 (−33 to −3)	.02	44 (67)	34 (48)	−19 (−35 to −3)	.04

JAMA. 2017 Aug 22;318(8):731-740

Effect of Ganciclovir on IL-6 Levels Among CMV + Critically Ill Adults

- Among CMV-seropositive adults with critical illness due to sepsis or trauma, ganciclovir did not reduce IL-6 levels
- Published literature and the current study do not support routine clinical use of ganciclovir as a prophylactic agent in patients with sepsis

JAMA. 2017 Aug 22;318(8):731-740

RSV

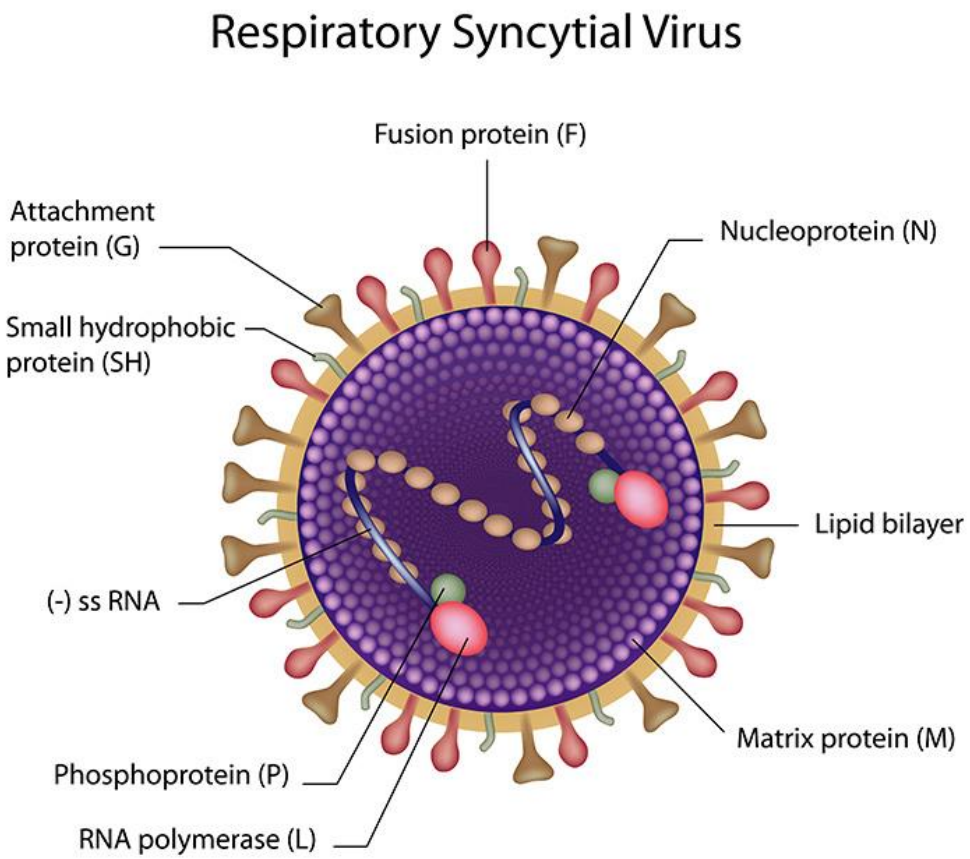
RSV

- Respiratory syncytial virus (RSV) is known to be an important cause of lower respiratory tract infections in infants and young children
- Impact in adults, often underappreciated
  - Infects 3%–10% of adults annually
  - 5%–15% of community-acquired pneumonia
  - 9%–10% of hospital admissions for acute cardiorespiratory diseases
- Little is known about the clinical manifestations, complications, and outcomes of severe RSV infections in adults
  - Exception of severely immunocompromised patients

Clin Infect Dis. 2013;57(8):1078–80

RSV

- Enveloped, non-segmented, single-stranded RNA virus
- Attachment (G) and fusion (F) proteins account for viral binding and penetration
- Classified as either A or B subgroups based on G protein
- F and G proteins are common targets for antivirals and vaccines



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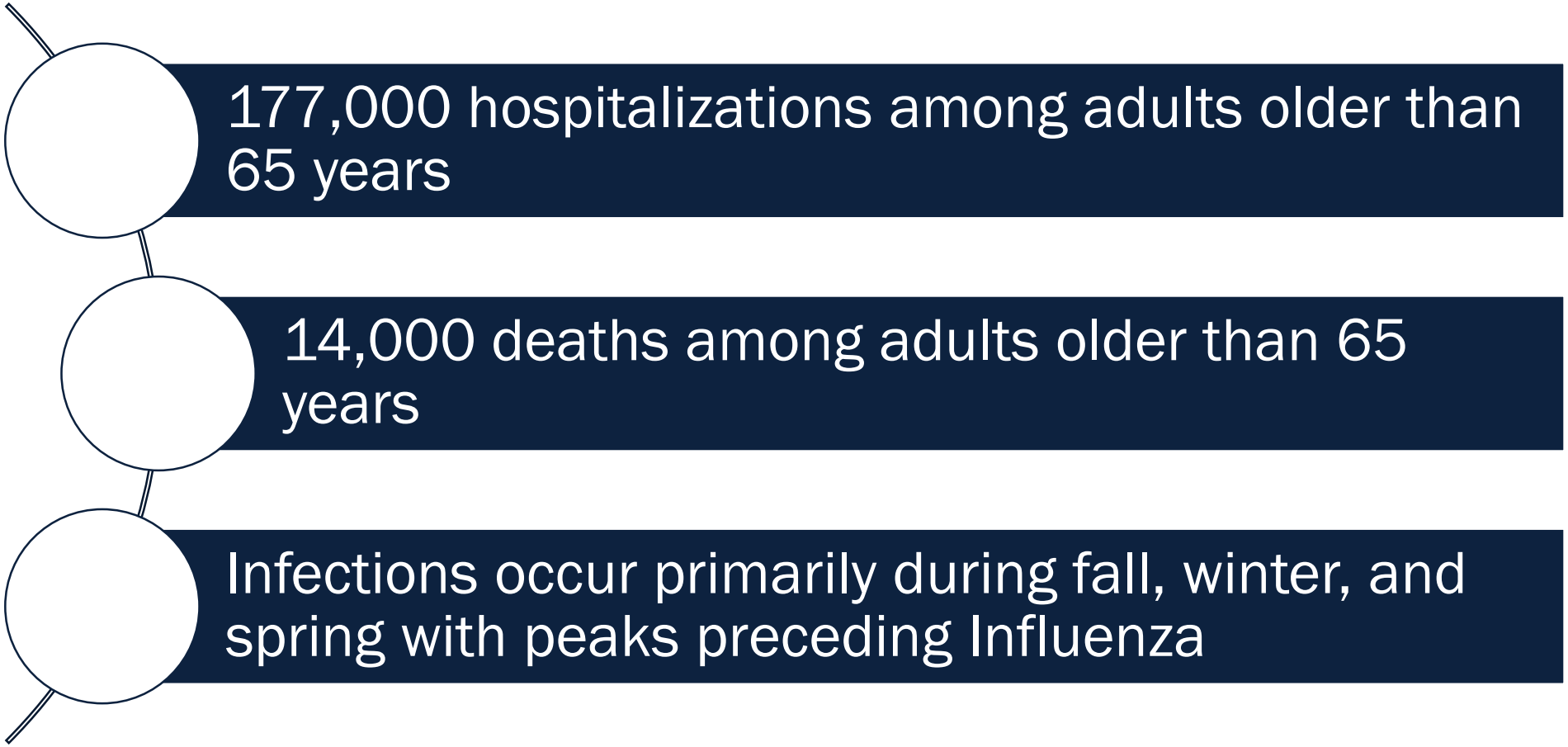
RSV

- Very common respiratory virus in children <2-3 years of age
- Second most common viral pathogen in adults >65 years after influenza
- Most infection cause mild symptoms, but can be a common cause of CAP and COPD exacerbations in older adults
- High-risk groups
  - Elderly
  - Chronic cardiopulmonary diseases
  - Immunosuppressed
- Use highly sensitive rRT-PCR assays for detection

Clin Infect Dis. 2013;57(8):1078–80

Epidemiology



Centers for Disease Control and Prevention. RSV: Summary for Clinicians. https://www.cdc.gov/rsv/clinical/index.html

Treatment

- Treatment in adults is limited to supportive care
  - Bronchodilators
  - Corticosteroids
  - Supplemental oxygen
- HCT patients may benefit from antiviral and immunotherapy
- Overall research in this area has been underappreciated
  - Insensitive point-of-care diagnostics
  - Lack of a distinct clinical syndrome
  - Broad epidemic curve overlapping influenza

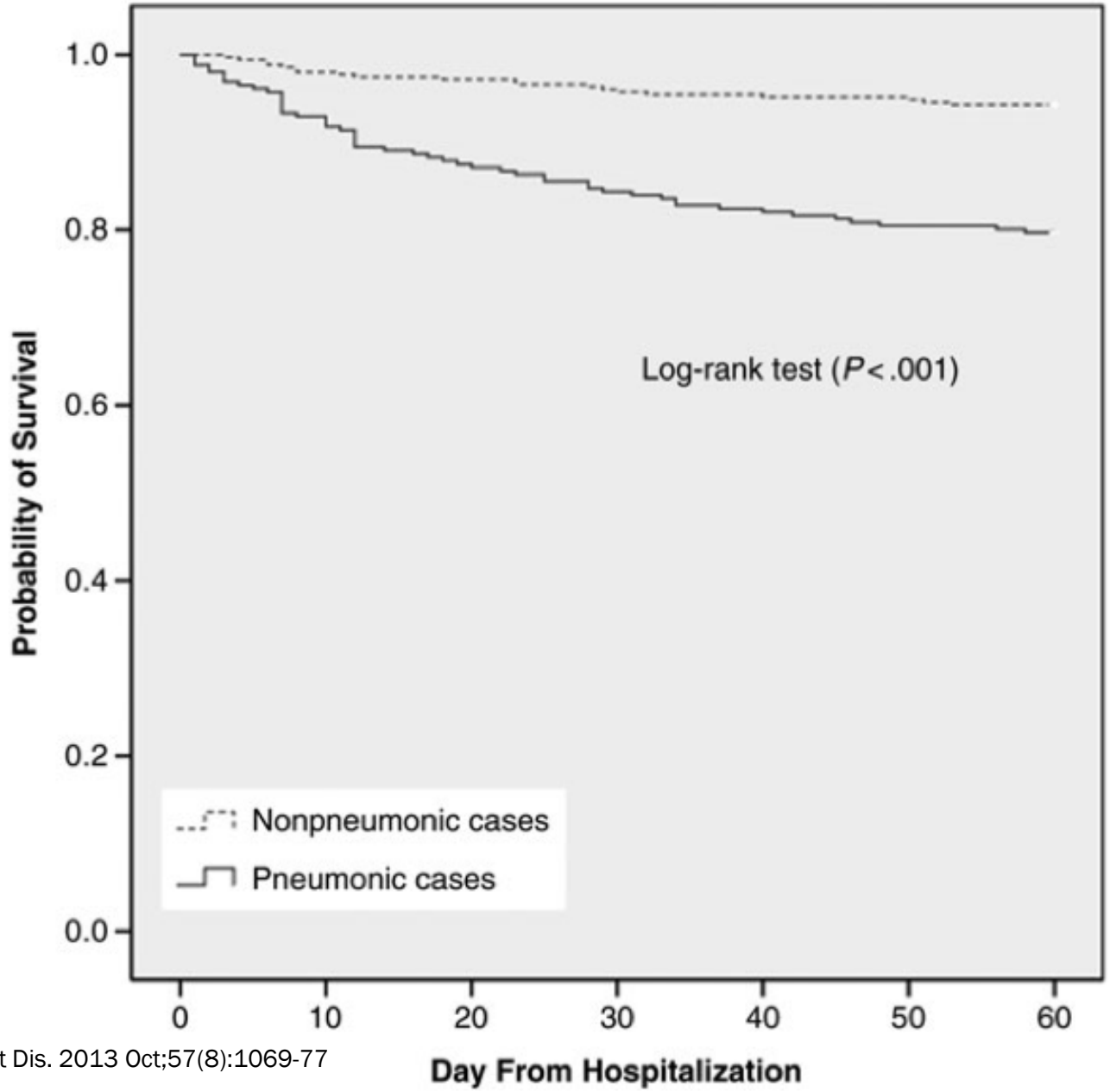
Baseline Characteristics, Presenting Symptoms, Complications, and Outcomes of 607 Adults Hospitalized With RSV Infection, 2009–2011

Variable	RSV (N = 607)	Influenza (N = 547)	*P* Value
Age, y, mean (SD)	75.1 (16.4)	74.7 (16.6)	.650
Male sex	48.6	49.5	.749
Resident of long-term care facility	32.9	30.5	.378
Comorbidity, major systemic (except chronic lung diseases)[a]	74.0	65.8	.003
Chronic lung diseases[a]	35.6	24.1	<.001
Symptom onset to admission, d, mean (SD)	2.6 (2.2)	2.0 (1.7)	<.001
Fever >37.5°C	75.0	94.2	<.001
Cough	87.5	85.7	.513
Sputum production	81.2	72.5	.010
Wheezy breathing and dyspnea	68.9	53.2	<.001
Sore throat	11.8	14.3	.364
Runny nose	25.6	30.2	.214
Pneumonia	42.3	36.7	.006
Lower respiratory complications[b]	71.9	55.6	<.001
Cardiovascular complications[b]	14.3	13.3	.653
Complications, any[b]	80.4	72.8	.002
Bacterial infection, overall[c]	14.8	14.3	.790
Bacterial infection, at presentation[c]	12.5	9.1	.066
Supplemental oxygen therapy	67.9	59.0	.002
Ventilation, noninvasive or invasive	11.1	6.2	.003
30-day mortality	9.1	8.0	.538
60-day mortality	11.9	8.8	.086
Time to death, d, median (IQR)	13 (7–29)	7 (3–13)	.001
Extended care in subacute hospitals	25.2	19.7	.027
Duration of hospitalization for survivors, d, median (IQR)	7 (5–14)	6 (5–11)	.238

Clin Infect Dis. 2013 Oct;57(8):1069-77

Variables Associated With Death in Hospitalized RSV Patients

- Advanced age (>75 years)
- Pneumonia
- Requirement of ventilator support
- Bacterial superinfection
- Serum urea concentrations
- Total WBC count



Clin Infect Dis. 2013 Oct;57(8):1069-77

Explanatory Variables Associated With Duration of Hospitalization Among Survivors (n = 535) as Shown in the Final Cox Proportional Hazards Mode

- Systemic corticosteroids were given to 38.9% of patients to treat acute airway diseases

Variables Associated With Duration of Hospitalization	Adjusted Hazard Ratio (95% Confidence Interval)	*P* Value
Advanced age (>75 y)	0.74 (.62–.89)	.001
Comorbidity, major systemic	0.77 (.64–.94)	.010
Requirement of ventilatory support	0.39 (.28–.54)	<.001
Use of systemic corticosteroids	0.76 (.63–.91)	.002

Clin Infect Dis. 2013 Oct;57(8):1069-77

RSV Takeaways and Future Direction

- RSV can cause severe lower respiratory complications in older adults
  - Respiratory failure
  - Prolonged hospitalization
  - High mortality similar to influenza
- Corticosteroids did not seem to improve clinical outcomes
- The unmet need for effective antiviral therapy and vaccination against RSV

Summary

- Influenza vaccine should be offered to patients ≥6 months of age every season
- High-dose oseltamivir may not provide additional benefit
- Early administration of oseltamivir has shown to shorten duration of hospitalization
- Optimal duration is uncertain for severe or complicated influenza
- CMV reactivation is associated with worse outcomes
- Routine use of ganciclovir for CMV prophylaxis in patients with sepsis is not recommended
- RSV can cause severe lower respiratory complications in older adults
- Corticosteroids did not seem to improve clinical outcomes
- Unmet need for effective antiviral therapy and vaccination against RSV

Learning Assessment Question #1

Influenza virus infection can lead to bacterial superinfection and pneumonia secondary to which of the following organisms.

A. *Streptococcus pneumoniae*

B. *Streptococcus pyogenes*

C. *Staphylococcus aureus*

D. All of the above

Learning Assessment Question #2

CMV infection that occurs in immunocompetent adults with critical illness most commonly occurs due to primary infection.

A. True

B. False