Influenza

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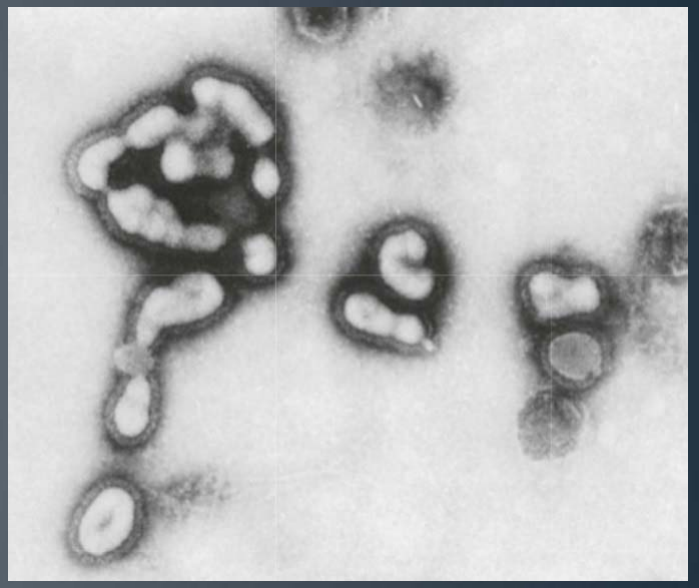
Infectious Disease

Outline

- History
- The Virus
- Current statistics
- Presentation
- Treatment
- Vaccination

Introduction

- Influenza viruses – enveloped, ss-RNA virus (Types A, B, C)
- Causes acute, febrile illness
  - Fever, cough, malaise are most common manifestations
- 2 Unique features of "the flu"
  - 1. Outbreaks annually every winter in temperate climates, year-round in tropical climates
  - Increased mortality due to pulmonary complications



Electron Micrograph of influenza A/USSR/77 H1N1 (x189,000). Figure 167-1, Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th *ed.*; Chapter 167: influenza (Including Avian Influenza and Swine Influenza).

History

- Flu causes respiratory epidemics every 1-3 years for at least the past 400 years
- Term “Influenza” may have originated in Italy with the thought that fever, cough and cold came from “influence” of the stars
- Other names of the flu:
  - Epidemic catarrh, grippe and the sweating sickness.
  - In the mid-17th century, New Englanders called the disease "the jolly rant" and “the new acquaintance." In England it was the “knock-me-down fever.”
  - May have plagued the Greeks fighting the Peloponnesian War in 430 B.C.
  - Decimated Charlemagne’s army in the late eighth century with a burning fever.

History

- Great pandemic flu 1918-1919 – Spanish influenza A H1N1
  - At least 20 million fatalities (possibly 50-100 million)
  - Over 575,000 in US
  - Mortality estimated at 5%, with up to 1/3 of all humans being infected
  - Flu may have become more virulent during 2nd outbreak
  - Community outbreaks occurred and were over quickly
- Influenza A finally isolated 1933
- Pandemic also in 1957-1958, 1967-1968

Historical photo of the 1918 Spanish influenza ward at Camp Funston, Kansas, showing the many patients ill with the flu https://rybicki.wordpress.com/2012/09/10/a-brief-history-of-influenza/

The Virus

- Orthomyxoviridae family of viruses
  - Classified into influenza A, B or C
- A/B case outbreaks and epidemics
- A thought to cause more severe and widespread disease
- C sporadic URI, not seasonal
- All influenza viruses share:
  - Presence of host cell derived envelope
  - Glycoproteins for viral entry/egress
  - Segmented negative sense ss-RNA genome
- Nomenclature: Type/place of isolation/strain designation/year
  - Virus from Puerto Rico; A/Puerto Rico/8/34
  - Influenza A further divided based on Hemagglutinin (H or HA) and neuraminidase (N or NA) antigens

The Virus

TABLE 167-1 Differences among Influenza A, B, and C Viruses

	INFLUENZA A	INFLUENZA B	INFLUENZA C
Genetics	8 gene segments	8 gene segments	7 gene segments
Structure	10 viral proteins	11 viral proteins	9 viral proteins
	M2 unique	NB unique	HEF unique
Natural host range	Humans, swine, equine, birds, marine mammals*	Humans only	Humans and swine
Epidemiology	Antigenic shift and drift	Antigenic drift only; two main lineages cocirculate	Antigenic drift only; multiple variants
Clinical manifestations	May cause large pandemics with significant mortality in young persons	Severe disease generally confined to older adults or persons at high risk; pandemics not seen	Mild disease without seasonality

The Virus

- 80-120nm enveloped virus with surface spikes of HA, NA
- HA – viral attachment protein
  - 16 (H1-H16) highly divergent antigenically distinct HA in influenza A
- NA – enzyme that catalyzes removal of terminal sialic acid from sialic acid-containing glycoproteins
  - At least 9 distinct NA (N1-N9)
- M2 protein present on outer envelope
- M1 protein – virus structure, assembly

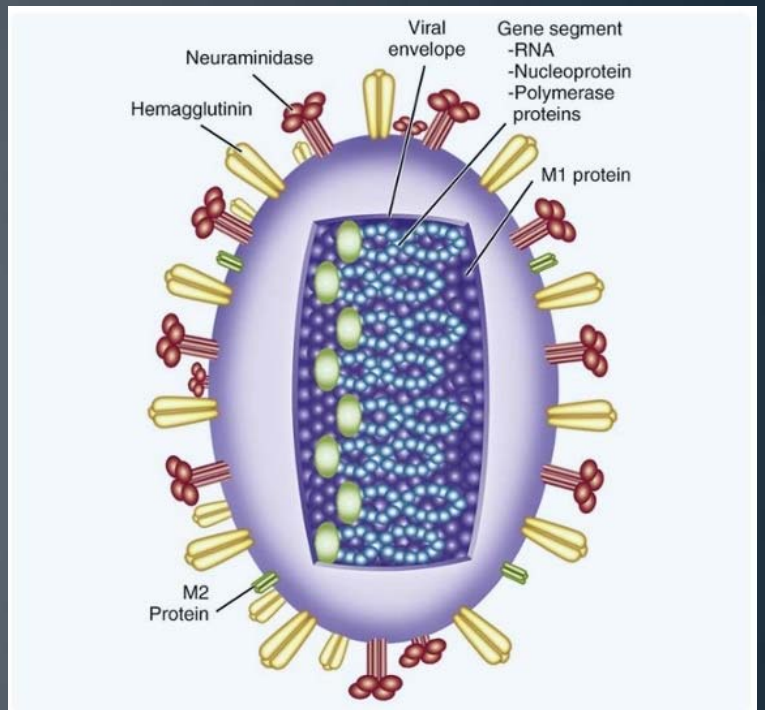
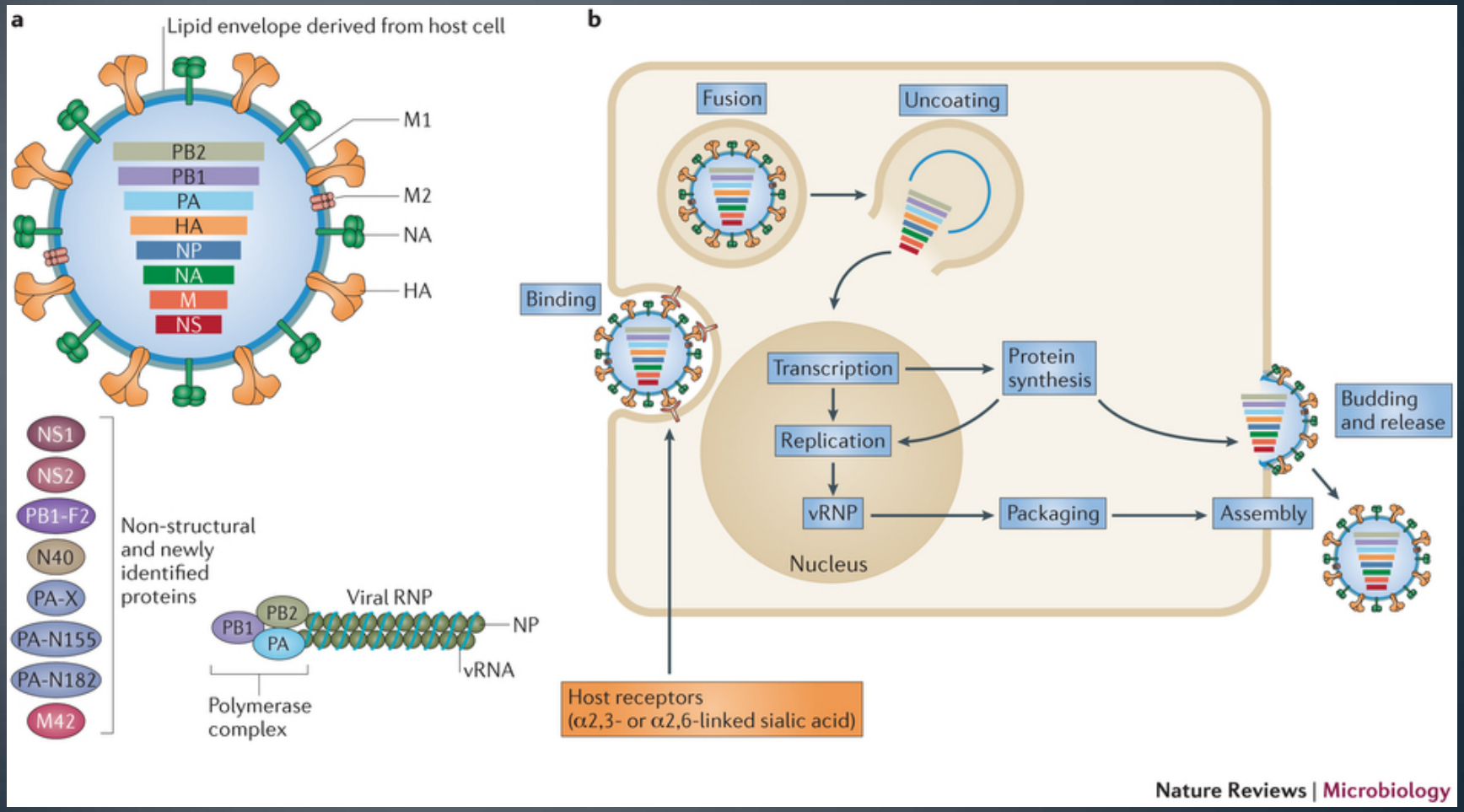


FIGURE 167-2 Schematic model of an influenza A virus.

The Virus

- HA attaches to sialic acid-containing receptors on the cell
- Virus internalizes into an endosome, undergoes conformational change then fuses viral endosome with viral envelope
- M2 protein acts as an ion channel to let viral gene segments leave virion and enter cytoplasm – "Uncoating"
- Viral gene segments transported to the nucleus and directs synthesis of progeny viral RNA and other pathogenic viral proteins
- New viral progeny transported to cytoplasm for assembly
- Virions acquire new envelope, HA, NA, M2
- NA removes sialic acid from cell surface receptors and progeny virus are released
- Segments are exchanged between different virus infecting the same cell – "Reassortment"

Lifecycle



Enabling the 'host jump': structural determinants of receptor-binding specificity in influenza A viruses Yi Shi, Ying Wu, Wei Zhang, Jianxun Qi & George F. Gao *Nature Reviews Microbiology* **12**, 822–831 (2014)

Epidemiology

- Epidemics express excess morbidity/mortality in excess pneumonia and influenza hospitalizations and deaths
- Attack rates usually highest in young, excess mortality in elderly
- Epidemic is an outbreak confined to one area typically with a characteristic pattern
- Attack rate of unvaccinated 10-50%

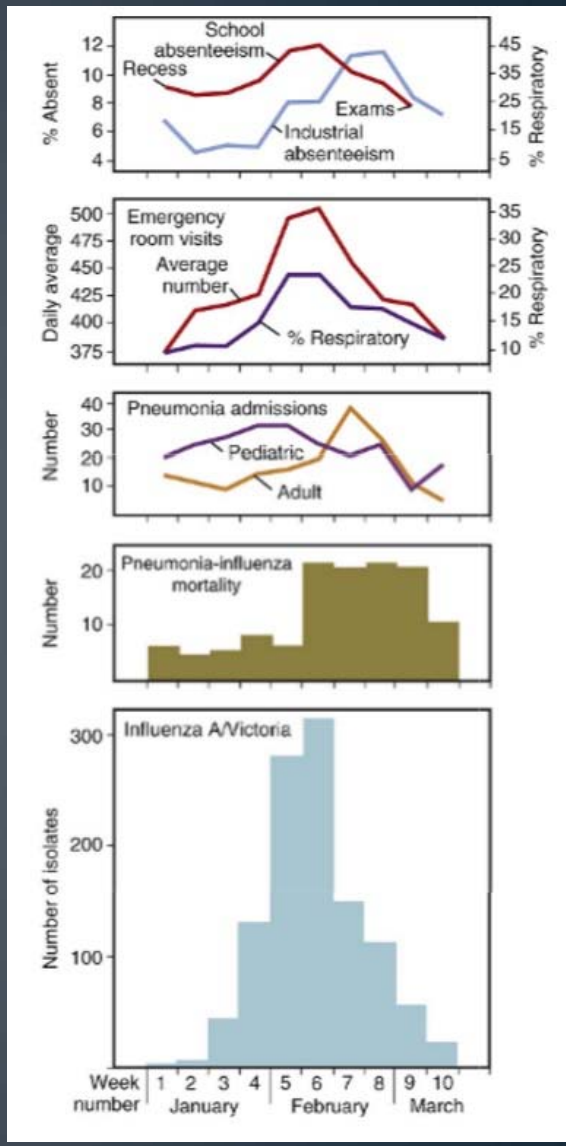


Figure 167-4: Correlation of the nonvirologic indexes of epidemiologic influenza with the number of isolates of A/Victoria virus according to week, Houston, 1976.

Epidemiology

- Pandemic – emergence of an antigenically variant influenza in which the population has little or no prior immunity
- May have higher attack rate, greater impact on young, occur outside normal season
- Antigenic variation – unique feature of the flu
- Alterations of HA, NA leads to infection with little to no resistance in the population
- Major reason why the flu is an annual problem

Drift and Shift

- **Antigenic drift** – minor changes within HA/NA in both viruses
- Gradual accumulation of amino-acid changes
- Immunologic selection of "new" virus
- **Antigenic Shift** – more radical changes in HA/NA or both result in viruses with little to no population immunity

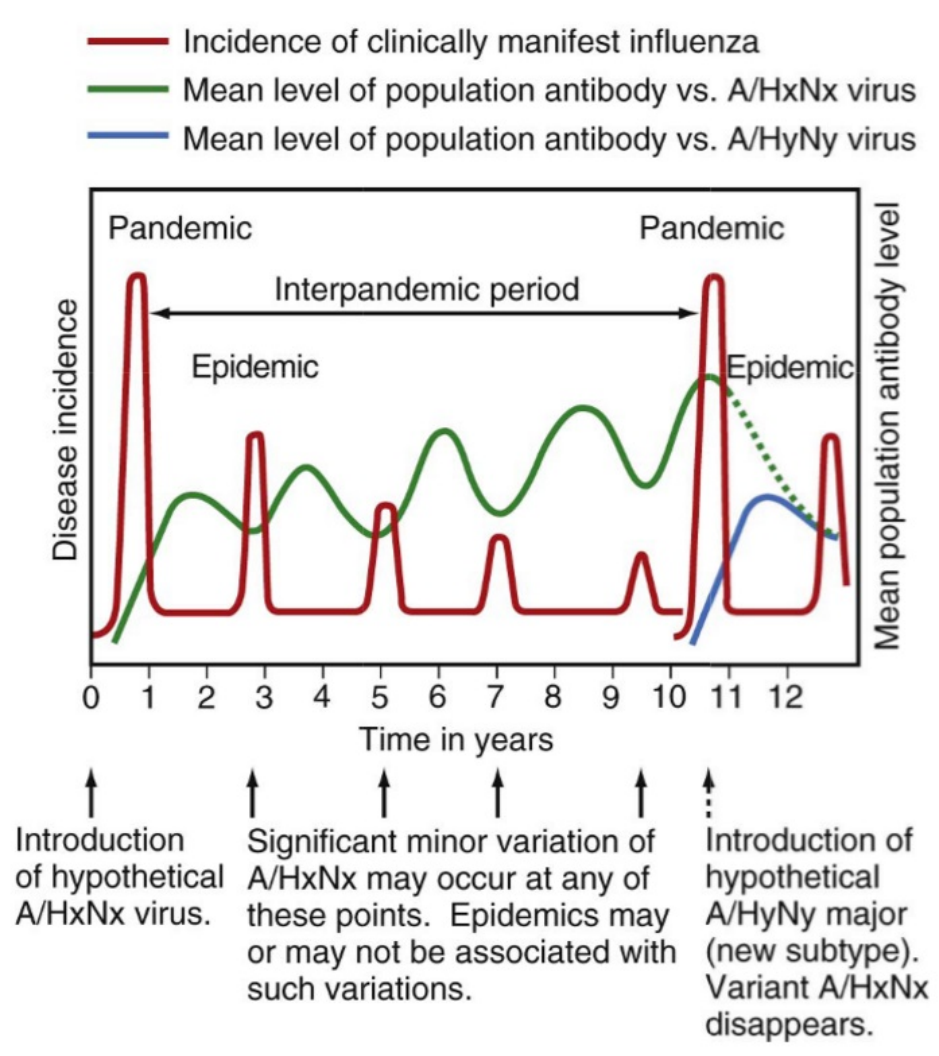


Figure 167-5 Schema of the occurrence of influenza pandemics and epidemics in relation to the level of immunity in the population

Pandemics

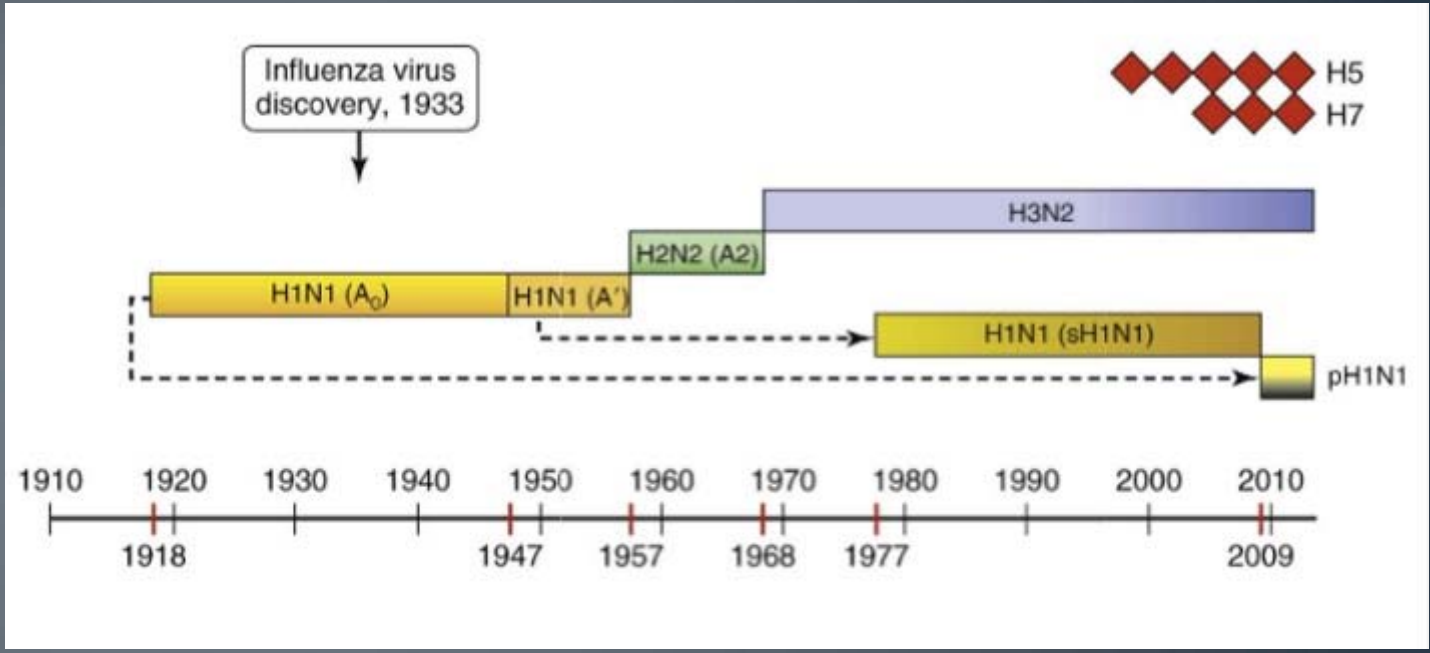
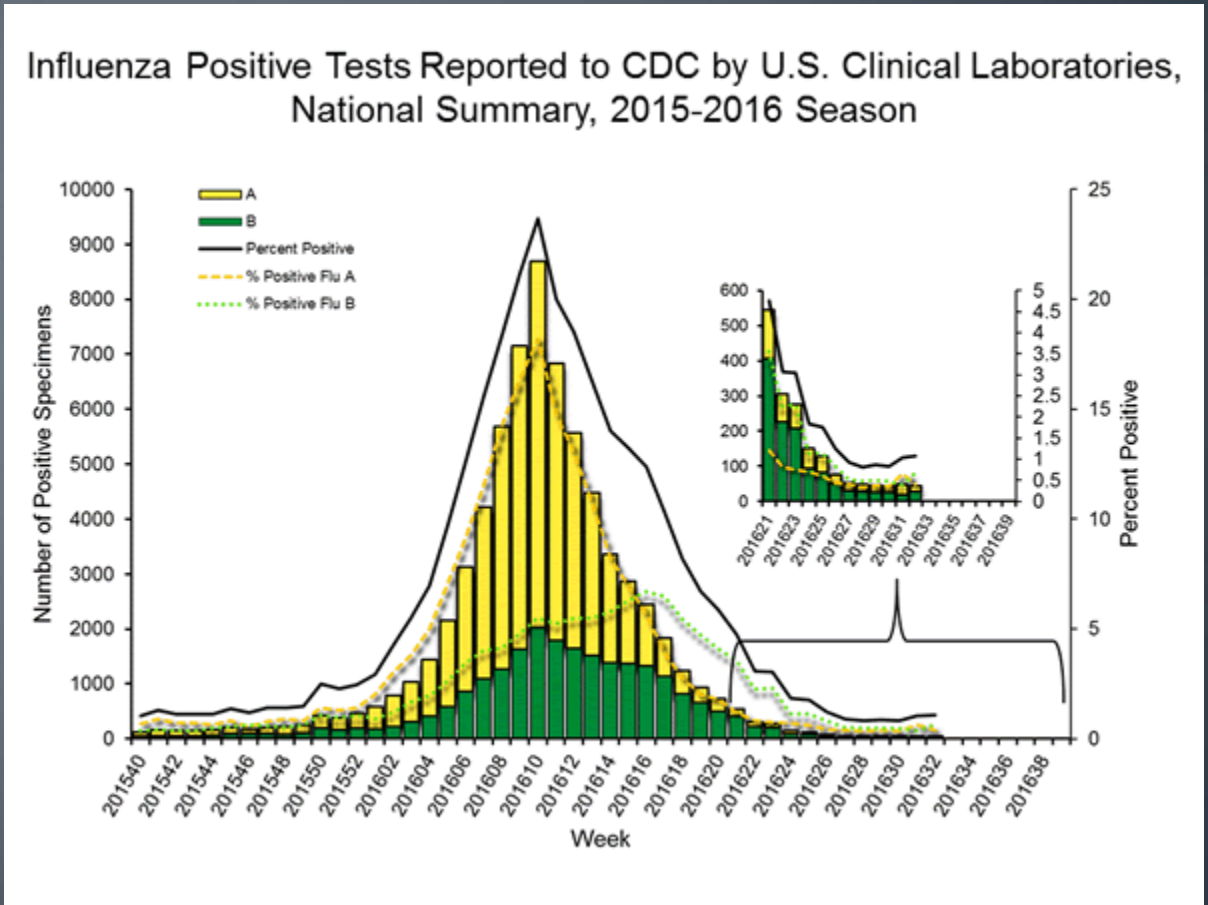


Figure 167-6 Recent pandemics of influenza

Flu 2015

- Activity increased in December 2015 and peaked week of March 12, 2016
- 157-168 Million doses injectable flu vaccine made
  - an A/California/7/2009 (H1N1)pdm09-like virus
  - an A/Switzerland/9715293/2013 (H3N2)-like virus
  - a B/Phuket/3073/2013-like virus. (This is a B/Yamagata lineage virus)
- Approximately 60% efficacious in 2015-2016
  - There were sufficient data from the U.S. Flu VE Network to also calculate more specific VE estimates:
  - 51 percent VE against the H1N1 viruses responsible for most flu illness this season
  - 76 percent VE against all influenza B viruses
  - 79 percent VE against the B/Yamagata lineage of B viruses

Flu 2015


Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, 2015-2016 Season
A
B
Percent Positive
% Positive Flu A
% Positive Flu B
Number of Positive Specimens
Percent Positive
Week

Pathogenesis

- Inhale virus containing respiratory secretions where it attaches, penetrates columnar epithelial cells
- Virus replicates, causes cell death by:
  - Shutoff host cell protein synthesis through several mechanisms
  - Cellular apoptosis
- Viral release lasts for several hours before cell death
- Released viruses infect neighboring cells
- Onset of illness occurs 18-72 hours after inoculation
- Viral shedding for 5-10 days (longer in children)
- Systemic symptoms due to release type I interferon, TNF, IL

Pathogenesis

- Healthy adults (nonasthmatic) can frequently have abnormal PFTs in uncomplicated influenza
  - Diminished forced flow, increased pulmonary resistance, increased resistance of small airways
  - PFT abnormalities may persist for weeks following clinical recovery
- Primary viral pneumonia may occur in severe influenza
- Bacterial superinfection is a significant cause of morbidity/mortality

Presentation

- Abrupt onset of symptoms 1-2 days after exposure
- Systemic symptoms –
  - Fever, shaking chills, headaches, myalgias, anorexia, malaise
  - Cough, pharyngeal pain, sinus/nasal congestion also present but initially overshadowed by systemic symptoms
- Fever, systemic symptoms usually persist for 3 days (up to 8)
- Convalescent period of 1-2 weeks + of cough, malaise
- Attack rates higher in children
- Fever, lymphadenopathy higher in children
- Pulmonary complications higher in adults

	PRIMARY VIRAL PNEUMONIA	SECONDARY BACTERIAL PNEUMONIA	MIXED VIRAL AND BACTERIAL PNEUMONIA	LOCALIZED VIRAL PNEUMONIA
Setting	Cardiovascular disease; pregnancy; young adult (pH1N1)	Adults and children	Any associated with A or B	?Normal
Clinical history	Relentless progression from classic 3-day influenza	Improvement, then worsening after 3-day influenza	Features of both primary and secondary pneumonia	Continuation of classic 3-day syndrome
Physical examination	Bilateral findings, no consolidation	Consolidation	Consolidation	Area of rales
Sputum bacteriology	Normal flora	*Pneumococcus, Staphylococcus, Haemophilus influenzae*	*Pneumococcus, Staphylococcus H. influenzae*	Normal flora
Chest radiography	Bilateral findings	Consolidation	Consolidation	Segmental infiltrate
Detection of influenza virus	Yes	Not always	Yes	Yes
Response to antibiotics	No	Yes	Often	No
Mortality	High	Variable	Variable	Very low

Non Pulmonary Complications

- Myositis with myoglobinuria
- Myocarditis, pericarditis
- Toxic shock syndrome
- CNS complications
  - Guillain-Barre Syndrome
  - Encephalitis
  - Transverse myelitis
  - Reye syndrome in children

Diagnosis

- Clinical diagnosis is #1
- Consider influenza during the flu season with fever, respiratory symptoms regardless of vaccination status
  - Clinical diagnosis up to 80-90% in a local area during an outbreak
- Diagnostic tests:
  - Rapid screen – results in 30 minutes
    - Respiratory secretion + mucolytic, reaction with Ab results in color change
    - Up to 70-90% Se in children, <40-60% Se in adults
    - More accurate early in illness when viral shedding higher
    - Sp 90-95%, false positives when community prevalence is low
  - RT-PCR – results 2-4 hours
    - Most sensitive test
    - Combined to detect other viral pathogens in many cases
    - Sensitivity depends on lab, sample sent
    - False negatives – from nasopharyngeal swab – lower respiratory samples still positive

Diagnosis

- Who should we test???

Table 2. Persons who should be tested for influenza.

During influenza season, testing should occur in the following persons if the result will influence clinical management
Outpatient immunocompetent persons of any age at high risk of developing complications of influenza (e.g., hospitalization or death) presenting with acute febrile respiratory symptoms, within 5 days after illness onset, when virus is usually being shed
Outpatient immunocompromised persons of any age presenting with febrile respiratory symptoms, irrespective of time since illness onset, because immunocompromised persons can shed influenza viruses for weeks to months
Hospitalized persons of any age (immunocompetent or immunocompromised) with fever and respiratory symptoms, including those with a diagnosis of community-acquired pneumonia, irrespective of time since illness onset
Elderly persons and infants presenting with suspected sepsis or fever of unknown origin, irrespective of time since illness onset
Children with fever and respiratory symptoms presenting for medical evaluation, irrespective of time since illness onset
Persons of any age who develop fever and respiratory symptoms after hospital admission, irrespective of time since illness onset
Immunocompetent persons with acute febrile respiratory symptoms who are not at high risk of developing complications secondary to influenza infection may be tested for purposes of obtaining local surveillance data
At any time of the year, testing should occur for the following persons
Health care personnel, residents, or visitors in an institution experiencing an influenza outbreak who present with febrile respiratory symptoms, within 5 days after illness onset
Persons who are epidemiologically linked to an influenza outbreak (e.g., household and close contacts of persons with suspected influenza, returned travelers from countries where influenza viruses may be circulating, participants in international mass gatherings, and cruise ship passengers), who present within 5 days after illness onset

Harper et al. Seasonal Influenza in Adults and Children – Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America. *CID.* 2009:48 (15 April).

Diagnosis

- A 60 year old male with PMHx significant for DM, HTN and cigarette smoking (30+ pack year) presents in March with fever, myalgias and shortness of breath for 3 days that started suddenly. He is hypoxic on room air with O2 sats of 85%. Initial workup reveals WBC 13.5K, Cr 1.7. CXR shows b/l interstitial opacities without consolidation. Rapid flu screen is negative. Nasopharyngeal swab is negative. On hospital day 1 his hypoxia worsens and he is transferred to the ICU where he is intubated. What diagnostic test should be ordered next to diagnose his respiratory condition?
  - A: Blood cultures
  - B: Procalcitonin
  - C: Repeat nasopharyngeal swab for respiratory pcr
  - D: BAL for respiratory pcr

Treatment

- Who should we treat???
  - Persons with lab confirmed or highly suspected influenza with high risk of developing complications within 48 hours of symptom onset
    - Fewer data available to make recommendations regarding treatment of persons >48 hours after symptom onset
    - Treat regardless of vaccination status or severity of illness
  - Persons requiring hospitalization for lab confirmed or highly suspected influenza illness, regardless of vaccination status within 48 hours of symptom onset. However, persons whose + lab test is obtained after 48 hours of symptom onset may also benefit from treatment
  - Outpatients at high risk of complication with symptoms >48 hours
  - Outpatients with symptoms <48 hours who wish to shorten illness duration or reduce risk of complications or are in close contact with those who would have high risks of complications

Treatment

Table 3. Persons at high risk of complications from influenza who should be considered for antiviral therapy.

Unvaccinated infants aged 12–24 months
Persons with asthma or other chronic pulmonary diseases, such as cystic fibrosis in children or chronic obstructive pulmonary disease in adults
Persons with hemodynamically significant cardiac disease
Persons who have immunosuppressive disorders or who are receiving immunosuppressive therapy
HIV-infected persons
Persons with sickle cell anemia and other hemoglobinopathies
Persons with diseases that requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease
Persons with chronic renal dysfunction
Persons with cancer
Persons with chronic metabolic disease, such as diabetes mellitus
Persons with neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions
Adults aged >65 years
Residents of any age of nursing homes or other long-term care institutions

NOTE. Although sufficient data do not exist to precisely define the extent of increased risk of influenza in these different groups of patients, there are data to suggest that the highest risk of both mortality and serious morbidity (e.g., hospitalization) occurs for severely immunocompromised patients (e.g., hematopoietic stem cell transplant patients) and very elderly (age, >85 years) residents of nursing homes; infants aged <24 months also have high hospitalization rates but lower case-fatality rates than do the other 2 groups. Data are from [3, 5].

Harper et al. Seasonal Influenza in Adults and Children – Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America. *CID.* 2009:48 (15 April).

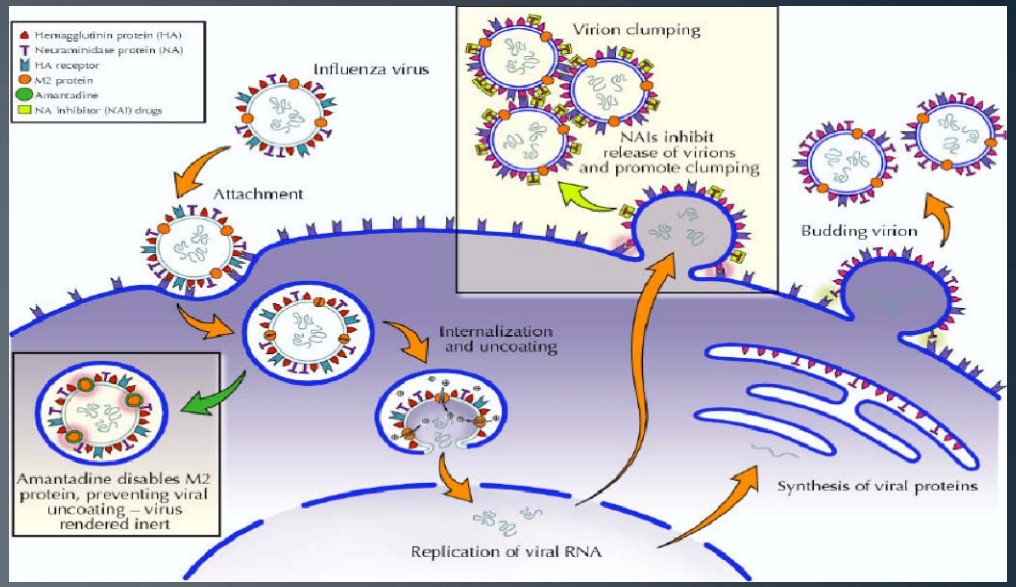
Treatment

TABLE 167-6 Antiviral Agents for Influenza

	AMANTADINE*	RIMANTADINE*	ZANAMIVIR	OSELTAMIVIR	PERAMIVIR
Protein target	M2	M2	Neuraminidase	Neuraminidase	Neuraminidase
Activity	A only	A only	A and B	A and B	A and B
Side effects	CNS (13%)	GI (6%)	? Bronchospasm	GI (9%)	GI (8%)
	GI (3%)	GI (3%)			
Metabolism	None	Multiple (hepatic)	None	Hepatic	None
Excretion	Renal	Renal + others	Renal	Renal (tubular secretion)	Renal
Drug interactions	Antihistamines, anticholinergics	None	None	Probenecid (increased levels of oseltamivir)	
Dose adjustments needed	≥65 yr old	≥65 yr old	None	CrCl <30 mL/min	CrCl <50 mL/min
	CrCl <50 mL/min	CrCl <10 mL/min		Severe liver dysfunction	
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airways disease		
FDA-Approved Indications					
Therapy	Adults and children aged ≥1 yr	Adults only	Adults and children aged ≥7 yr	Adults and children aged ≥2 wk	Adults who can't take oral or inhaled medications
Prophylaxis	Yes	Yes	Adults and children aged ≥5 yr	Adults and children aged ≥1 yr	

Treatment

- M2 Inhibitors – Amantadine, Rimantadine
  - Not used because of widespread resistance
  - Inhibits M2 ion channel, acidifies interior of virus, which inhibits viral uncoating
  - Only active against influenza A
- Neuraminidase Inhibitors – Zanamivir, Osteltamivir, Peramivir
  - Inhibits viral neuraminidase (blocks cleaving of sialic acid from glycoproteins)
  - New virus remains attached to host cell and other virions
  - May decrease virus ability to penetrate respirator tract secretions



Silver, G. (2003) The treatment of influenza with antiviral drugs. Canadian Medical Association Journal 168 (1), 49–57.

Treatment

TABLE 167-7 Antiviral Chemotherapy and Chemoprophylaxis for Influenza

INFECTION	DRUG	ROUTE	DOSAGE
Influenza A and B: treatment	Oseltamivir	Oral	Adults: 75 mg bid × 5 days Children aged 1-12 years: 30-75 mg bid, depending on weight†, × 5 days
	Zanamivir	Inhaled orally	Adults and children aged ≥7 yr: 10 mg bid × 5 days
	Peramivir	Intravenous	Adults (≥18 years of age) who cannot take oral or inhaled drugs one dose of 600mg IV
Influenza A: treatment	Amantadine*	Oral	Adults: 100 mg qd or bid × 5-7 days Children aged 1-9 yr: 5 mg/kg/day (maximum, 150 mg/day) × 5-7 days
	Rimantadine*	Oral	100 mg qd or bid × 5-7 days in adults
Influenza A and B: prophylaxis	Oseltamivir	Oral	Adults: 75 mg/day Children aged ≥1 yr: 30-75 mg/day, depending on weight†
	Zanamivir	Inhaled orally	Adults and children aged ≥5 yr: 10 mg/day
Influenza A: prophylaxis	Amantadine* or rimantadine*	Oral	Adults: 200 mg/day Children aged 1-9 yr: 5 mg/kg/day (maximum, 150 mg/day)

Treatment

- An 82 year old female resident of an assisted living facility is admitted to the hospital with acute Influenza A in early October. You are the director of the assisted living facility and have not yet completed flu vaccinations for your residents. Which of the following actions should you take?
  - A: Tell all of your residents to wash their hands and avoid sick contacts
  - B: Vaccinate your residents with the seasonal influenza vaccine
  - C: Start chemoprophylaxis with oseltamivir 75mg/day x14 days and vaccinate them
  - D: Start treatment with oseltamivir 75mg BID x5 days and vaccinate them

Vaccination

- Recommended for 6 months and older
- Inactivate Influenza Vaccine - contain three strains – A/H3N2, A/H1N1, B virus
  - 2016-2017:
    - A/California/7/2009 (H1N1)pdm09-like virus
    - A/Hong Kong/4801/2014 (H3N2)-like virus
    - B/Brisbane/60/2008-like virus (B/Victoria lineage)
  - Serum antibody concentrations peak at 2-4 months but fall to baseline before 1 year
  - Efficacy around 60%
  - Decreased work, school absenteeism
- Live-Attenuated Influenza Vaccine
  - Available but currently not recommended due to inefficacy

Questions?

References

- 1. Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed.; Chapter 167: influenza (Including Avian Influenza and Swine Influenza). 2000 – 2024.
- 2. https://rybicki.wordpress.com/2012/09/10/a-brief-history-of-influenza/
- 3. http://nieman.harvard.edu/wp-content/uploads/pod-assets/microsites/NiemanGuideToCoveringPandemicFlu/AnIntroduction/InfluenzaAtAGlance.aspx.html

4. Enabling the 'host jump': structural determinants of receptor-binding specificity in influenza A viruses Yi Shi, Ying Wu, Wei Zhang, Jianxun Qi & George F. Gao *Nature Reviews Microbiology* 12, 822–831 (2014)

5. http://www.cdc.gov/flu/about/season/flu-season-2015-2016.htm

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