

# INFLUENZA

## Update

### Past, Present, Future

Kurt Wiese, MD

Grand Rounds, October 17, 2017



# Introduction

- **Hippocrates first described the symptoms of influenza in “Of the Epidemics” circa 400 B.C.**

- **Hirsch tabulated 299 outbreaks of illness from 1173 to 1875 thought to be influenza.**

Hirsch, A. (1883). *Handbook of geographical and historical pathology* (Vol. 1). New Sydenham Society.

- **The first clearly recognized influenza epidemic was in 1510.**

Morens, D. M., Taubenberger, J. K., Folkers, G. K., & Fauci, A. S. (2010). Pandemic influenza's 500th anniversary. *Clinical Infectious Diseases*, 51(12), 1442-1444.

The word *Virus* Comes from the  
Latin for “Poison”

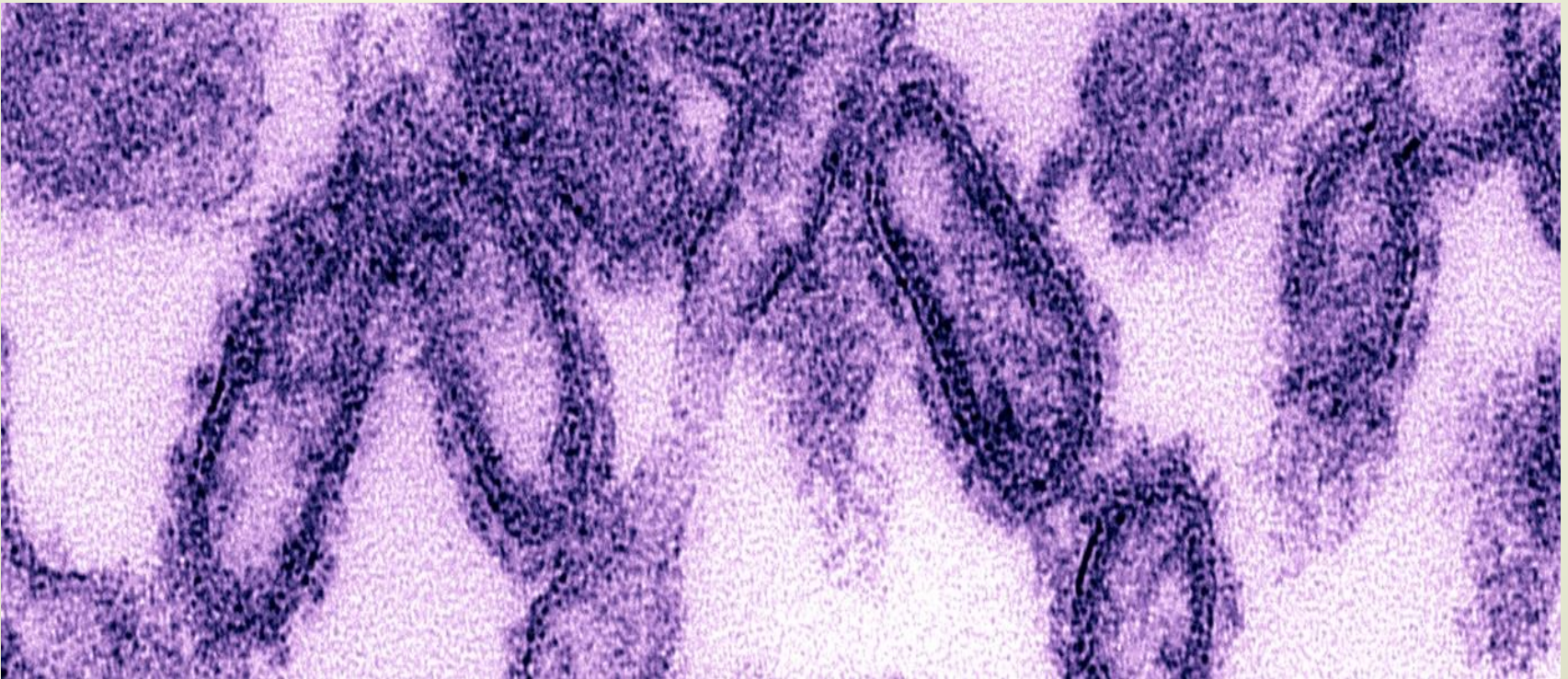


# *Where does the name Influenza come from?*

- **Influenza Celestial - “Heavenly influence” - (Italian/Latin, from the Middle Ages)**
- **Influenza del Freddo - “Influence of the cold” (Italian, from the 17-18<sup>th</sup> Centuries)**



How can something that is  $1/10,000^{\text{th}}$  of a millimeter be so deadly?



# Outline

- **Epidemiology**
- **Statistics, costs to society**
- **Clinical description**
- **Treatment options**
- **Molecular biology and pathophysiology**
- **Viral mutation: Drift and Shift**
- **History (espec. 1918-1919 worldwide pandemic)**
- **Birds, Swine, and Humans**
- **Immunology**
- **Influenza Vaccines**

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# Deadly Statistics

- **15-20 million cases per year in the USA**
- **100's of millions worldwide**
- **Estimated 500,000 deaths worldwide annually**
- **USA; 200-250,000 hospitalizations, and 30-40,000 deaths annually**  
**(About a 1/10,000 risk of death in the USA)**

# “Cost of Illness”

- 20% - medical costs
- 80% - non-medical, loss of productivity, etc.
- In the USA, estimated costs associated with influenza are \$10 Billion/year

(If a 1918-like virus reoccurred, the economic costs could be \$700 Billion and would drop the GDP by 5%).





# The “Spanish Flu” 1918-1919

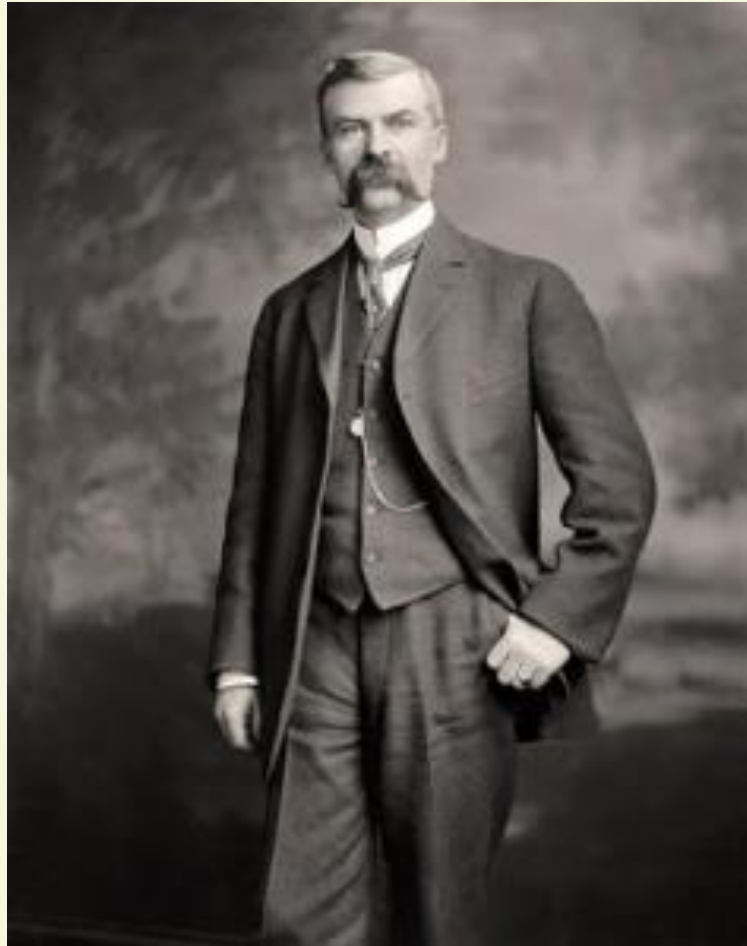
- WWI was raging in Europe
- Woodrow Wilson was President
- Viruses were not understood
- It was a record cold Winter



- Nothing was out of the ordinary until January and February (1918) in Haskell County, Kansas (just west of Dodge City).
- A sudden increase of severe influenza cases was noted, with a significant number of deaths.



# Loring Miner, MD



“His patients said they’d rather have him drunk than someone else sober.”

- He reported a large number cases which he called “influenza of severe type”.
- This was the only warning of any kind for the first 6 months of 1918.
- This was reported in “Public Health Reports” (which later became the MMWR).
- This was suggestive of a new virus adapting to humans.
- Veterinarians were noticing many cases of influenza in swine that year also.



- The next influenza outbreak was at Camp Funston at Fort Riley, Kansas (west of Topeka).
- Home to 56,000 troops at that time



- On March 4, 1918 a cook named Arthur Mitchell reported ill at sick call with “the flu.” (He had been serving soldiers in the mess hall the previous two days.)
- Within 3 weeks, > 1100 soldiers were hospitalized, and many more were very ill.
- “The timing of the Camp Funston explosion strongly suggests that the influenza outbreak there came from Haskell County.”
- Barry, J. M. (2005). *The Great Influenza: The story of the deadliest pandemic in history*. Penguin.



- Frank MacFarlane Burnet (Nobel Laureate) who lived through the pandemic and studied influenza most of his career, stated:

“The evidence was strongly suggestive that the 1918 pandemic began in the U.S. and that its’ spread was intimately related to war conditions, and especially to the arrival of American troops in France”.





# Biology of Influenza

- Influenza:
  - A – Fowl, Swine, Humans
  - B – Humans, Ferrets, Seals, Whales
  - C – Humans, Swine, Canines
  - D – Cattle

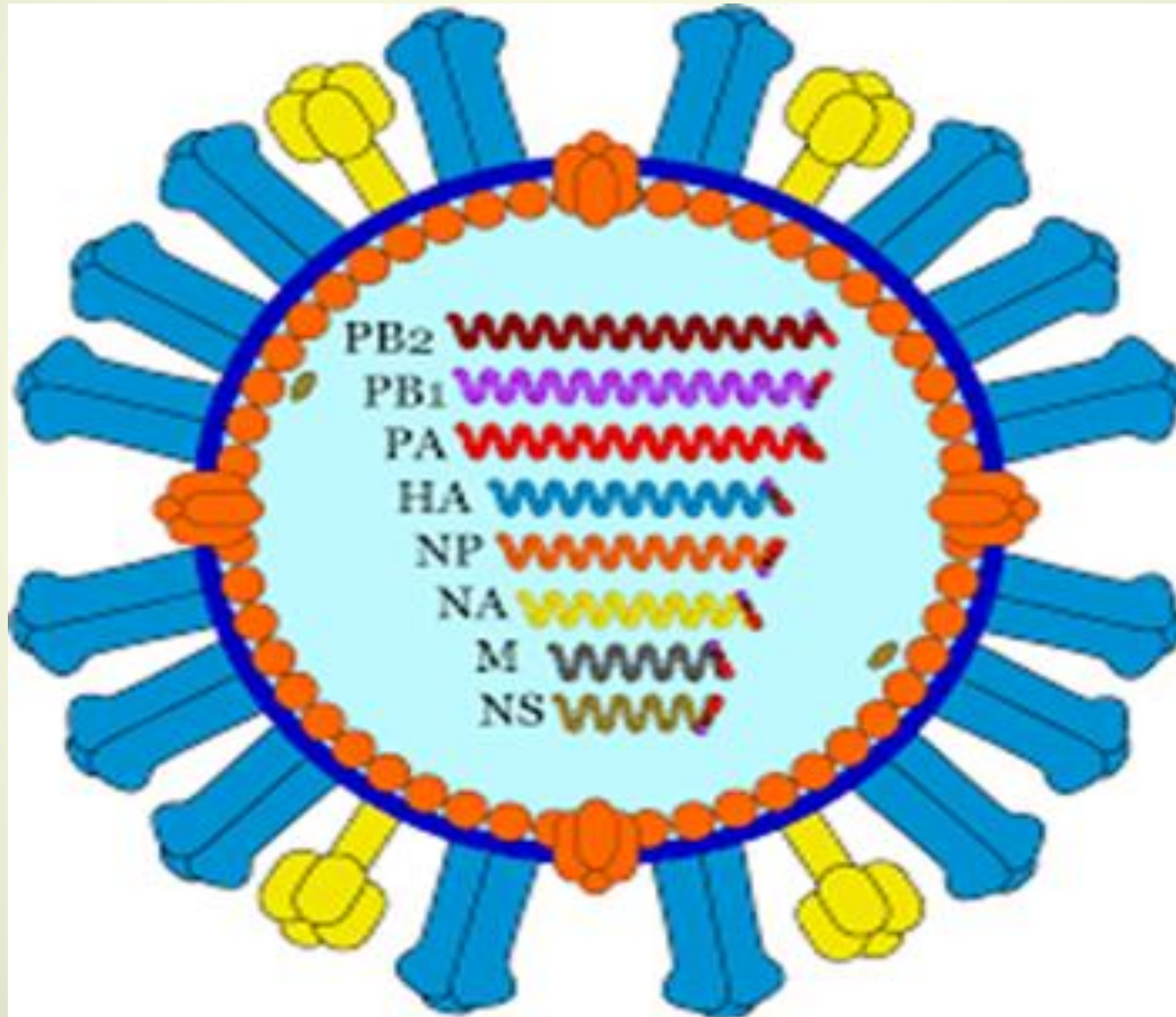
There are many other animal species susceptible to influenza with other strains of the virus.

- The natural hosts for **Influenza A** are birds.
- Therefore, all Influenza A is or has been “Bird Flu” or “Avian Influenza” at one time.



- It reproduces primarily in their GI tract, and to a lesser degree in their respiratory tract.

# Molecular Biology



# Influenza A Genetics

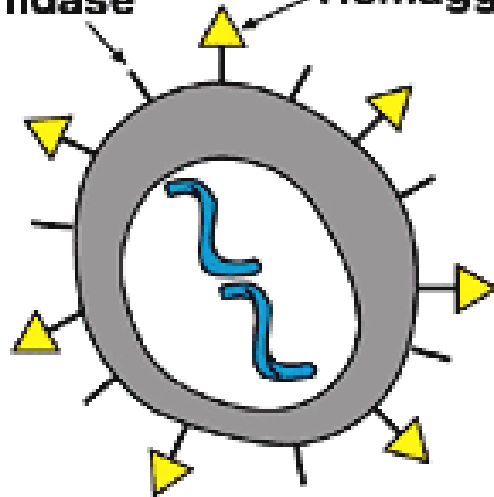
- RNA Virus, with only 11 genes
- Mutates frequently
- Mutation rates:  
RNA Virus > DNA virus > bacteria
- Influenza A lacks a proofreading enzyme, and mutations occur at about 1/10,000 bases, which is approximately the length of the Influenza genome.
- Thus, just about every virus has at least one mutation.
- “Mutant Swarm”



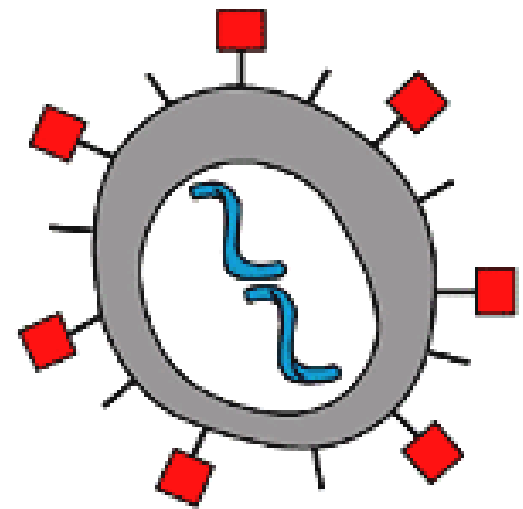
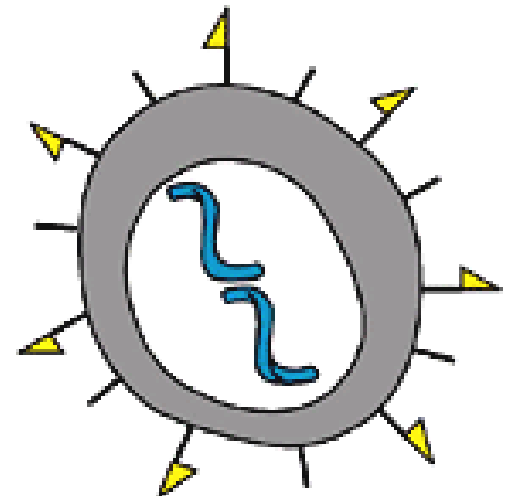
# Viral Mutation

- Leads to a variable virulence
- Highly adaptable
- Influenza A can occasionally cross species, if further reassortment occurs  
(e.g. the 2009 H1N1 pandemic came from a triple reassortment of avian, swine, and human influenzas)
- Antigenic drift
- Antigenic shift
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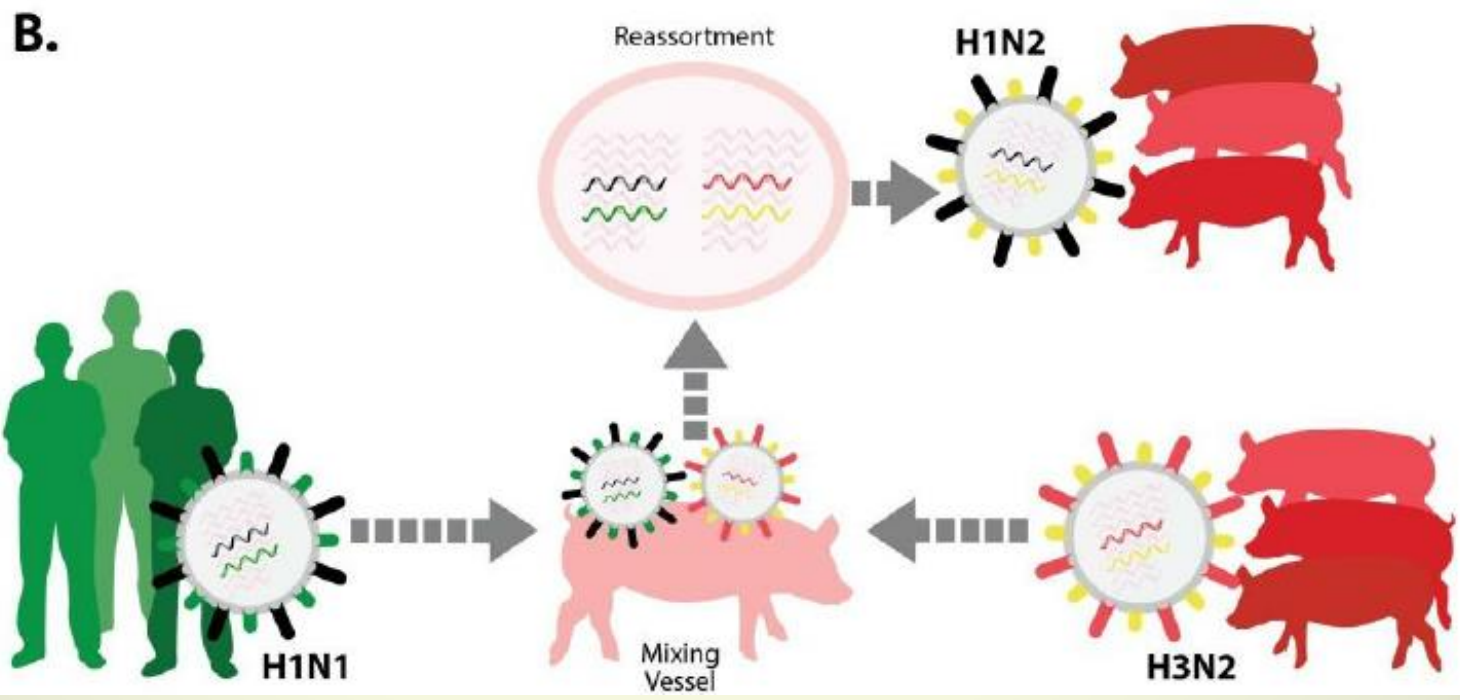
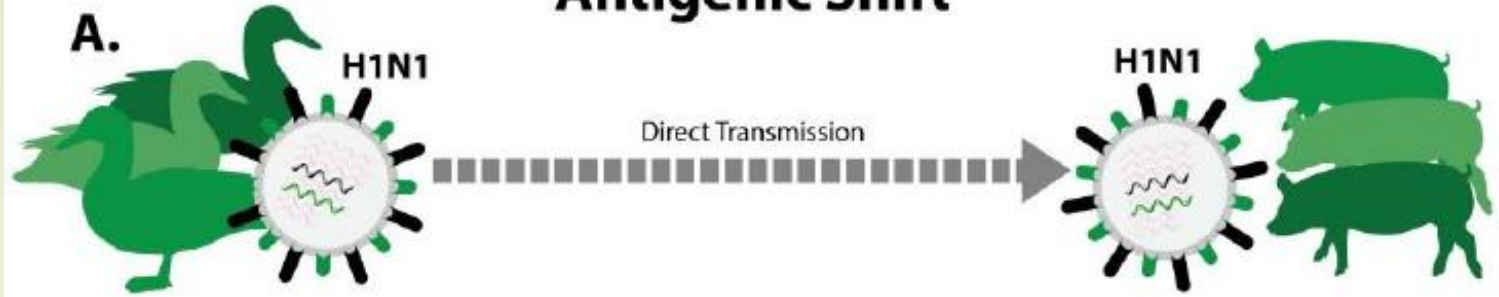
Neuraminidase Hemagglutinin

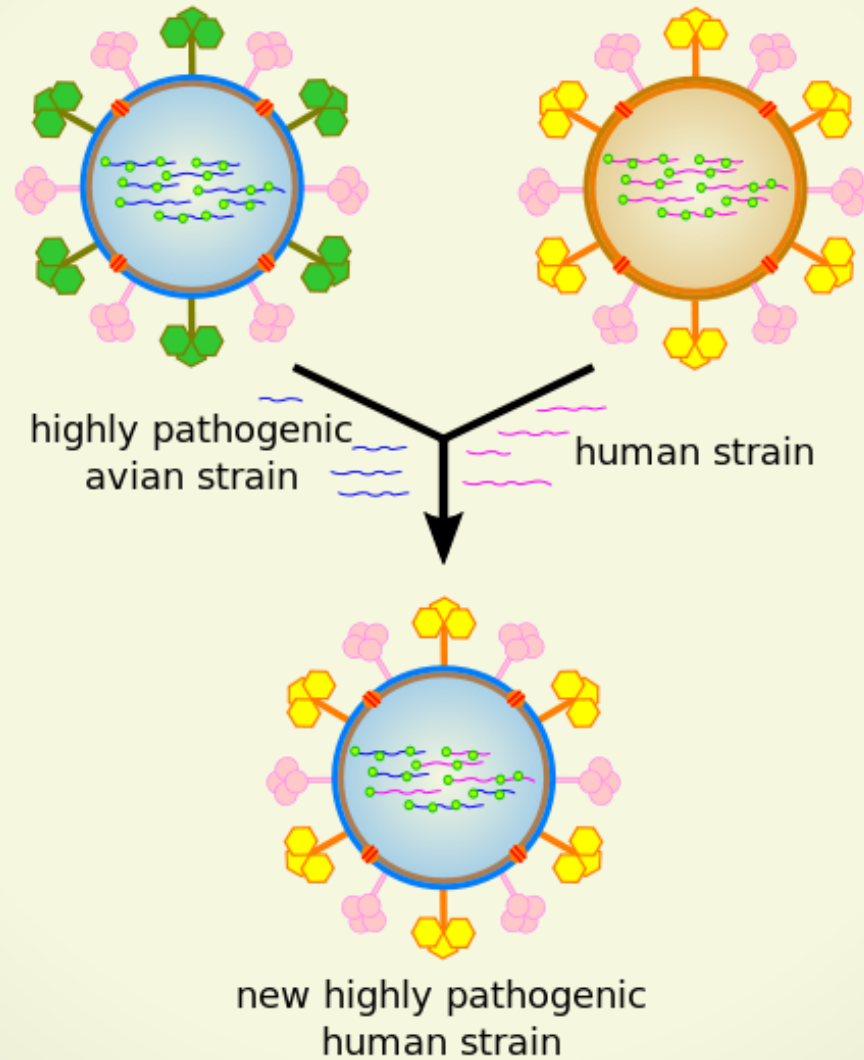


Influenza Virus

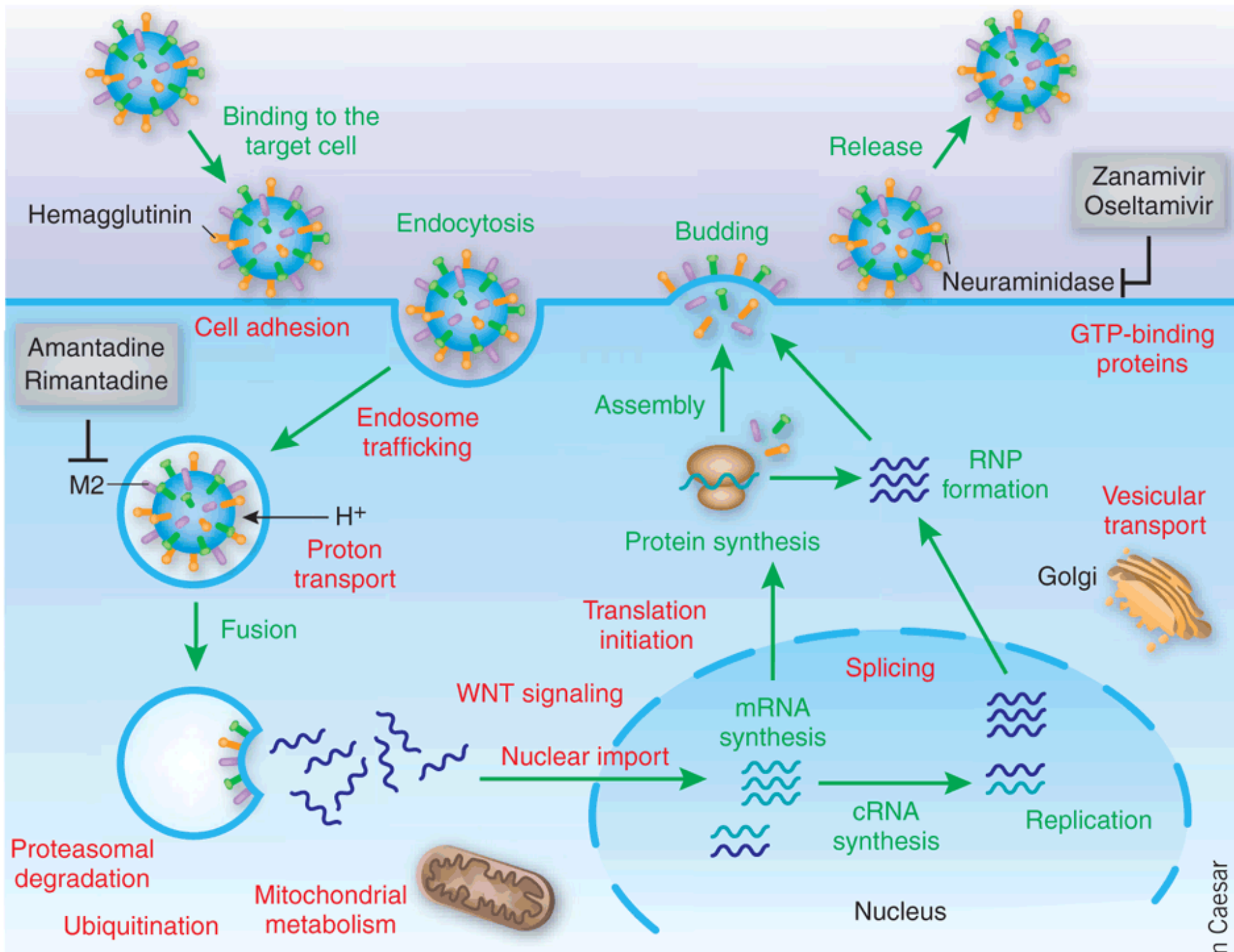


# Antigenic Shift









- Influenza A can only reproduce in the respiratory tract in humans and swine. It reproduces primarily in the GI tract of birds.



- It can infect WBCs but it cannot reproduce in them. It just kills those cells. This explains the low WBC count seen in an acute infection.

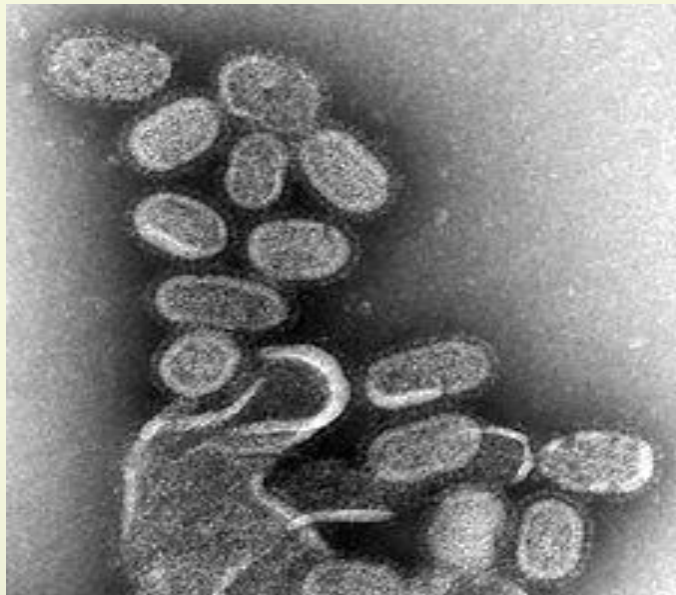
- So, if influenza only multiplies in our respiratory tract, why is it such a systemic illness?
- We all recognize a case of influenza: high fever, headache, myalgias, arthralgias, everything-algia, dry cough, sore throat, confusion, anorexia, malaise, etc.
- “Doc, I feel awful.”



- They look bad, sound bad, appear toxic, often dehydrated, weak, irritable, etc.
- These patients are sick all over, it's not just a respiratory illness.

# Why the illness has systemic symptoms

- Influenza kills WBCs – endogenous pyrogens released
- Potent inducer of cytokines: Interferon, Interleukin, TNF, and others
- Rapidly multiplies (9-10 hours per cycle)



# The Spanish Flu Pandemic of 1918

Killed more people than any other disease in history

Caused more deaths than WWI, WWII, the Korean War, and the Vietnam War combined

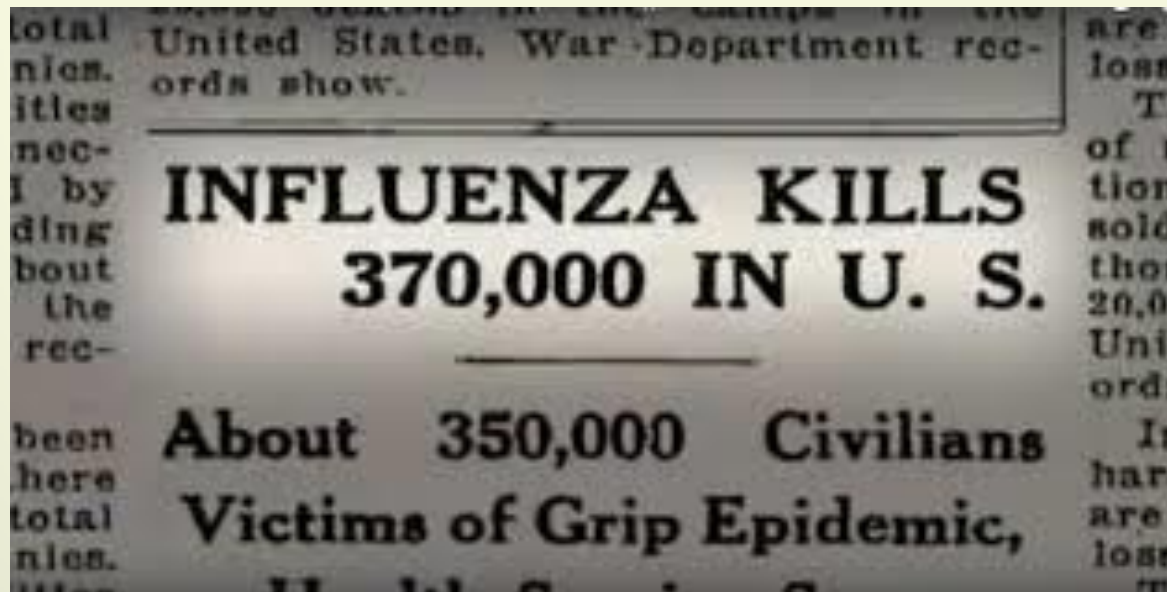
Unusually high attack rates among young and otherwise healthy adults (soldiers)



Doughboys - 1918  
[Info.detnews.com](http://Info.detnews.com)

# 1918-1919 Pandemic

- H1N1 Influenza A
- Avian origin
- The greatest pandemic in history
- Estimated > 50 million people died worldwide  
(More in 1 year than the Bubonic Plague killed in over 100 years)



# Why was the 1918 Influenza so bad?

- Double antigenic shift; both the HA and NA changed (the previous virus had been H3N8)
- Lack of immunity in the younger population; 99% of illness/deaths < 65 years old
- Highly virulent strain, multiplied more rapidly than others. Its genome has been duplicated in the laboratory. In animal models, the recreated virus produced 40,000 times more virions than the currently circulating virus does.
- People had a poor understanding of infectious diseases.
- It was 1918 – the status of medical care was not what it is today.
- All infectious disease was frightening at that time.



# Why the “Spanish Flu”?

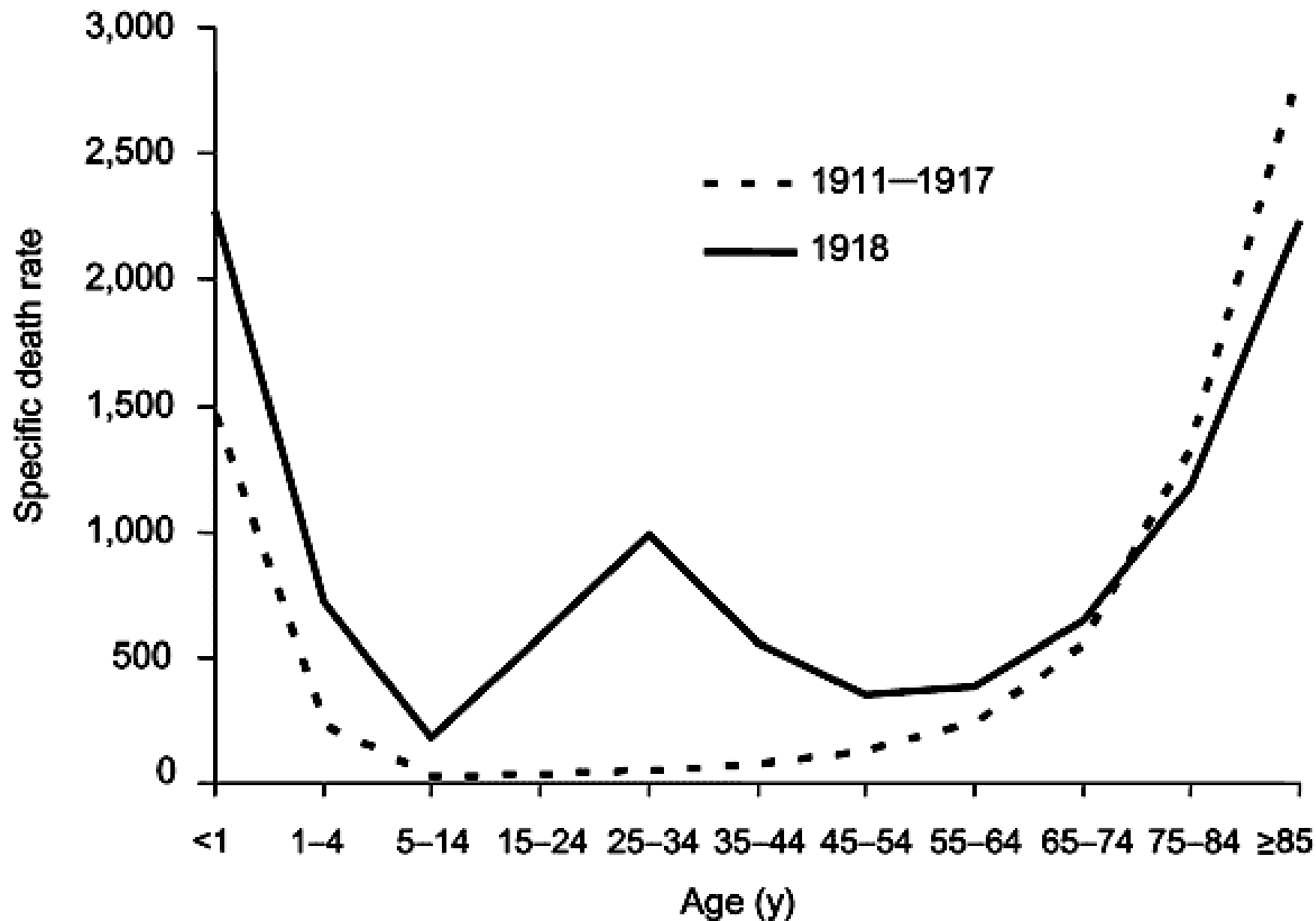
- WWI
- Newspapers were instructed to report nothing negative; bad news was downplayed to maintain morale.
- Spain was neutral; their press was free to report on the war and the epidemic and they did so, especially when King Alphonse XIII became seriously ill with the flu in May, 1918.





# 1918-1919

- 99% of all deaths were in people < 65 years old
- > 50% of mortalities were between ages 20-40
- An estimated 3-5% of the world population died.
- Sir William Osler caught the flu in October 1919, developed pneumonia, then empyema, and ultimately died Dec. 29, 1919.
  - “I’ve been watching this case for two months and I’m sorry I shall not see the post mortem”.
- “Encephalitis lethargica” was seen in the 1920’s and 30’s.
  - We now recognize this as post-influenza asthenia.



# Transmission

- Large particles – sneeze or cough
  - 30-40,000 particles/sneeze
  - 500,000 virions/sneeze
- Small particle – aerosol (can remain suspended in air)
- Direct contact – hand to face
- Influenza survives:
  - On hard surfaces = 1-2 days
  - If mucus is present = 2 weeks
  - On human skin = 5 minutes
  - If frozen = indefinitely

# Viral Shedding

- **Begins 12 hours after infection**
- **Peaks on Day 2 after infection**
- **Symptoms usually start on day 3**
- **Shedding continues for 5-7 days**
- **Studies in volunteers**
- **33% were asymptomatic**
- **What does this mean?**



Wellcome Images

- Carrat, F, et al. (2008). Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *American Journal of Epidemiology*, 167(7), 775-785.

# Why is Influenza Seasonal?

- Northern Hemisphere: October – April
- Southern Hemisphere: May – September
- Tropics: Year round
- Theories:
  - Airborne survivability
  - Cooler temperature, lower humidity = increased survival
  - UV light?
  - Vitamin D levels?
  - Behavioral ?
  - Crowding?

*We don't really know.*

# Testing for Influenza

- Rapid Antigen test averages 65% sensitivity (range 50-90%)
- The PCR test is 98 – 99% sensitive (expensive)
- Viral culture – 100%
- Remember, it's a clinical diagnosis.

(Loring Miner did not need a nasopharyngeal swab to diagnose the flu in 1918).



# Vaccines

- ACIP and CDC recommend vaccination for everybody over 6 months old
- 3 main ones: IIV3 (trivalent) - H1, H3, Bv  
IIV3 (high dose – HD) - H1, H3, Bv  
IIV4 (quadrivalent) - H1, H3, Bv, Bv
- Others: recombinant, adjuvant, egg free, LAIV (LAIV is not recommended this year)



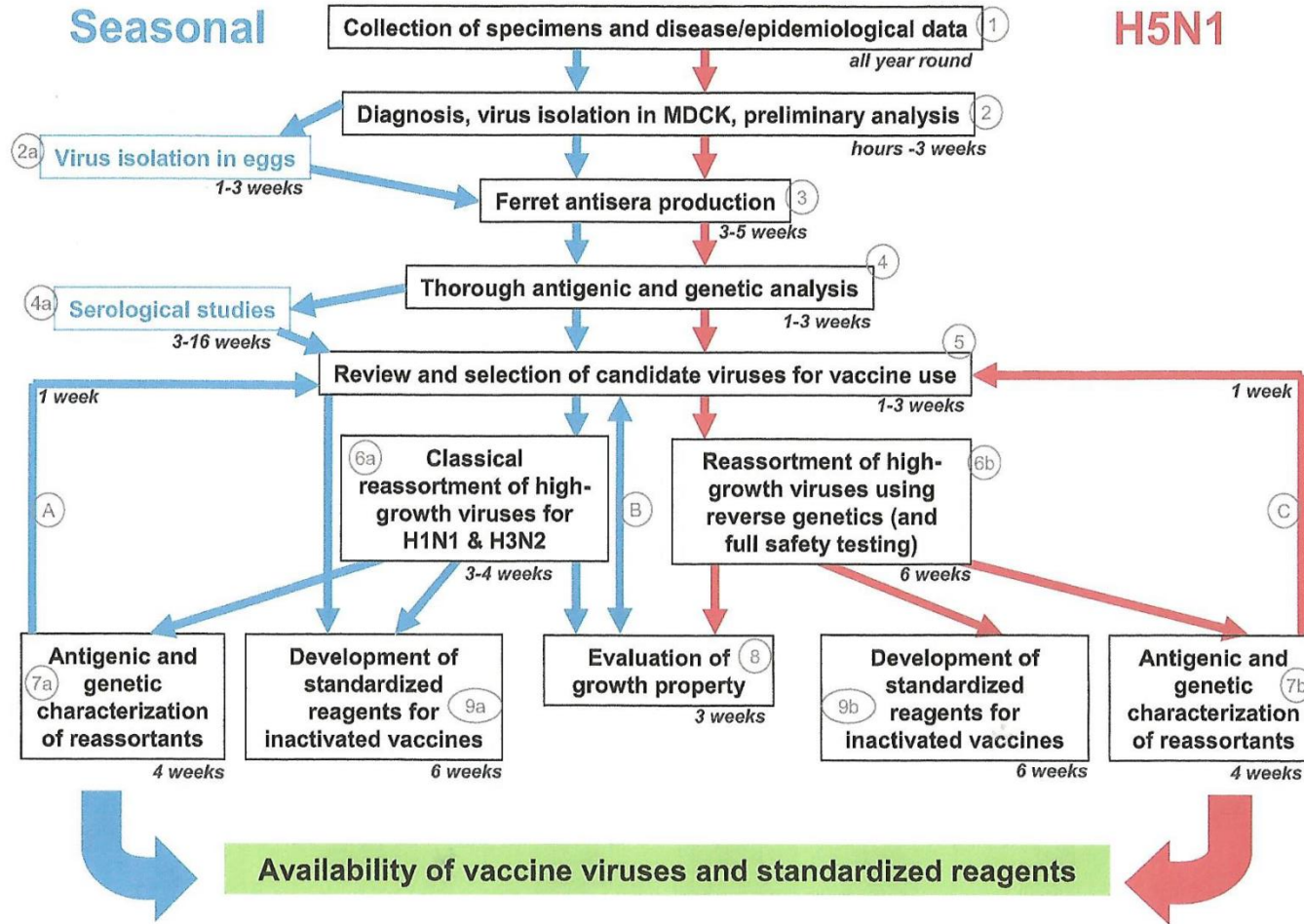
# Vaccines

- Annual effectiveness ranges from 10-70%
- How are the target viruses selected?
  - WHO – worldwide surveillance
  - Strains are picked in February for the vaccine in the upcoming season
  - Which vaccine should you give a patient?
    - ACIP – no preference
    - CDC – no preference
    - Up to Date – give IIV3 high dose (HD) for > 65 years old (especially if on a statin)
    - “The availability of a specific vaccine is often the main determining factor”.

Treanor, J. (2016). Influenza vaccination, *New England Journal of Medicine*, 375, 1261-8.



# Process of influenza vaccine virus selection and development



CAUTION



# Influenza Vaccine Risks

- Local reactions range from 10-50% and generally resolve quickly
- Systemic symptoms from the vaccine are no higher than placebo – (multiple studies)

Nicholet, K.L. al. (1996). Side effects associated with influenza vaccination in healthy working adults: a randomized, placebo-controlled trial. *Archives of Internal Medicine*, 156(14), 1546-1550.

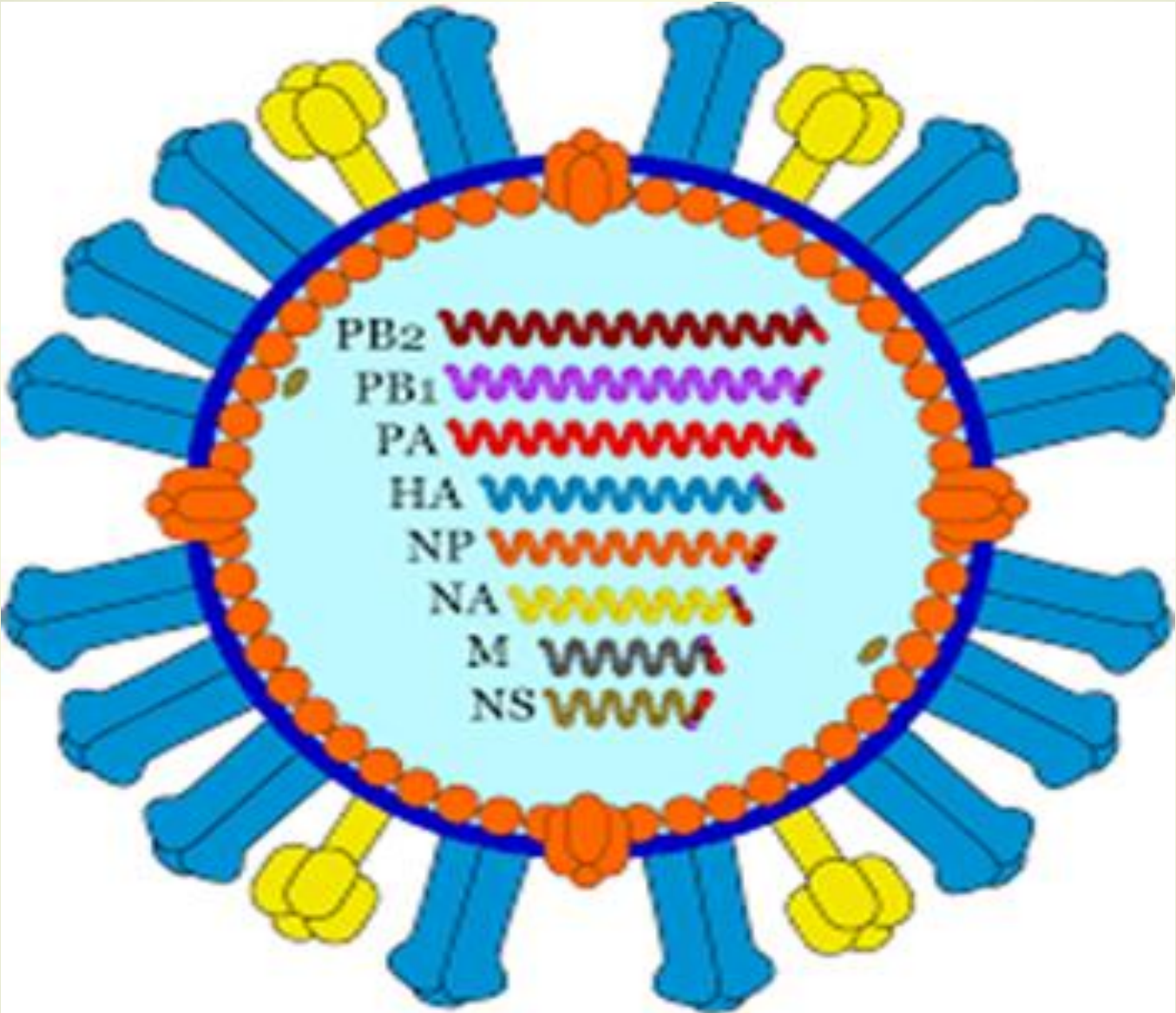
- Guillain Barré syndrome (GBS) risk approx. 1/1,000,000 vaccines

Lasky, et al. (1998). The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *New England Journal of Medicine*, 339(25), 1797-1802.

Vellozzi, C., et al. (2009). Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine*, 27(15), 2114-2120.

- In the USA, GBS incidence is 10-20/1,000,000 in the general population
- If you get influenza in the USA:
  - Death risk approx. 1/10,000
  - Additional GBS risk approx. 1/100,000

- Sivadon-Tardy, et al. (2009). Guillain-Barré syndrome and influenza virus infection. *Clinical Infectious Diseases*, 48(1), 48-56.



# Influenza Treatment

M2 Inhibitors: Amantadine, Rimantadine

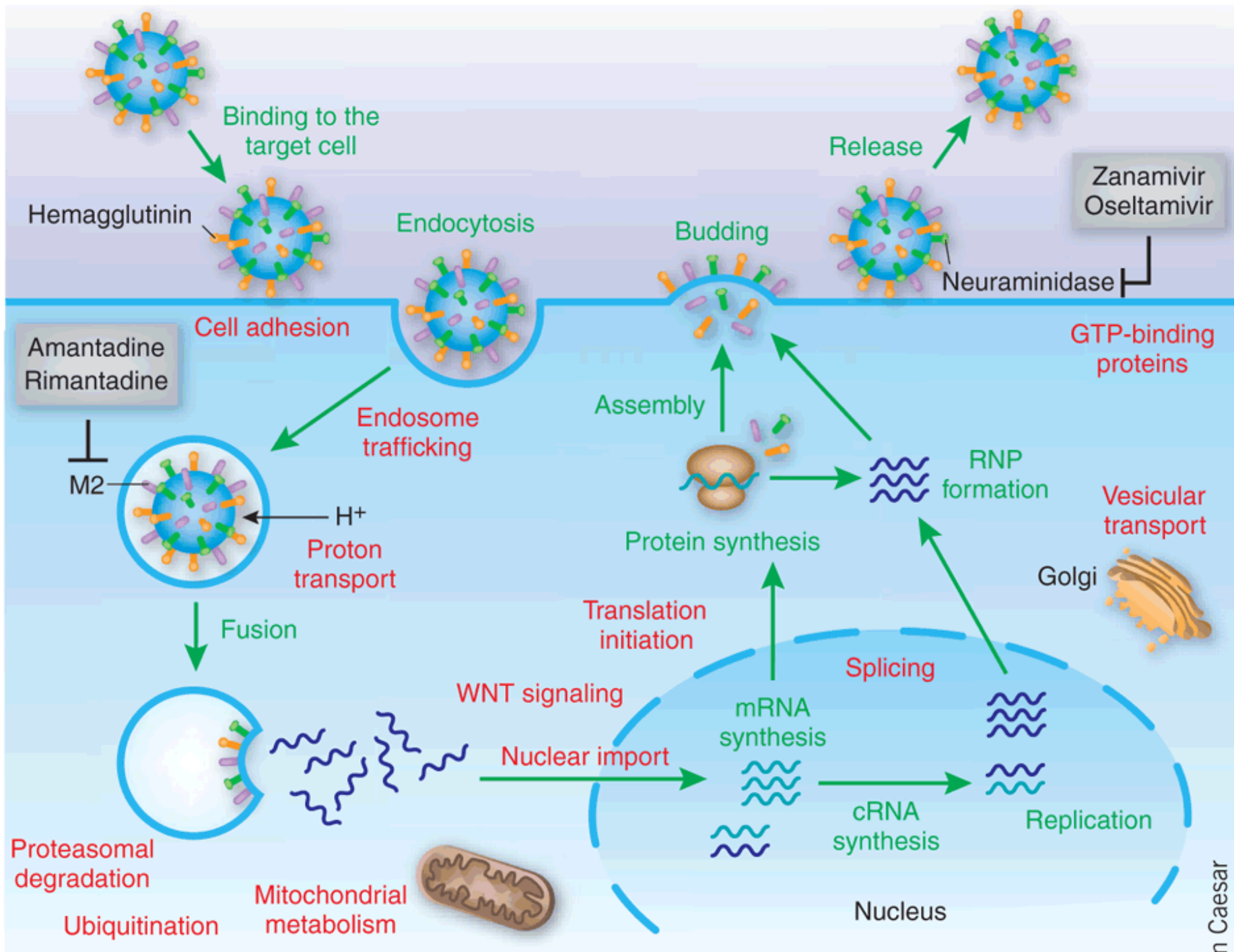
Inhibit viral uncoating (required to release the RNA)

- Amantadine –  
CNS side effects  
Accumulates if GFR is low
- Rimantadine – few side effects

Neuraminidase (NA) Inhibitors: Oseltamivir, Zanamivir

Similar efficacy, 5-day course

- Oseltamivir – po, few side effects
- Zanamivir – powder for inhalation  
potential for bronchospasm  
pt. must cooperate
- Peramivir (Rapivab) – IV only  
600 mg, single dose



# WHAT IF?

If an influenza strain with the equivalent virulence to 1918 happened today it would kill an estimated 50-90 million people worldwide.

Murray, C. et al. (2007). Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *The Lancet*, 368(9554), 2211-2218.



No wonder the WHO has influenza as a top priority.

- The 1918 strain of Influenza A is only 8 amino acids different from the currently circulating H1N1 Influenza.





**“Characterization of the reconstructed 1918 Spanish influenza pandemic virus.”**

**Tumpey, et al. *Science* 2005; 310 (5745): 77**

- **Used reverse genetics to generate the virus**
- **High growth phenotype**
- **High virulence phenotype**
- **Caused death in mice and embryonated chicken eggs (other influenza strains don't)**

**“It’s always 1918 at the  
CDC”**



**“Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors”,  
Yu, et al. *Nature* 2008; 455 (7212): 532.**

- Found 32 individuals born before 1915
- Had antibodies against the 1918 influenza strain
- Their serum protected mice from lethal infection

# Other Influenzas (A) of Note

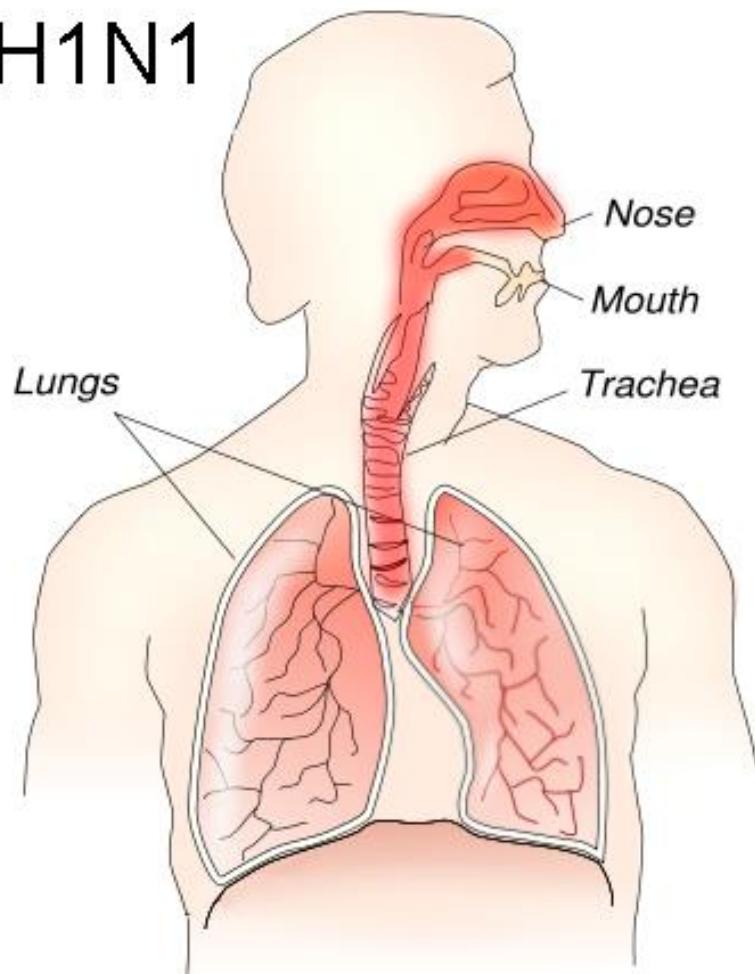
- H1N1 and H3N2 are currently circulating in humans.
- H5N1 – Avian flu (Bird flu) is endemic in birds around the world now, but has not adapted to transmission in humans yet. In cases from Vietnam and Hong Kong, it only occurred in those exposed to dead or dying poultry.
- H9N2 – less common, (more virulent to birds)
- H7N9 – occurred in China in 2013 (20 cases)
- H3N2 – August 2016 in the USA - all associated with swine exposure at livestock fairs; 18 cases: Michigan 12, Ohio 6 (none transmitted human to human)



# Chinese Chicken Market

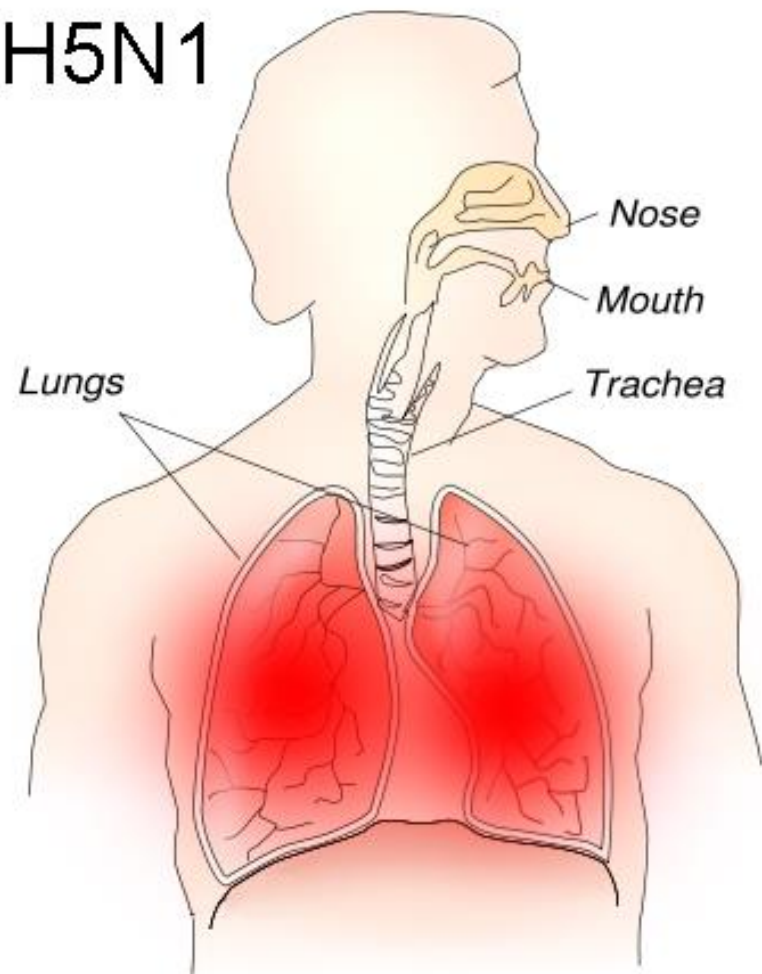


# H1N1



**Easily spread**  
**Rarely fatal**

# H5N1



**Spreads slowly**  
**Often fatal**

