

# All about Flu: The Virus & the Vaccine

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The University of Vermont  
LARNER COLLEGE OF MEDICINE

# Disclosures

- I have no conflicts of interest to disclose

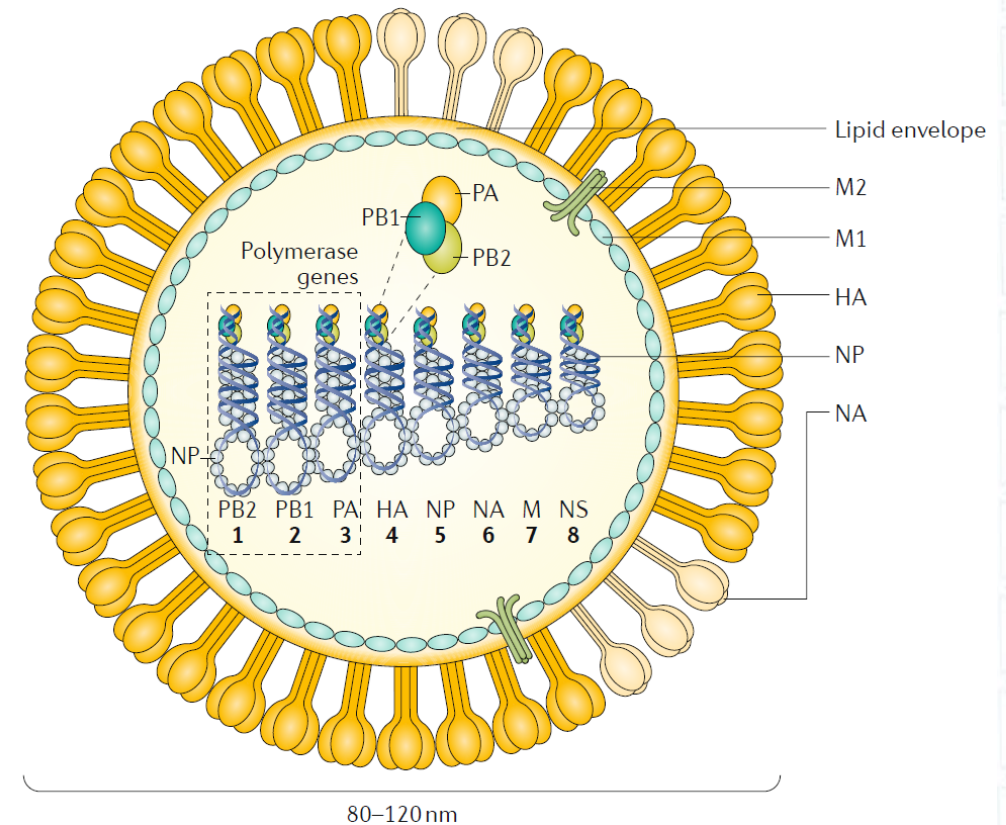


# Objectives

- Gain working knowledge of influenza virus
  - Virology
  - Epidemiology
  - Signs, symptoms, and complications
  - Pandemic vs seasonal flu
- Understand the basics of influenza vaccination
  - Benefits and limitations
  - Current landscape
  - Future goals

# What is influenza?

- Influenza is a single stranded RNA virus
  - Segmented genome, 8 gene segments
- Two main types in humans
  - Influenza A
  - Influenza B



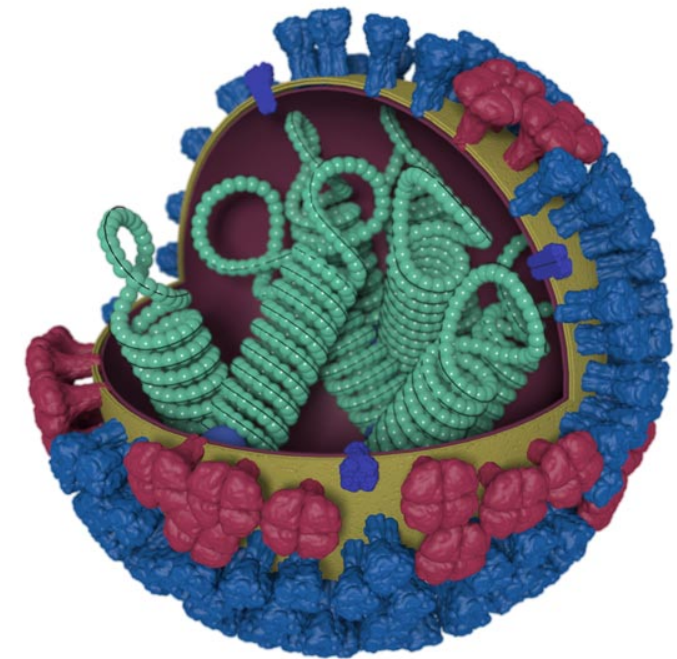
Krammer et al, Nature 2018.



# Influenza: simplified nomenclature

- Influenza A classified into subtypes
  - HA, hemagglutinin (H1 through H18)
  - NA, neuraminidase (N1 through N11)
  - Example: H1N1
- Two lineages of influenza B viruses
  - Yamagata
  - Victoria

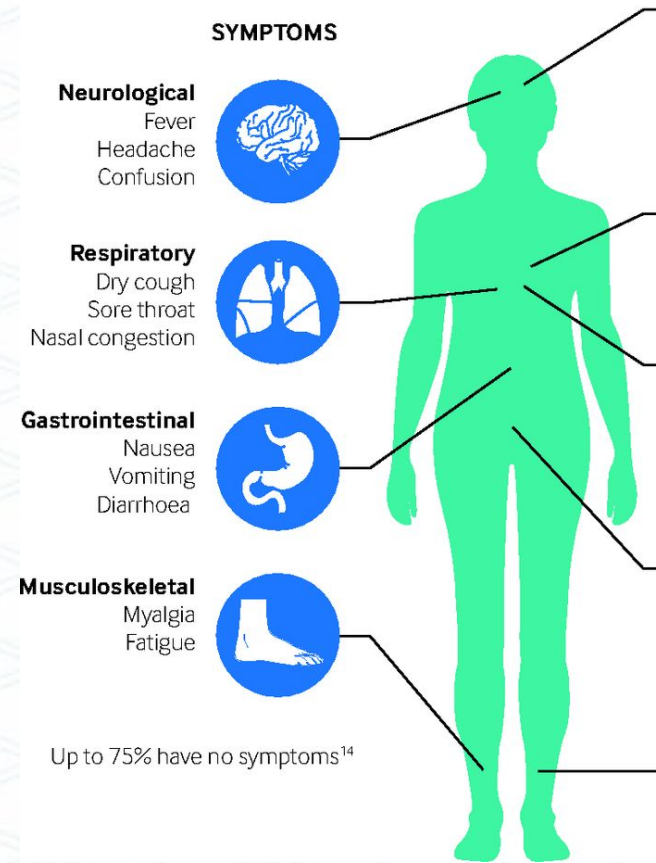
AN INFLUENZA VIRUS



<https://www.cdc.gov/flu/images/virus/fluvirus-antigenic-characterization-large.jpg>

# What does influenza do?

- Influenza causes seasonal respiratory infection and illness (i.e. “the flu”)





# Influenza symptoms

## Is it a cold or flu?



### 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



# WHO world-wide estimates

## Yearly seasonal influenza

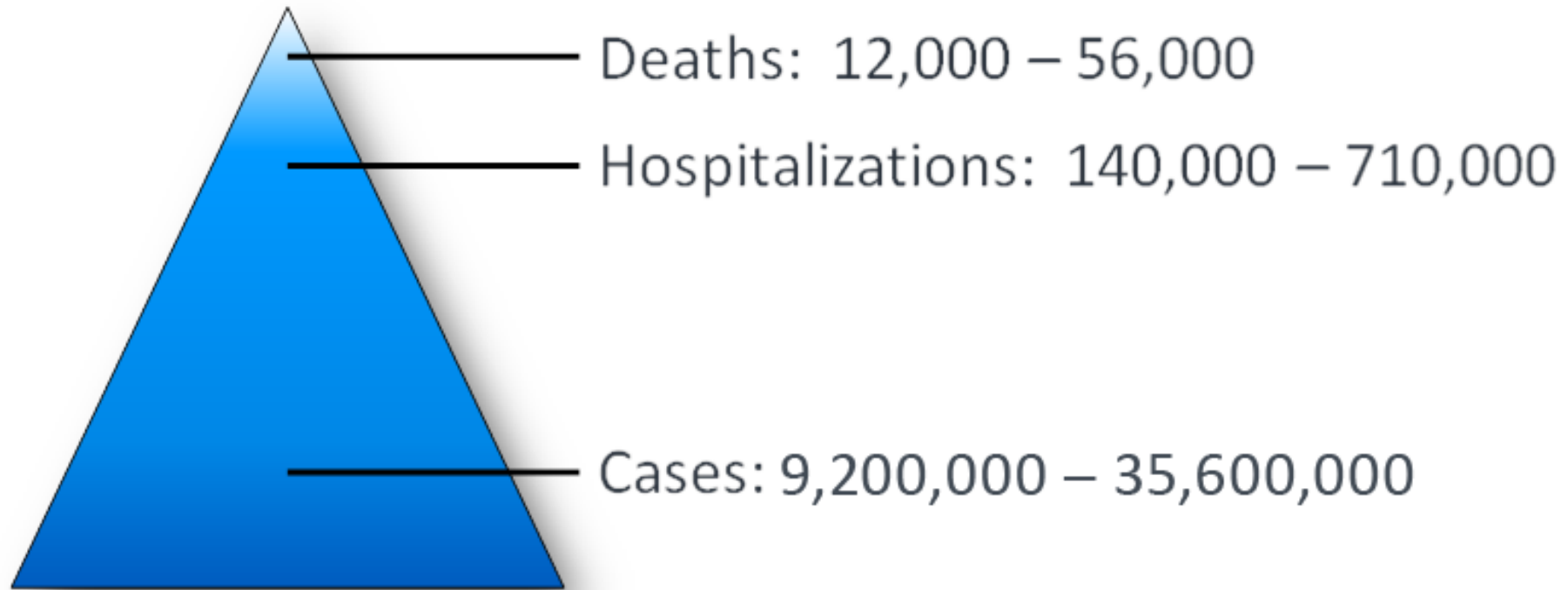
- ~1 billion infections
- ~5 million cases of severe illness
- ~290,000-650,000 deaths

## 2014-15 West Africa Ebola outbreak

- 28,616 cases
- 11,310 deaths



# CDC estimates of seasonal influenza burden in the US:



# Influenza

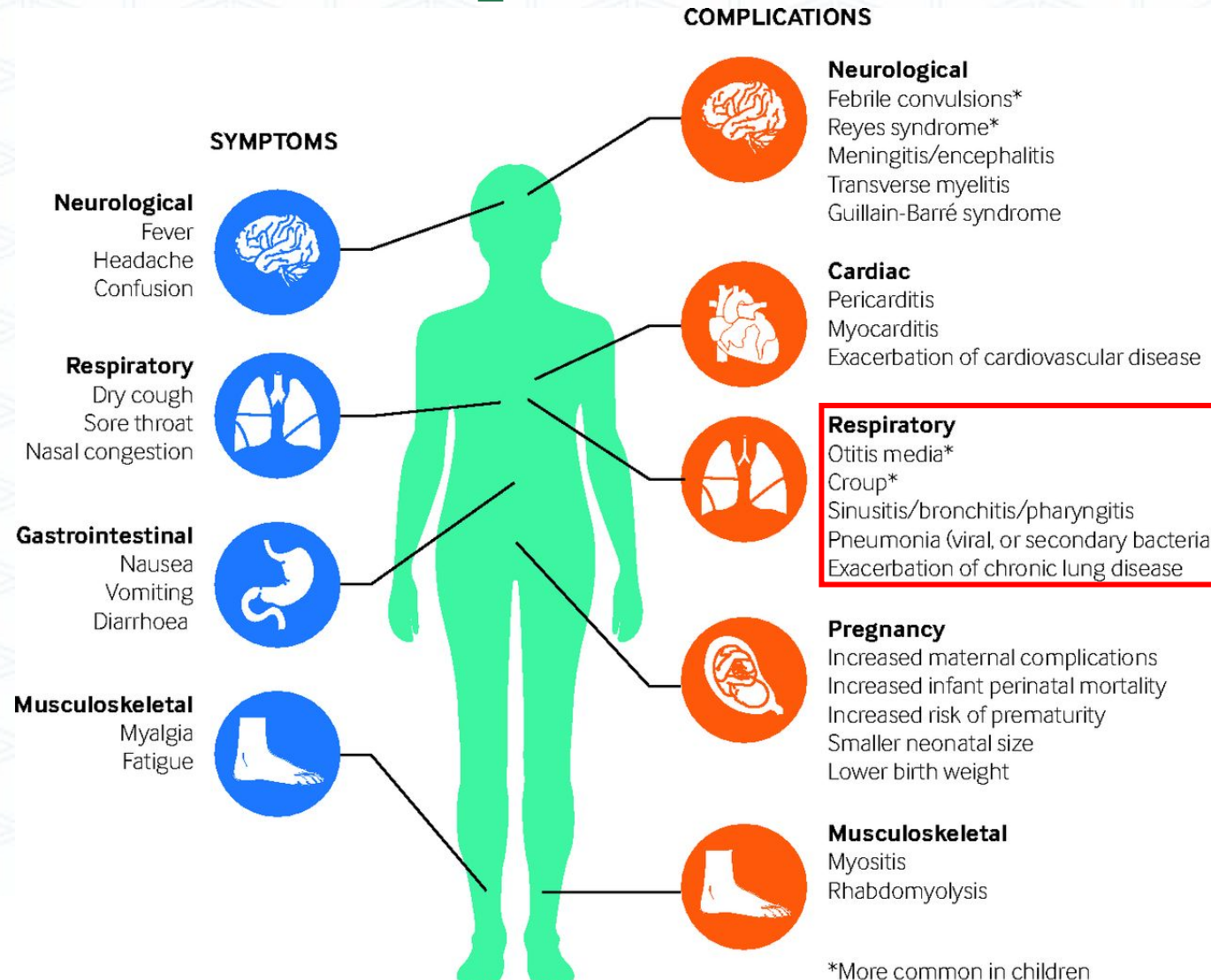
- Most will recover from influenza within a week, sometimes two
- People are usually contagious from the day before developing symptoms through about one week; contagiousness usually correlates with fever
- Some may go on to have severe complications



# Who is at highest risk?

- Children <5 (particularly <2)
- Adults 65 and older
- Pregnant women
- People in nursing homes or other long-term care facilities
- Native American/Alaska Natives
- People with:
  - Asthma or other lung disease
  - Heart disease
  - Neurological conditions
  - Immunocompromised (e.g. HIV/AIDS), cancer
  - Obesity

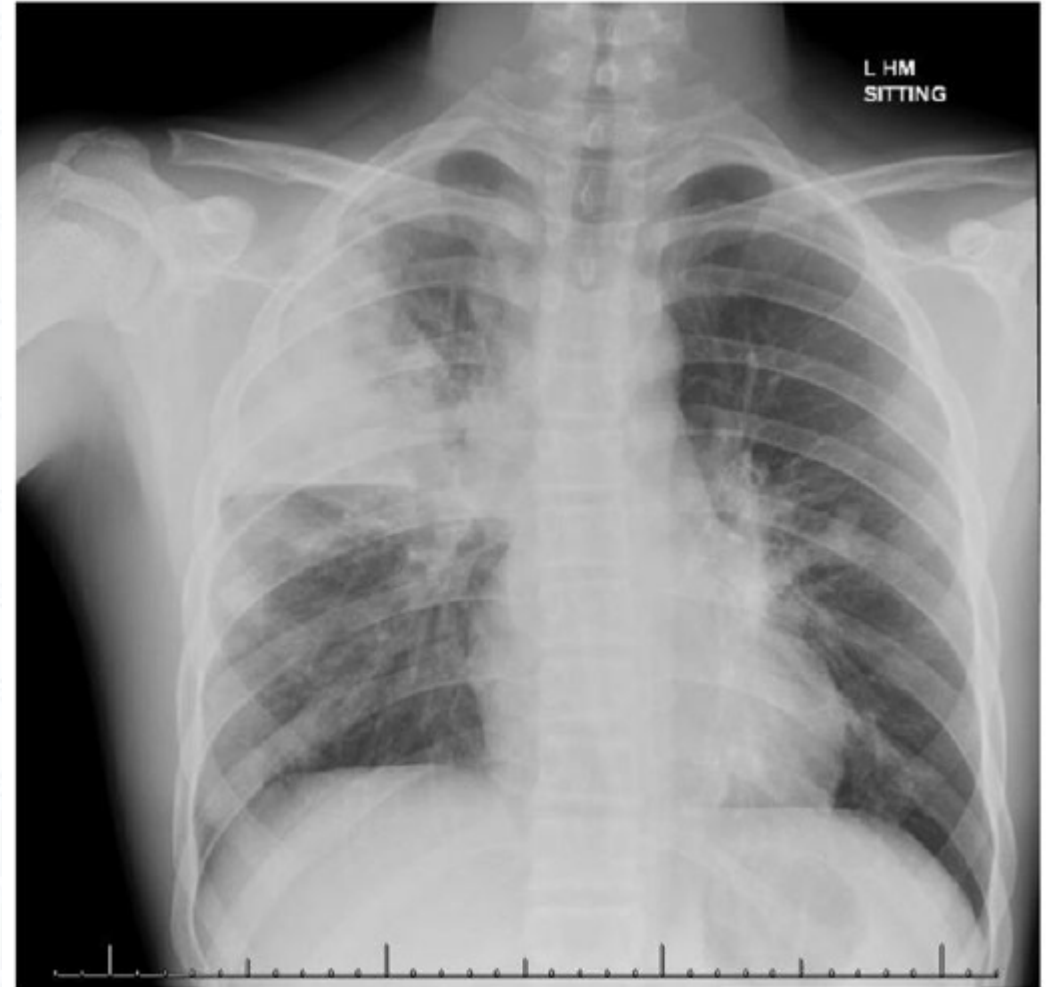
# What are the complications of influenza?





# Influenza and pneumonia

- Pneumonia – infection and inflammation in the lower respiratory tract, lungs
- During influenza, pneumonia can be caused by the influenza virus (primary) itself or by superinfection with bacteria (secondary)
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*



# MYTH

- Healthy people are not at high risk for complications from influenza



# Leading causes of mortality, USA 2015

#1 cause of death  
due to infection in  
the US is lung  
infections caused by  
influenza or  
bacterial  
pneumonia



1. Diseases of heart (heart disease)
2. Malignant neoplasms (cancer)
3. Chronic lower respiratory diseases
4. Accidents (unintentional injuries)
5. Cerebrovascular diseases (stroke)
6. Alzheimer's disease
7. Diabetes mellitus (diabetes)
8. Influenza and pneumonia
9. Nephritis, nephrotic syndrome and nephrosis (kidney disease)
10. Intentional self-harm (suicide)

[https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66\\_06.pdf](https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf)

**Table 1. Characteristics of 272 Hospitalized Patients Who Were Infected with the 2009 H1N1 Virus in the United States (April–June 2009).**

Characteristic	No. (%)
Female sex	132 (49)
Age group*	
0–23 mo	23 (8)
2–4 yr	20 (7)
5–9 yr	29 (11)
10–17 yr	50 (18)
18–49 yr	104 (38)
50–64 yr	32 (12)
≥65 yr	14 (5)
Race or ethnic group†	
Hispanic	83 (30)
Non-Hispanic white	73 (27)
Black	53 (19)
Native Hawaiian, Asian, or Pacific Islander	15 (6)
Native American	9 (3)
Multiracial, not further defined	2 (1)
Unspecified	37 (14)

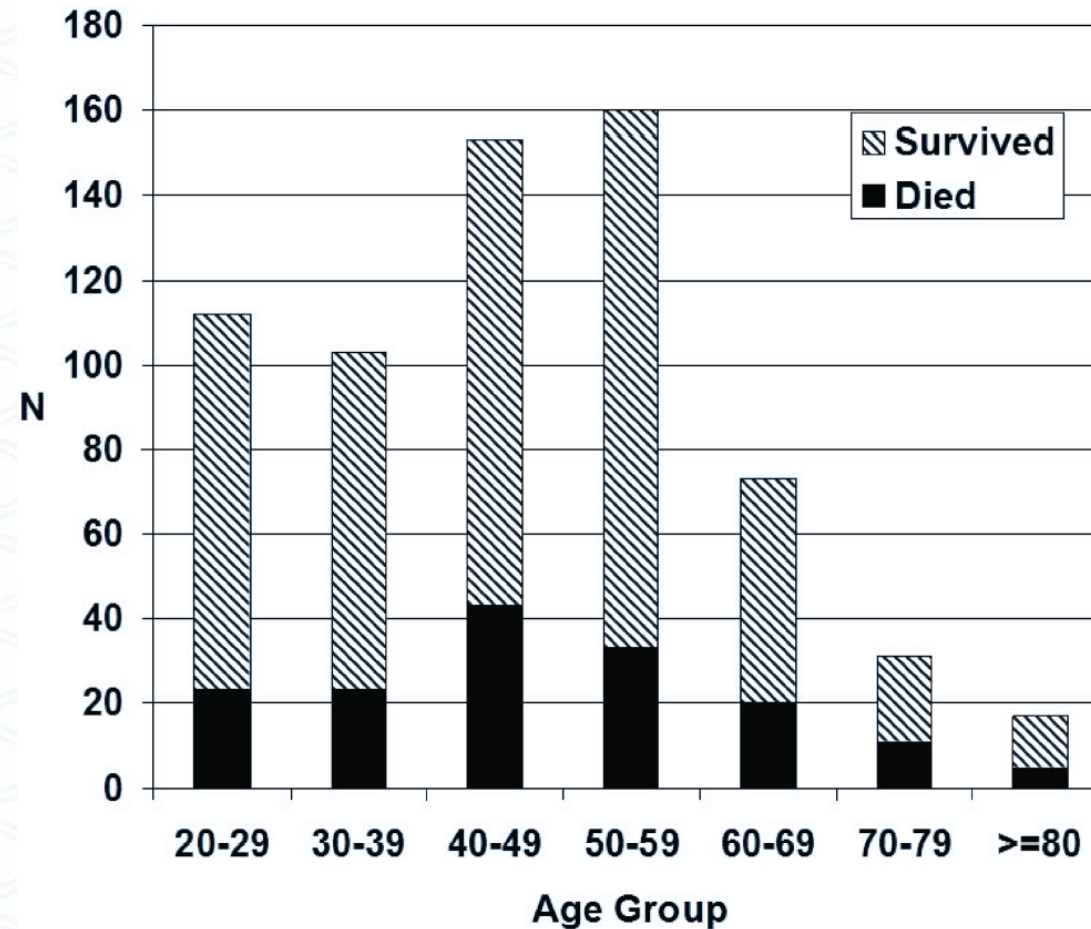
Median age = 21 years



**Table 4.** Characteristics of Hospitalized Patients Who Were Not Admitted to an Intensive Care Unit (ICU) and Survived and Patients Who Were Admitted to an ICU or Died.\*

Characteristic	Patients Who Were Not Admitted to an ICU and Survived (N = 205)	Patients Who Were Admitted to an ICU or Died (N = 67)
Age		
Median — yr (range)	19 (21–80)	29 (1–86)
<18 Yr — no. (%)	98 (48)	24 (36)
Shortness of breath — no. (%)	104 (51)	58 (87)
Neurocognitive disorder — no. (%)	11 (5)	9 (13)
Neuromuscular disorder — no. (%)	10 (5)	9 (13)
Pneumonia seen on chest radiography on admission — no./ total no. (%)	51/182 (28)	49/67 (73)
Antiviral treatment — no./total no. (%)		
Any — no./total no. (%)	144/203 (71)	56/65 (86)
≤2 Days after onset of symptoms — no./total no. (%)	62/139 (45)	13/56 (23)
Days from onset of symptoms to initiation — no. (range)	3 (0–29)	5 (0–24)
Antibiotic treatment — no./total no. (%)	144/195 (74)	62/65 (95)
Corticosteroid treatment — no./total no. (%)	57/183 (31)	29/56 (52)

# Mortality in US adults admitted to ICUs with 2009 pH1N1 infection

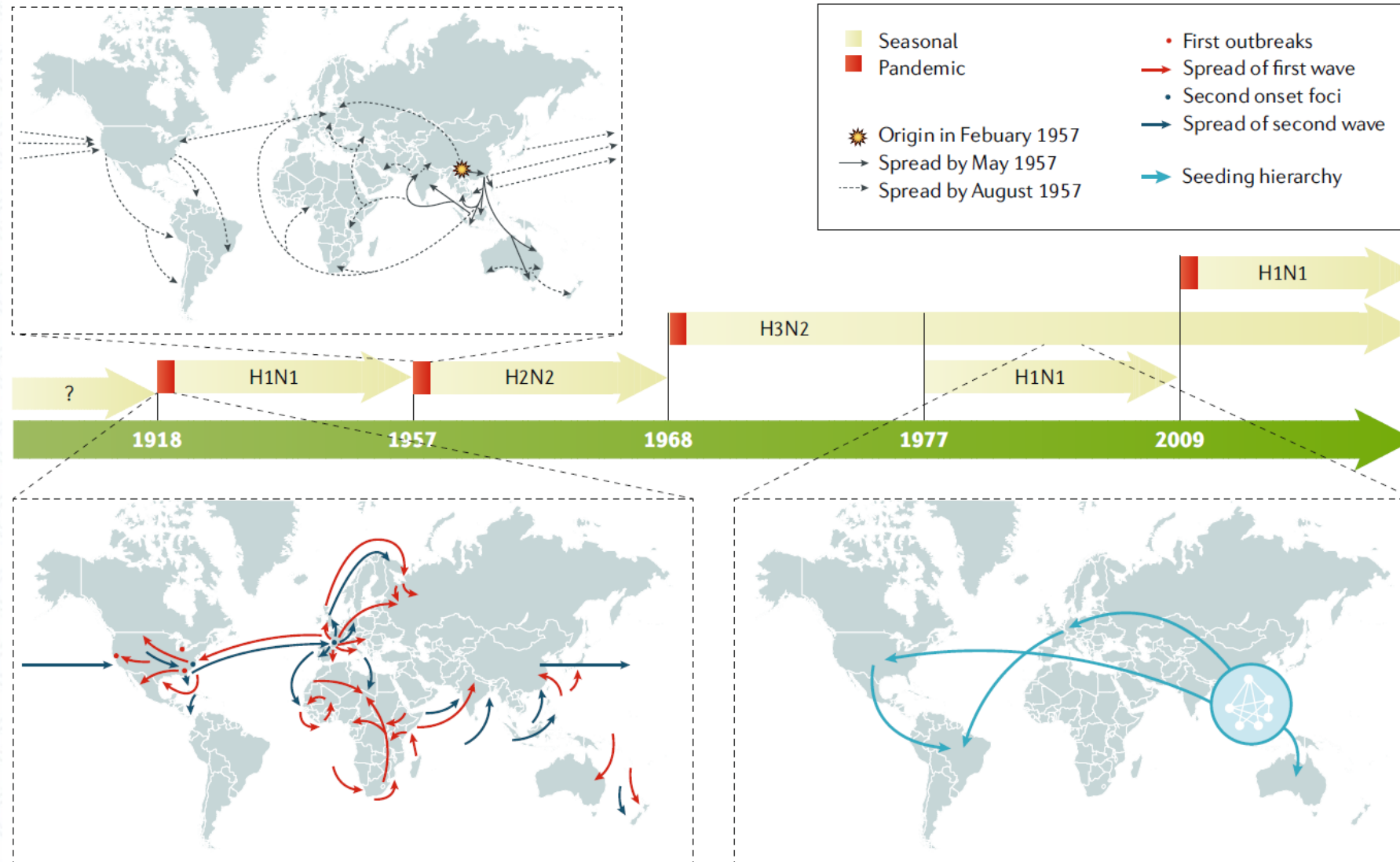




# Pandemic vs seasonal epidemics

- “A pandemic is the worldwide spread of a new disease” (WHO)
  - Influenza pandemics are caused by new subtypes of influenza A
- Most influenza infections occur in the context of seasonal epidemics
  - “The occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time” (CDC)

# A brief history of pandemic influenza





# 1918 “Spanish flu” pandemic

- 50-100 million deaths
  - ~5% of world population
  - Case-fatality rates 100-fold higher normal





# Why was the Spanish flu so deadly?

- A perfect storm of factors
  - WWI
  - Mass movements of vulnerable populations
  - *Emergence of a novel pandemic strain*



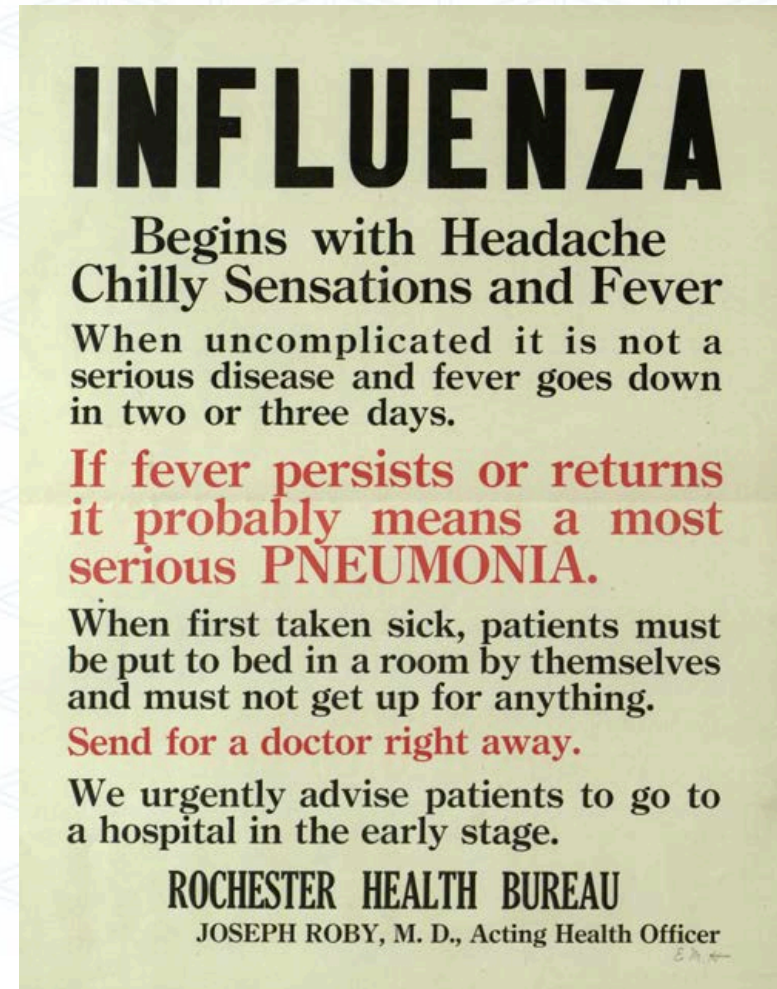


# Why was the Spanish flu so deadly?

- Exact pathogenesis still not quite clear
- Aberrant immune responses
- Secondary bacterial pneumonia  
~80-90% of all deaths

Morens et al. J Infect Dis 2008

Morens et al. Crit Care Med 2010



**INFLUENZA**

Begins with Headache  
Chilly Sensations and Fever

When uncomplicated it is not a serious disease and fever goes down in two or three days.

**If fever persists or returns it probably means a most serious PNEUMONIA.**

When first taken sick, patients must be put to bed in a room by themselves and must not get up for anything.

**Send for a doctor right away.**

We urgently advise patients to go to a hospital in the early stage.

**ROCHESTER HEALTH BUREAU**  
JOSEPH ROBY, M. D., Acting Health Officer

# Influenza A: Potential for pandemic strains

- Two mechanisms for pandemic strain emergence
  - Direct animal to human transmission of new strain
  - Gene reassortment



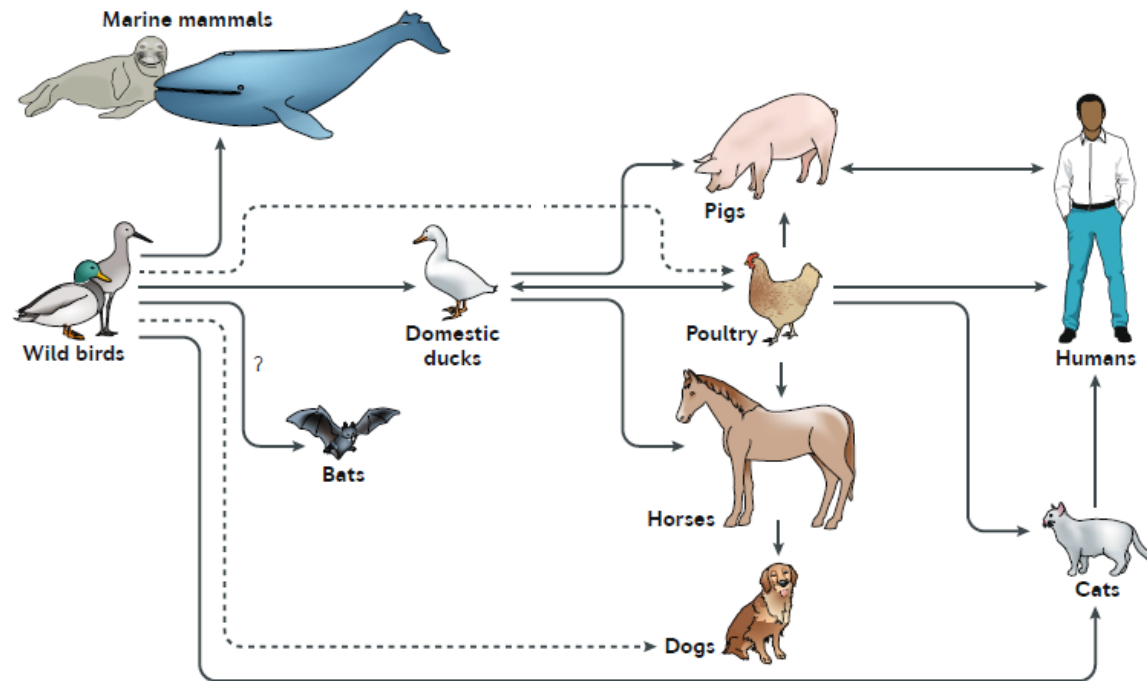
# Influenza: Not just for people

- Birds
  - Wild aquatic birds, waterfowl
  - **Domestic waterfowl, poultry**
- Mammals:
  - **Pigs**
  - Dogs, cats, horses, bats, seals, whales



<http://www.regenerationinternational.org/2016/05/10/strange-farmfellows-pigs-and-chickens-regenerate-the-land-in-bela-bela-south-africa/>

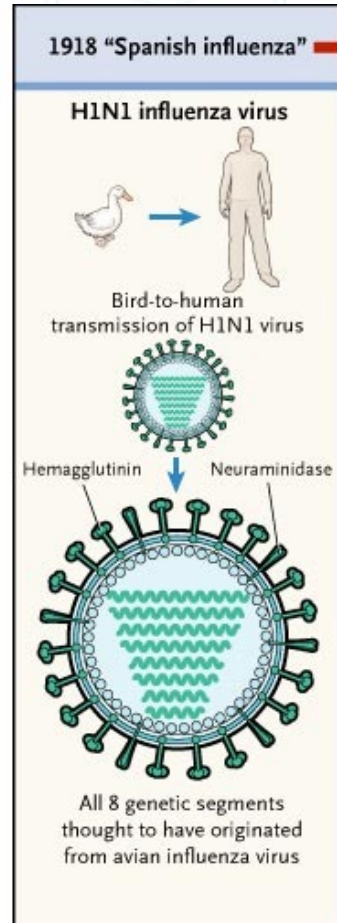
# Influenza A: Potential for pandemic strains



Krammer et al, Nature 2018.



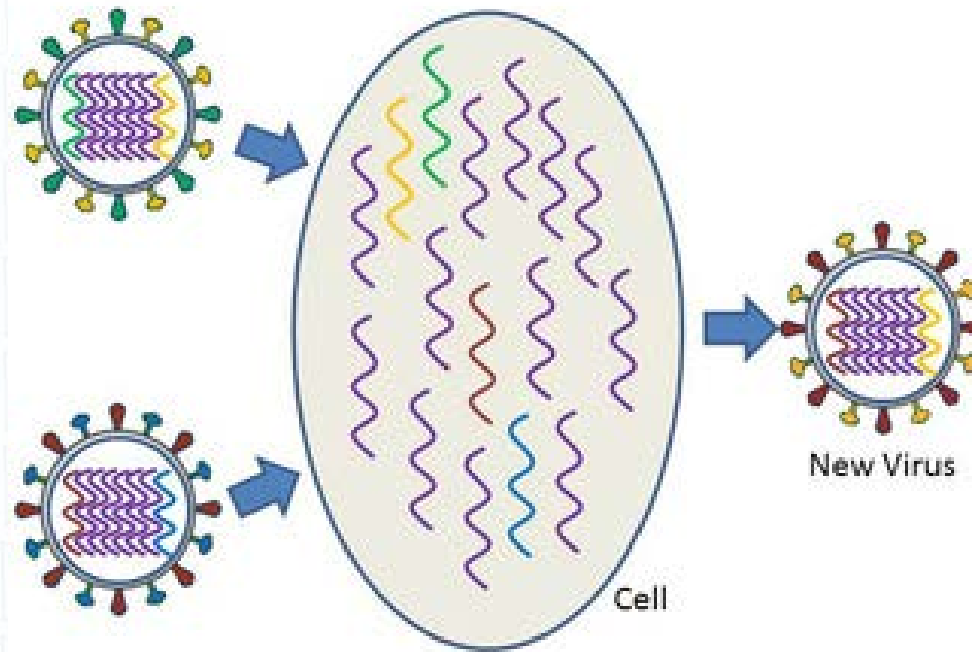
# Influenza A: Potential for pandemic strains



Belshe, NEJM 2005.

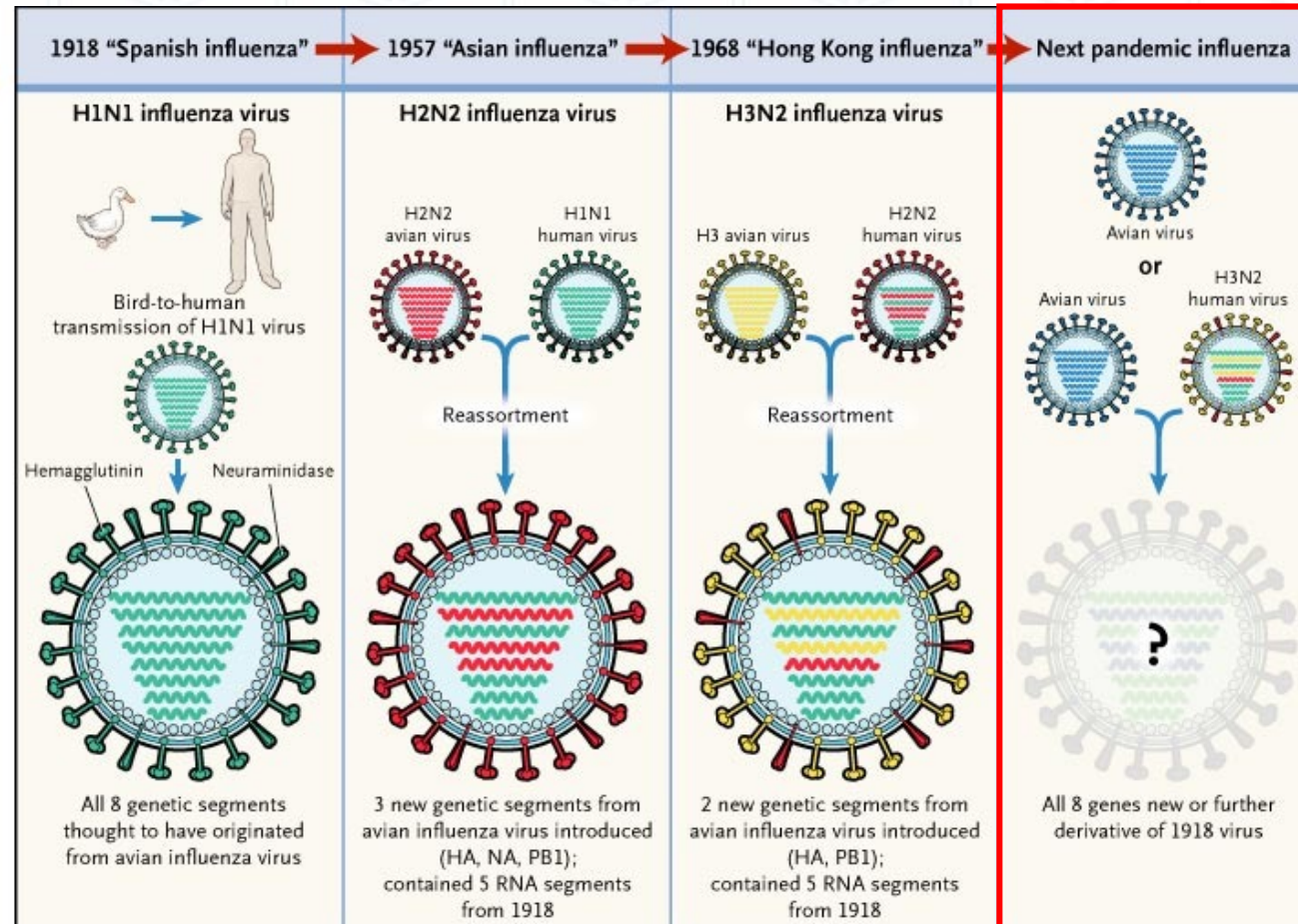
# Influenza A: Potential for pandemic strains

- Segmented genome allows opportunity for gene reassortment





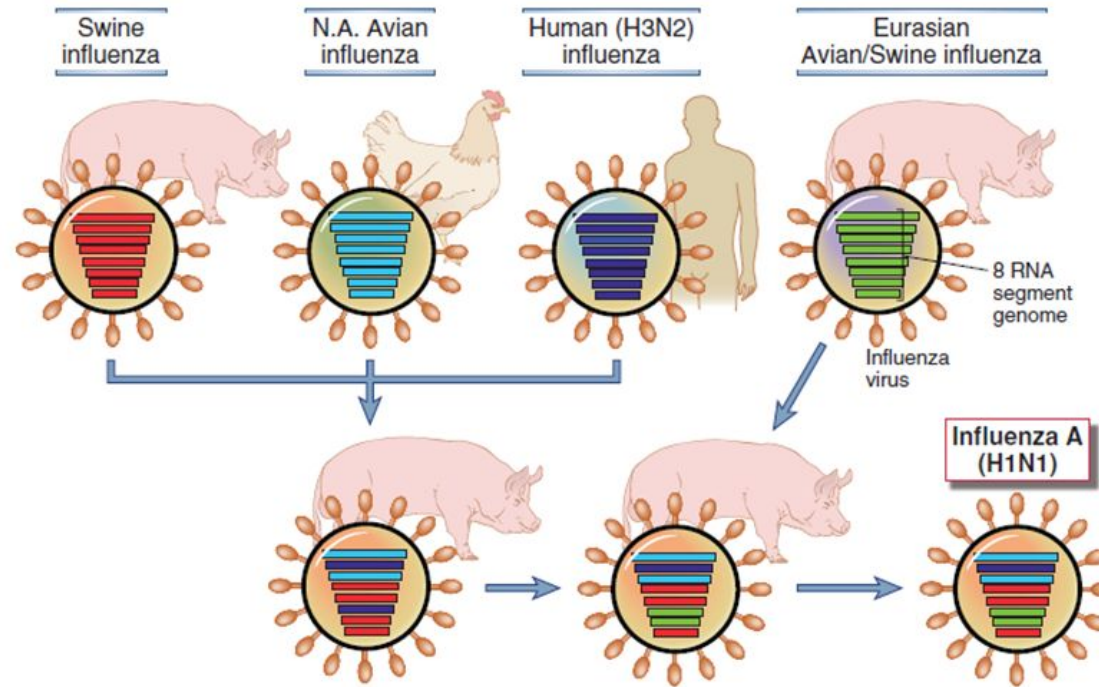
# Influenza A: Potential for pandemic strains



Belshe, NEJM 2005.

# 2009 novel H1N1 influenza (“swine flu”)

Generation of new influenza virus strains  
by genetic recombination (antigenic shift)



Cellular and Molecular Immunology, 7th ed., 2012 Elsevier



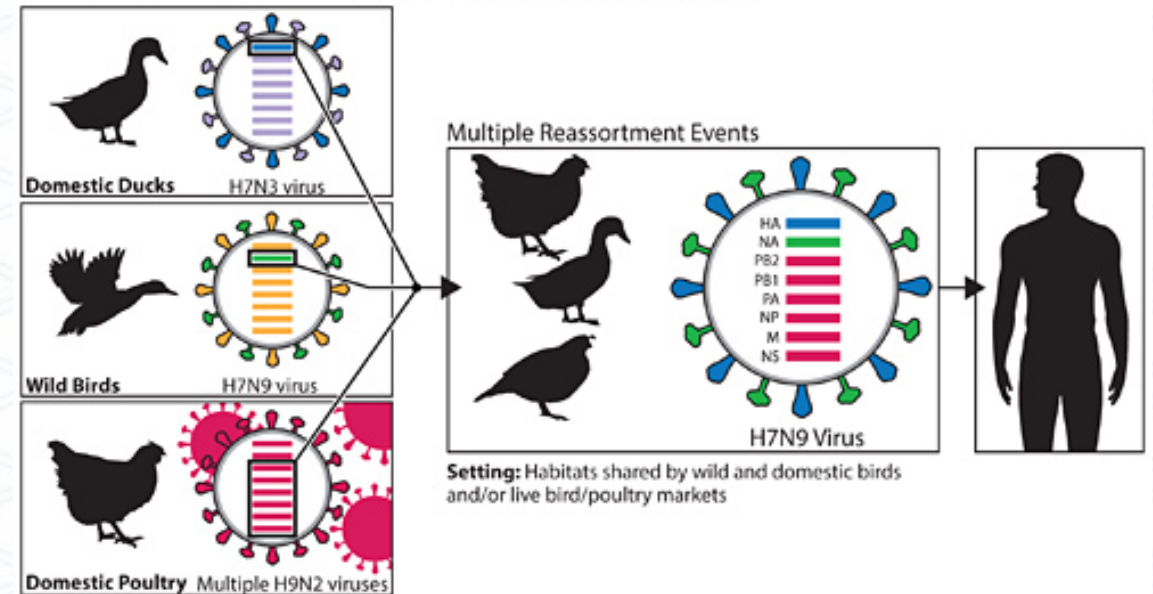
# Where will the next pandemic come from?

- Anyone's guess, but some areas to watch



[http://www.chinadaily.com.cn/china/2013-04/17/content\\_16416341.htm](http://www.chinadaily.com.cn/china/2013-04/17/content_16416341.htm)

Genetic Evolution of H7N9 Virus in China, 2013



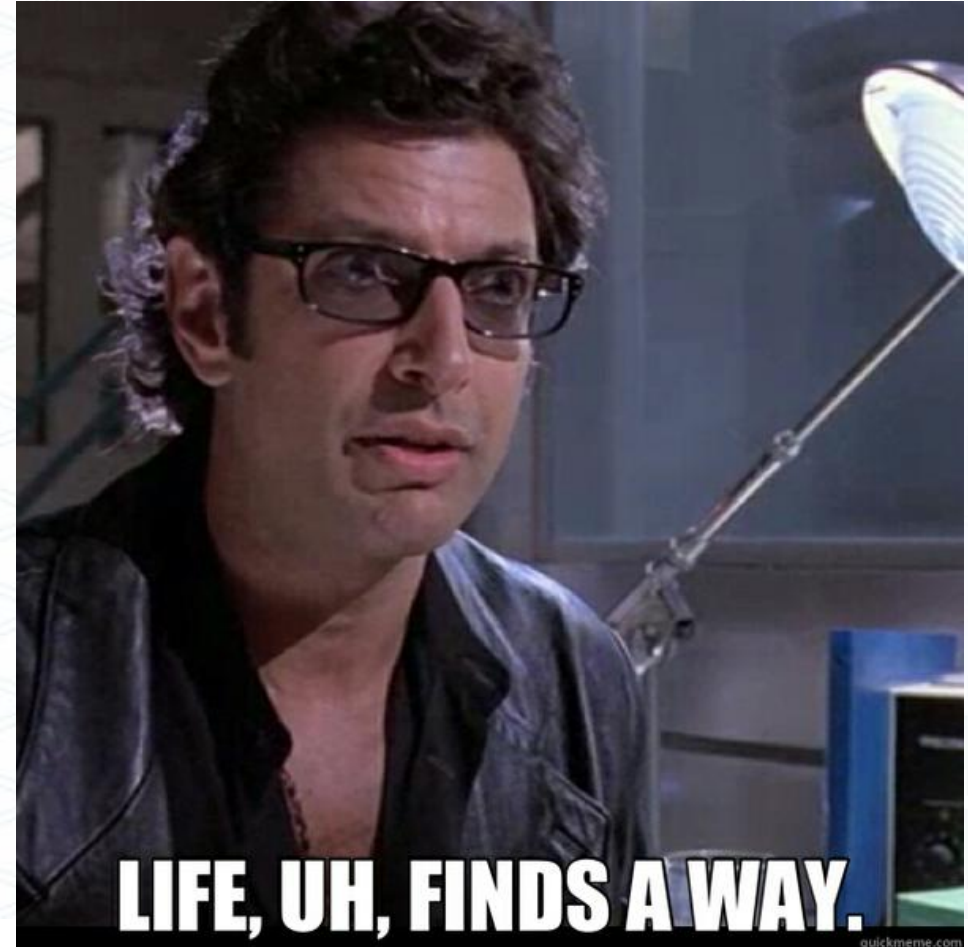
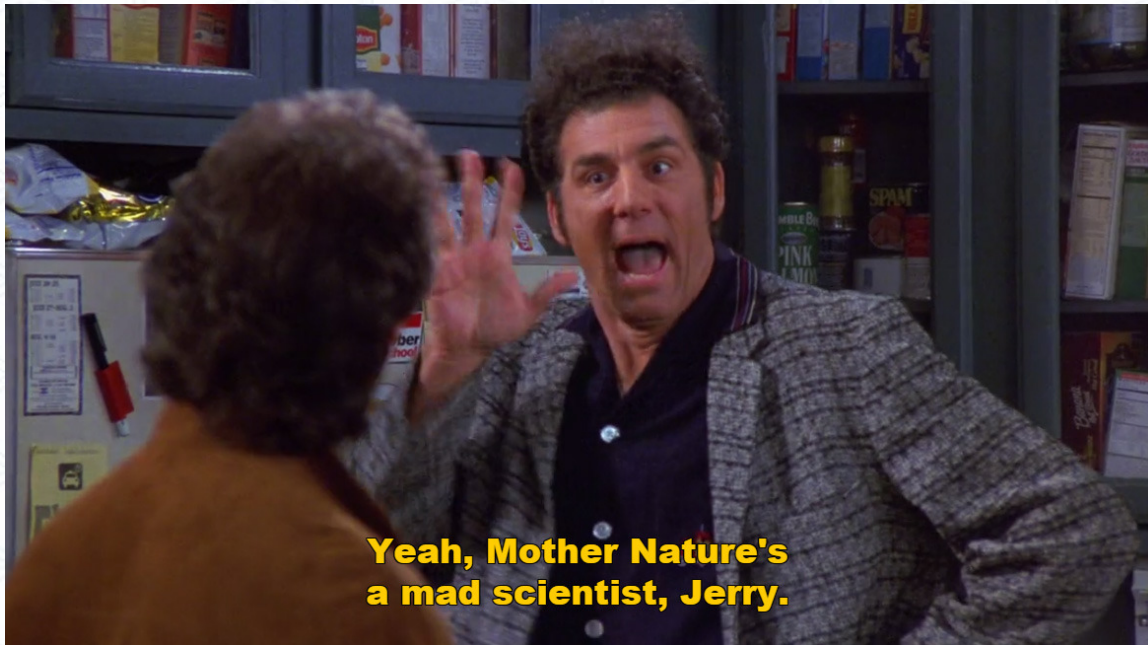
[https://www.cdc.gov/flu/other/transmission.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fabout%2Fviruses%2Ftransmission.htm](https://www.cdc.gov/flu/other/transmission.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fabout%2Fviruses%2Ftransmission.htm)

# Where will the next pandemic come from?

- Characteristics of viruses required for new pandemic:
  - Viruses that are antigenically new
  - Can easily be passed person to person
- Several viruses out there haven't yet developed necessary mutations to pass efficiently person-to-person
  - Avian H5N1, H7N9
  - Swine, or variant influenza: H3N2v



# Where will the next pandemic come from?



# What is certain in life?

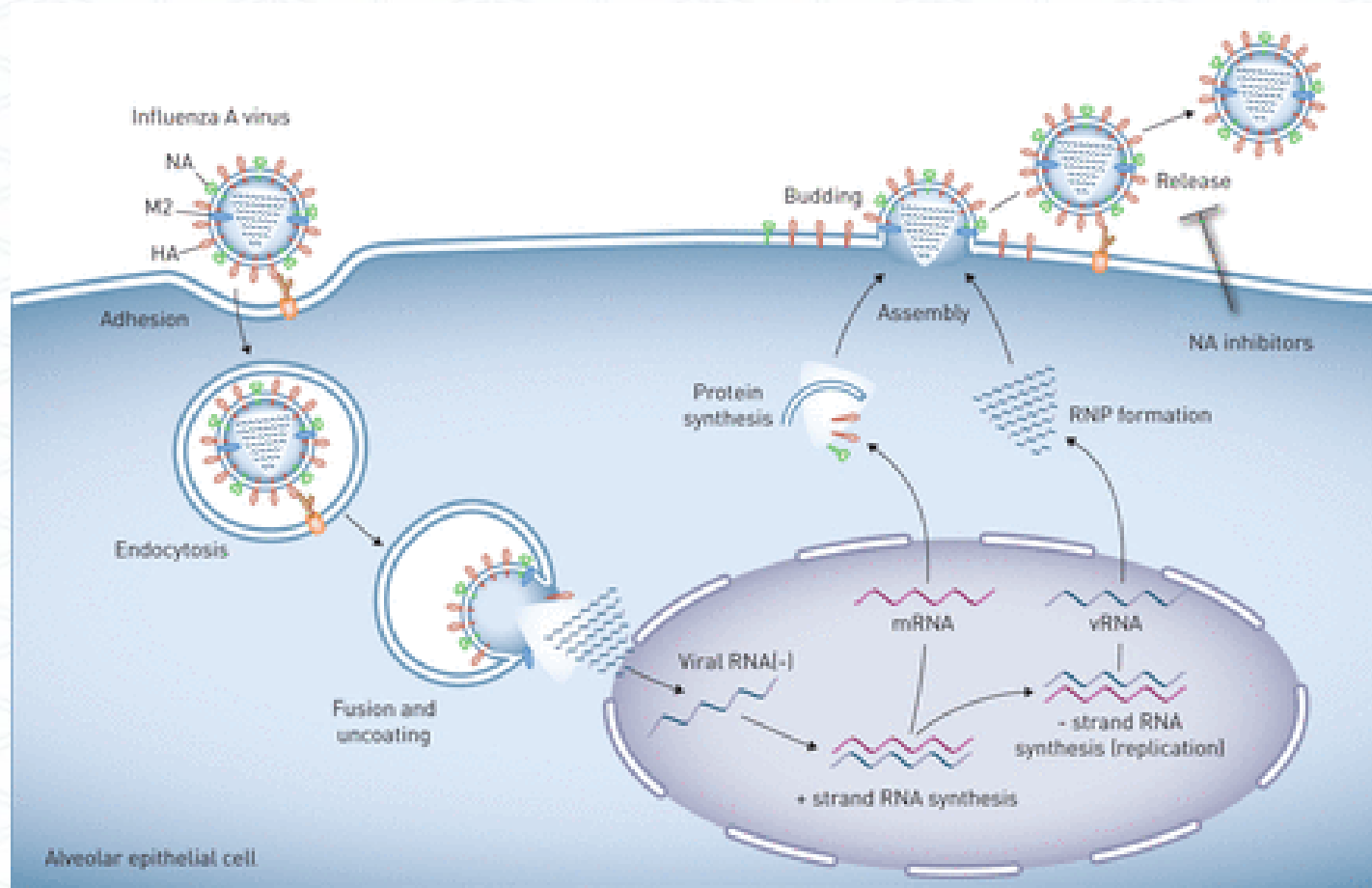
- Death, taxes, and seasonal influenza



# Pandemic vs seasonal influenza

- Emergence of pandemic strains results from *antigenic shift*
  - The surface proteins (HA, NA) look completely different from anything the population has seen before
  - Fortunately, this occurrence is relatively rare
- Every year, influenza viruses undergo a different process, known as *antigenic drift*
  - The surface proteins (HA, NA) are generally the same but have mutated just enough that the immune system can't recognize them as well as before

# Influenza gene mutation



Error rate of RNA replication is 1 mutation/virion

1 infected cell can therefore generate  
10,000 mutated viruses!

(Boivin et al. J Biol Chem 2010.)

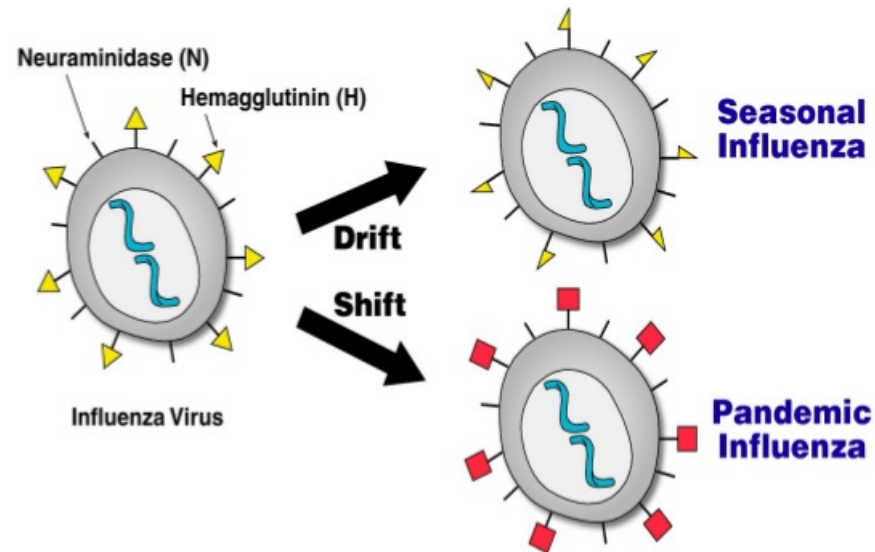
Herold et al. Eur Resp Journal 2015.



# Pandemic vs seasonal influenza

- Antigenic drift (small changes that accumulate in the outer flu proteins over the course of the year) is the reason that flu is a problem every winter, leading to *seasonal influenza* epidemics

## Influenza: Antigenic Drift and Shift

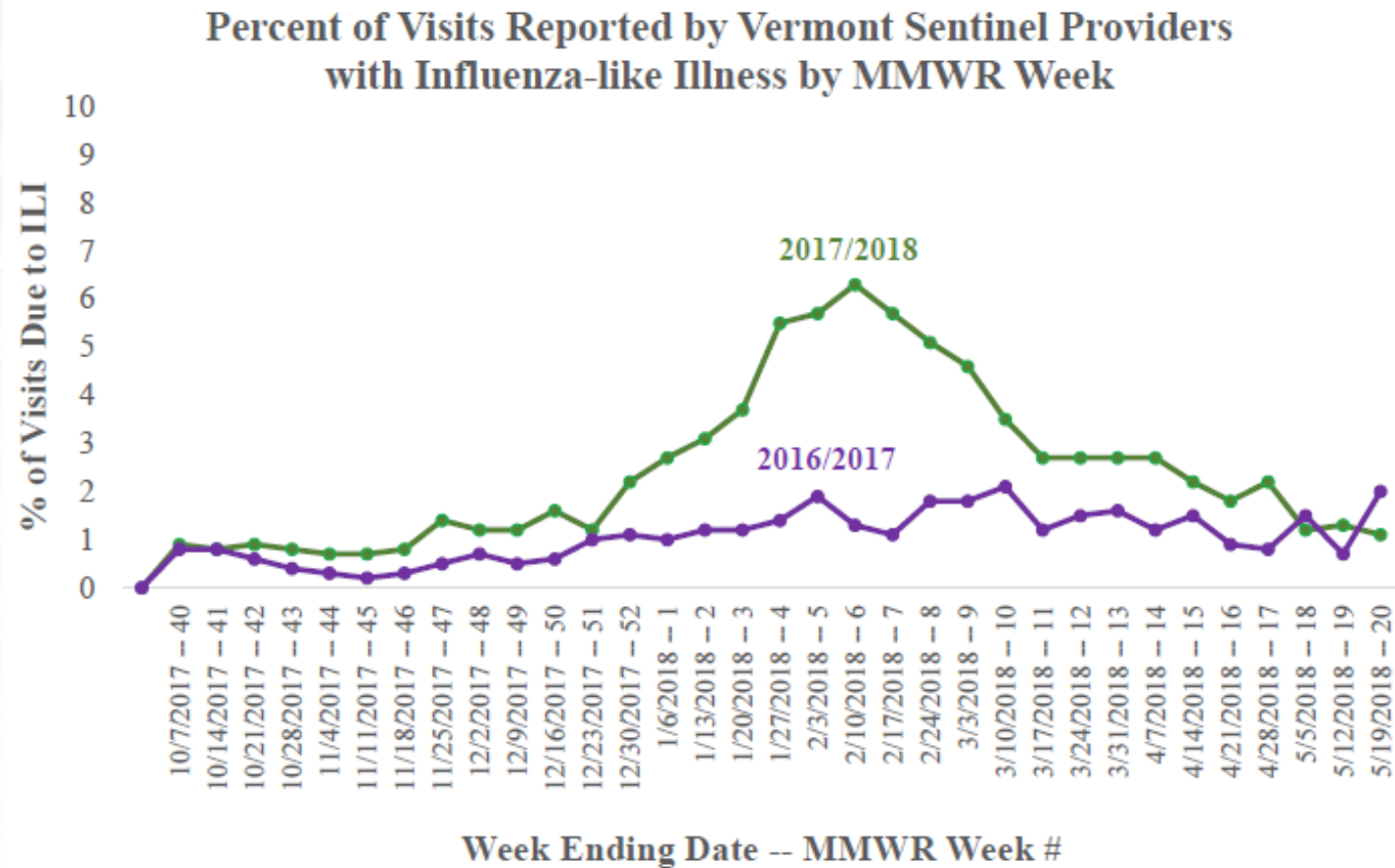


# Seasonal influenza: epidemiology

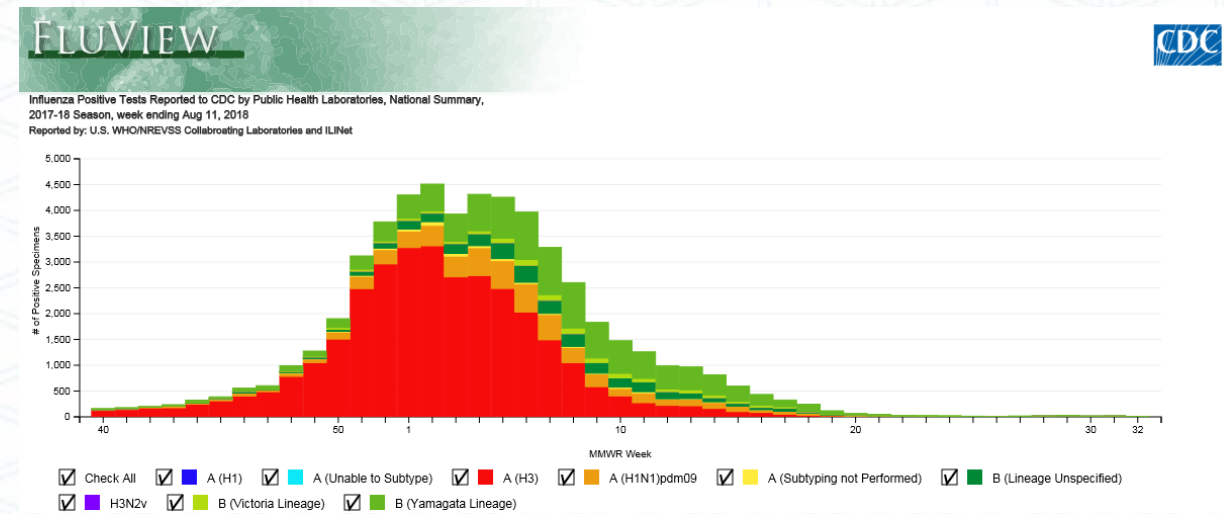
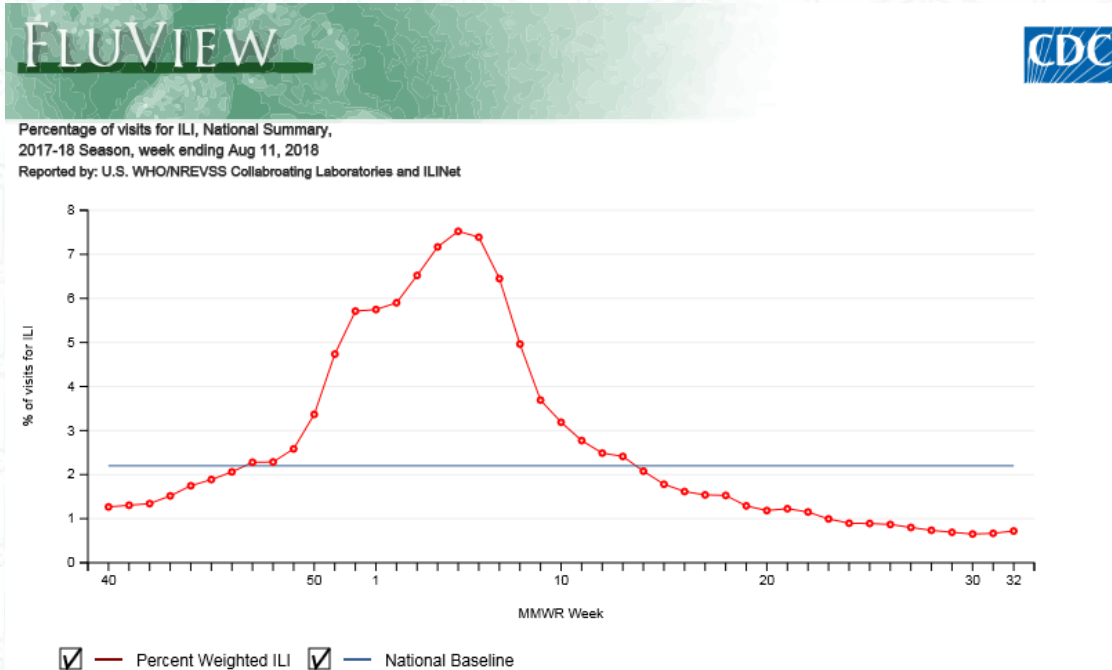
- “Flu season” occurs during the winter months in temperate climates
- In tropical climates, the season is less well defined and the viruses may circulate at lower levels year-round
- Reasons for this are still incompletely understood but likely related to temperature/humidity and possibly even school calendars



# Seasonal influenza: epidemiology



# Seasonal influenza: epidemiology

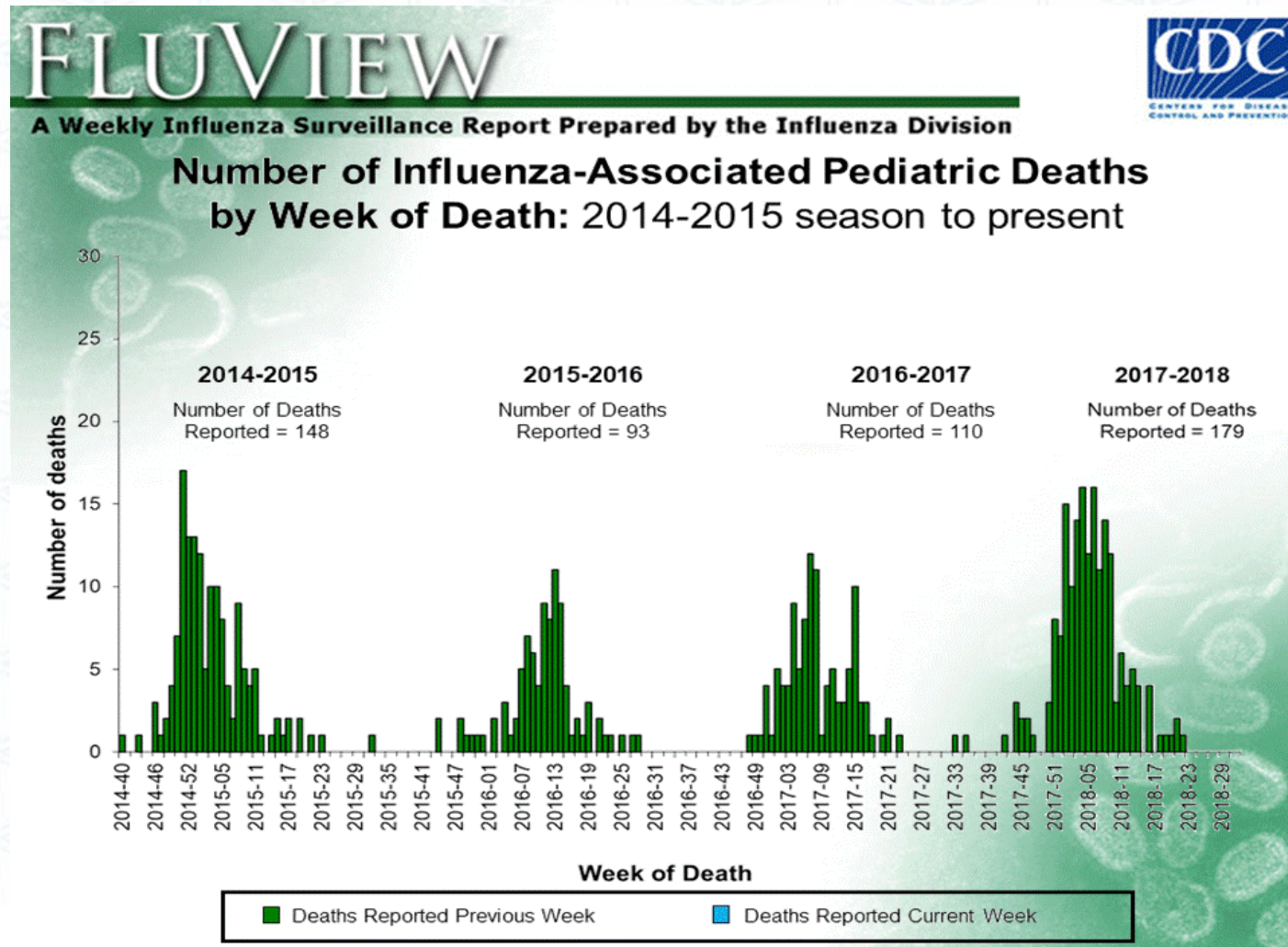




# Seasonal influenza and deaths

- Every winter, we see death due to influenza
- Severity of season typically tracked by monitoring pediatric deaths
  - Nationally notifiable condition
  - General overall estimate of severity of each season

# Seasonal influenza: epidemiology





# Seasonal influenza and *Staphylococcus aureus*

- *Staphylococcus aureus* pneumonia carries a high risk of mortality in young, immunocompetent patients
- The greatest risk factor for this type of pneumonia is influenza

Clinical characteristics			
Secondary CAP	3/50 (6)	13/55 (23.6)	0.012
Antibiotics before admission	9/50 (18)	7/55 (12.7)	0.45
Duration of symptoms, days, mean $\pm$ SD	3.8 $\pm$ 2.9	4.7 $\pm$ 2.5	0.11
Influenza-like symptoms	32/46 (69.6)	14/47 (29.8)	<0.001
Other viral disease	3/43 (7)	2/42 (4.8)	1.00
Fever	35/41 (85.4)	37/39 (94.9)	0.27
Cough	29/44 (65.9)	23/44 (52.3)	0.19
Chest pain	8/42 (19)	9/41 (22)	0.74
Gastrointestinal symptoms	8/43 (18.6)	6/42 (14.3)	0.59
Rash	12/44 (27.3)	4/45 (8.9)	0.024
Confusion/lethargy	5/40 (12.5)	6/39 (15.4)	0.71
Shock	34/40 (85)	15/35 (46.9)	0.001
Tachypnea	28/29 (96.6)	27/29 (93.1)	1.00
Airway hemorrhage	20/40 (50)	12/34 (35.3)	0.20
Severe pneumonia	33/33 (100)	22/31 (71)	0.001

Vardakas Int J Tuberc Lung Dis 13:1476, 2009

# Summary, Part I

- Influenza is an important cause of seasonal respiratory illness
- Yearly seasonal influenza epidemics are certain to occur
- Worldwide pandemic influenza is always a possibility
- Influenza can be an important cause of mortality, even *in the otherwise young and healthy*



# So, what to do?



*"I'll have an ounce of prevention."*

# Pandemic influenza vs seasonal influenza

- We may not be able to predict/prevent the next influenza pandemic
- But there ARE many things we can do to combat influenza

God grant me the serenity  
to accept the things I cannot change  
courage to change the things I can;  
and wisdom to know the difference!



# An ounce of prevention is worth a pound of cure

- Practice good respiratory etiquette and hand hygiene
- Stay home when you are sick
- **VACCINATION** is the single best way to prevent influenza infection

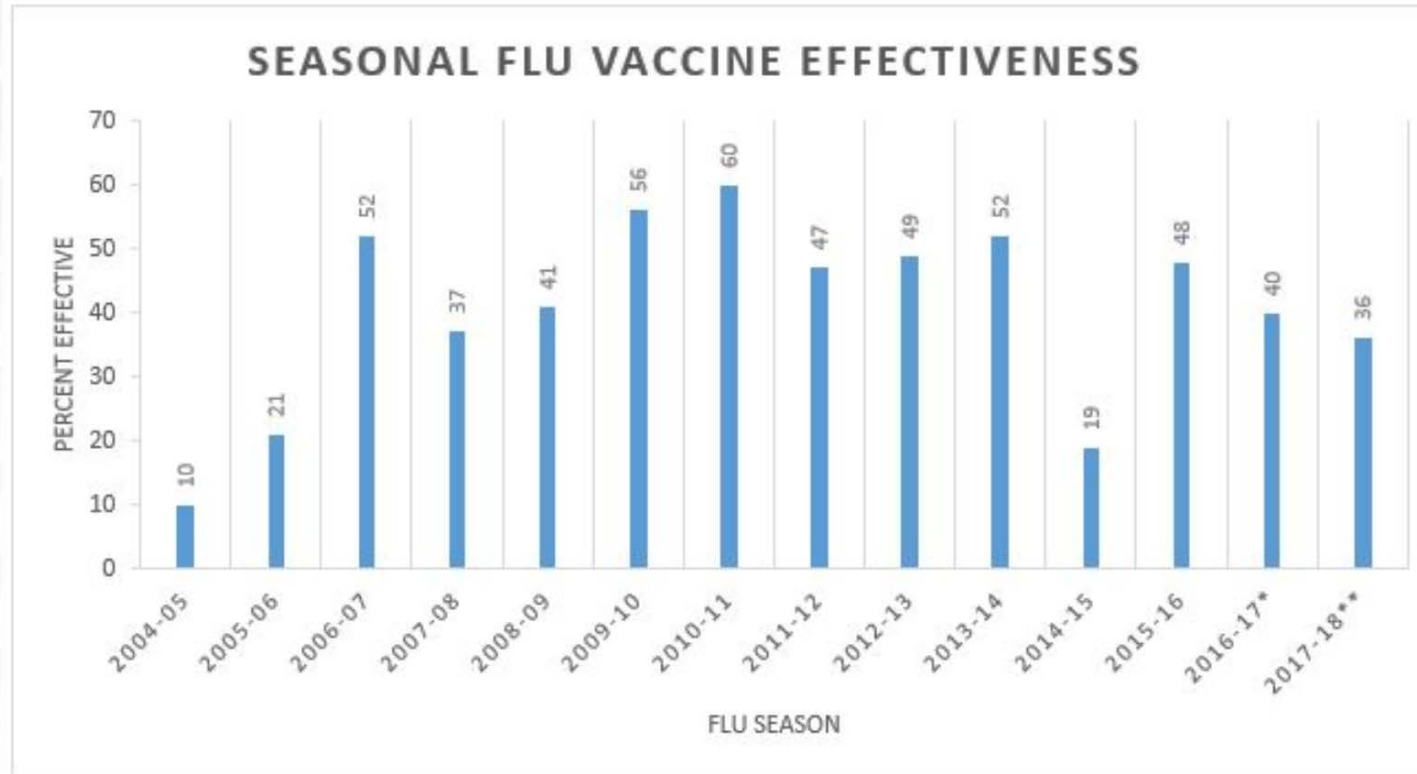


# Who should get vaccinated?

- EVERYBODY  $\geq$  6 months of age



# MYTH: The flu vaccine doesn't work



<https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm>

# Flu vaccine effectiveness

- Flu vaccine effectiveness is usually determined by measuring how many outpatients who got vaccinated get confirmed influenza compared to those who don't (US Flu VE Network) and only tell part of the story
- Inpatient studies to determine prevention of hospitalizations began in 2016 (US Hospitalized Adult Influenza Vaccine Effectiveness Network, HAIVEN)
- Most large studies fail to accurately capture other effects of vaccination
  - Decreased severity/duration of symptoms
  - Decreased complications
  - Decreased transmission to others
- Other studies have clearly demonstrated increased benefits in specific sub-groups (e.g. those with diabetes, pregnant women, other high-risk conditions)



# MYTH: The flu vaccine doesn't work

## the **benefits** of flu vaccination 2016-2017

The estimated number of flu **illnesses prevented** by flu vaccination during the 2016-2017 season:

**5.3 million,**  
about the population of the  
Atlanta metropolitan area.



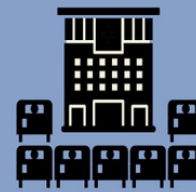
The estimated number of flu **medical visits prevented** by vaccination during the 2016-2017 season:

**2.6 million,**  
or more than the number of  
students in all K-12 schools  
in Florida.



The estimated number of flu **hospitalizations prevented** by vaccination during the 2016-2017 season:

**85,000,**  
or more than the number of  
hospital beds in California and  
Oregon.



DATA: Influenza Division program impact report 2016-2017, <https://www.cdc.gov/flu/about/disease/2016-17.htm>.

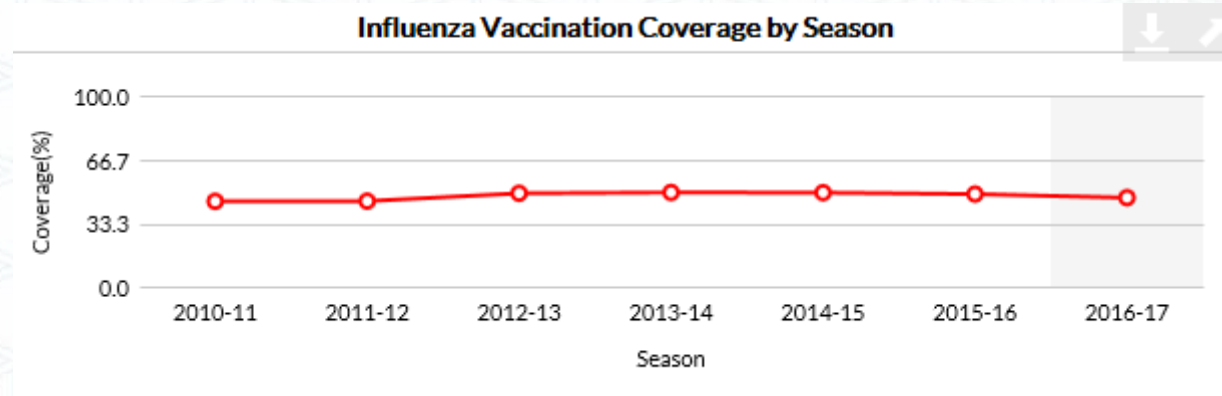
get vaccinated  
[www.cdc.gov/flu](http://www.cdc.gov/flu)



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# Vaccine coverage

- IN 2017, only 38% of all US citizens got a flu shot prior to peak of flu season!
- Vermont tends to do slightly better than national average:





# MYTH: The flu vaccine is dangerous

- You CANNOT get the flu from flu vaccine
- The most common side effects of flu vaccine:
  - Redness, swelling, pain at injection site
  - Headache
  - Low-grade fevers
  - Nausea
  - Muscle aches (myalgias)

# Influenza vaccines: many options

Manufacturer	Trade Name (vaccine abbreviation) <sup>1</sup>	How Supplied	Mercury Content (mcg Hg/0.5mL)	Age Group	Vaccine Product Billing Code <sup>2</sup>	
					CPT	Medicare
GlaxoSmithKline	Fluarix (IIV4)	0.5 mL (single-dose syringe)	0	6 months & older	90686	90686
ID Biomedical Corp. of Quebec, a subsidiary of GlaxoSmithKline	FluLaval (IIV4)	0.5 mL (single-dose syringe)	0	6 months & older	90686	90686
		5.0 mL (multi-dose vial)	<25	6 months & older	90688	90688
MedImmune	FluMist <sup>3</sup> (LAIV4)	0.2 mL (single-use nasal spray)	0	2 through 49 years	90672	90672
Protein Sciences Corp.	Flublok (RIV3)	0.5 mL (single-dose vial)	0	18 years & older	90673	90673
	Flublok (RIV4)	0.5 mL (single-dose syringe)	0	18 years & older	90682	90682
Sanofi Pasteur, Inc.	Fluzone (IIV4)	0.25 mL (single-dose syringe)	0	6 through 35 months	90685	90685
		0.5 mL (single-dose syringe)	0	3 years & older	90686	90686
		0.5 mL (single-dose vial)	0	3 years & older	90686	90686
		5.0 mL (multi-dose vial)	25	6 through 35 months	90687	90687
		5.0 mL (multi-dose vial)	25	3 years & older	90688	90688
	Fluzone High-Dose (IIV3-HD)	0.5 mL (single-dose syringe)	0	65 years & older	90662	90662
	Fluzone Intradermal (IIV4-ID)	0.1 mL (single-dose microinjection system)	0	18 through 64 years	90630	90630
Seqirus	Afluria (IIV3)	0.5 mL (single-dose syringe)	0	5 years & older <sup>4</sup>	90656	90656
		5.0 mL (multi-dose vial)	24.5		90658	Q2035
	Afluria (IIV4)	0.5 mL (single-dose syringe)	0	5 years & older <sup>4</sup>	90686	90686
		5.0 mL (multi-dose vial)	24.5		90688	90688
	Fluad (aIIV3)	0.5 mL (single-dose syringe)	0	65 years & older	90653	90653
	Fluvirin (IIV3)	0.5 mL (single-dose syringe)	≤1	4 years & older	90656	90656
		5.0 mL (multi-dose vial)	25		90658	Q2037
	Flucelvax (ccIIV4)	0.5 mL (single-dose syringe)	0	4 years & older	90674	90674
		5.0 mL (multi-dose vial)	25		90749/90756 <sup>5</sup>	Q2039/90756 <sup>6</sup>

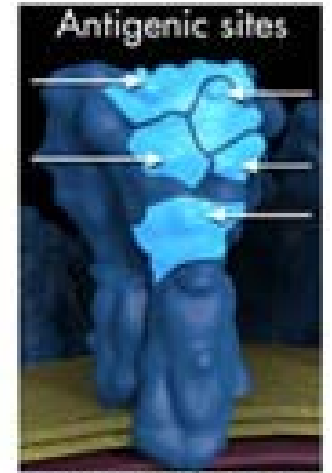


# Influenza vaccines

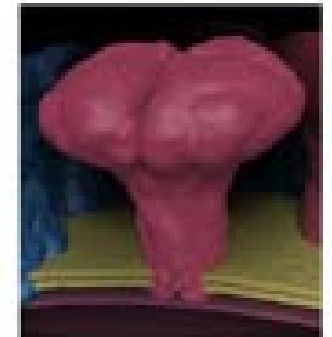
- Trivalent versus quadrivalent
- Inactivated vs live-attenuated
- Method of manufacture

# Influenza vaccines: a long road...

- Step 1: Strain selection for this year's vaccine
- Recommendations made by WHO
  - Circulating viruses from over 100 countries reviewed
  - 5 WHO reference labs in USA, UK, Australia, Japan, China
- In USA, FDA reviews WHO recommendations, makes final determination of which strains to include



Hemagglutinin



Neuraminidase



# Flu vaccine strains, 2018-2019

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-00190/2016 (H3N2)-like virus
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

# Trivalent versus quadrivalent vaccines

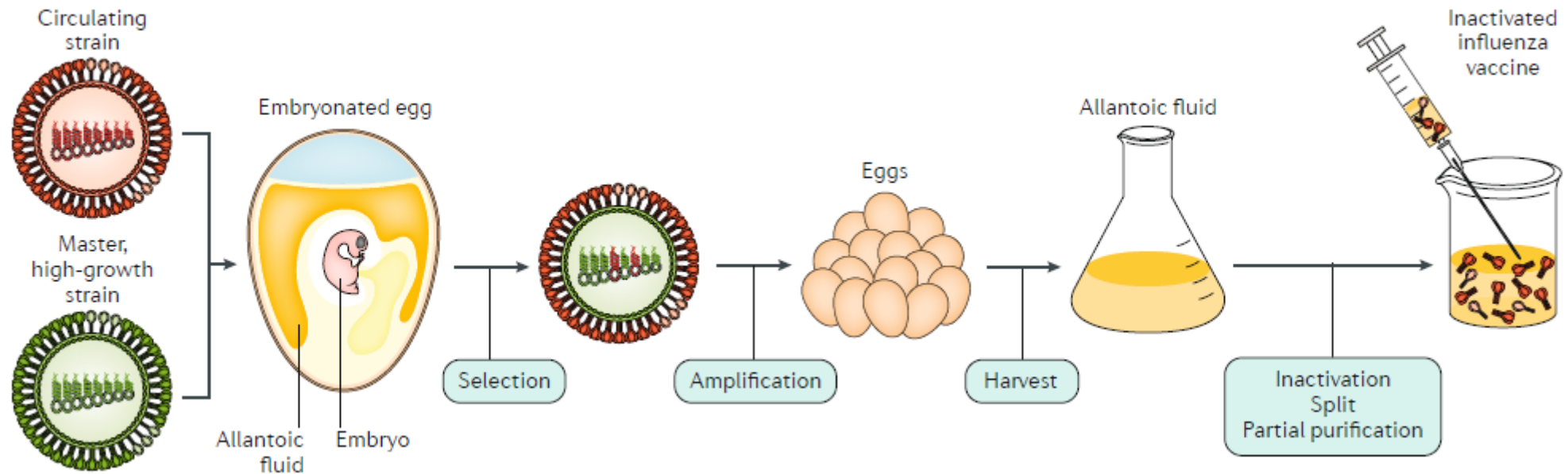
- Trivalent vaccines contain 3 strains of flu
  - Always contain 2 strains of influenza A PLUS
  - 1 lineage of influenza B (Victoria or Yamagata)
- Quadrivalent vaccines contain two strains of influenza B
- Most common influenza A viruses currently are H1N1, H3N2



# Inactivated influenza vaccines

- Killed viruses or individual proteins (not infectious virus)
  - Multiple methods of manufacture
  - Traditional method: egg-based
  - Alternative methods
    - Cell-based
    - Recombinant protein-based

# Egg-based influenza vaccines





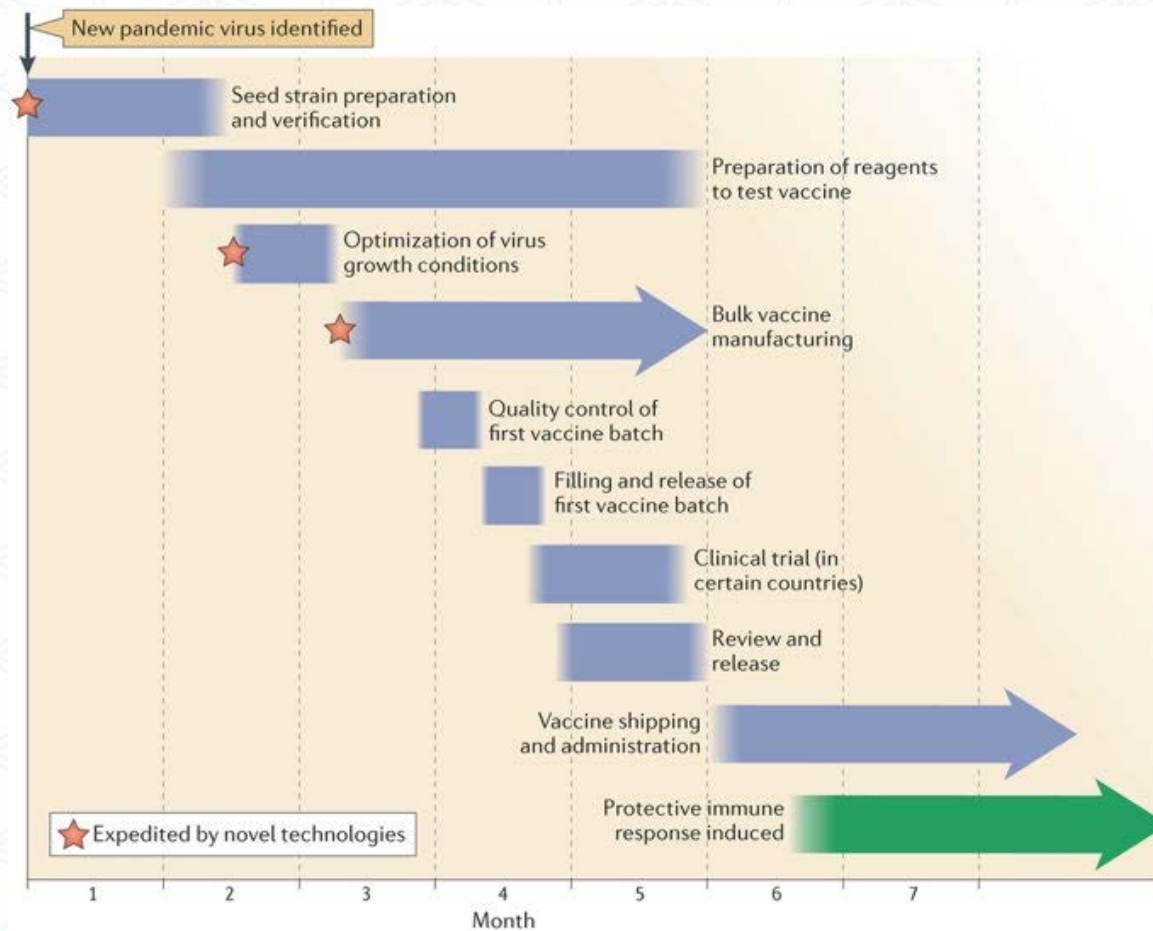
# Egg-based influenza vaccines

- Remains the mainstay of vaccine production
- Disadvantages
  - Long production time
  - Viruses become modified during culture, which may affect antibody targets



*Seasonal influenza vaccine production timeline (Source: NIAID)*

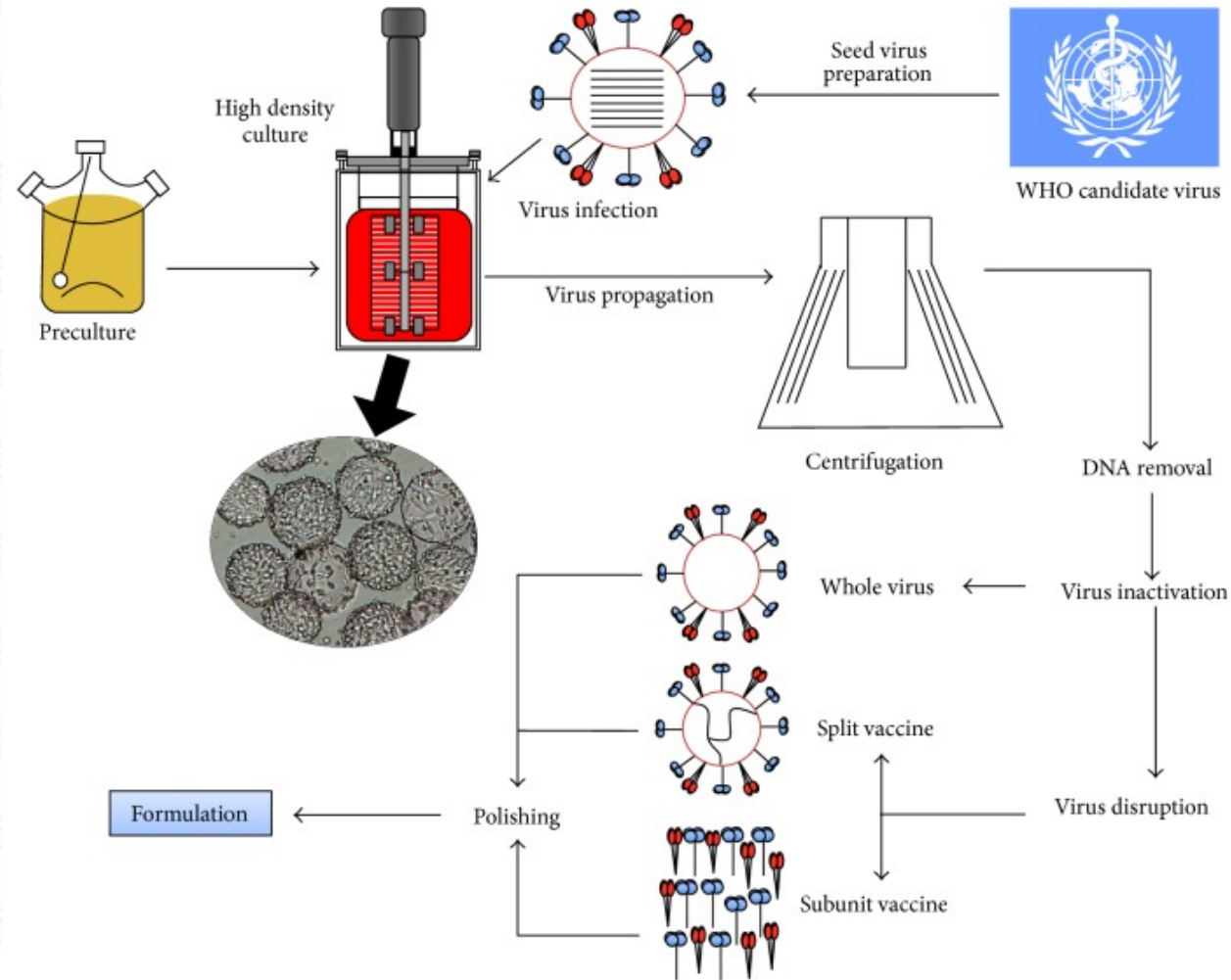
# Egg-based influenza vaccines



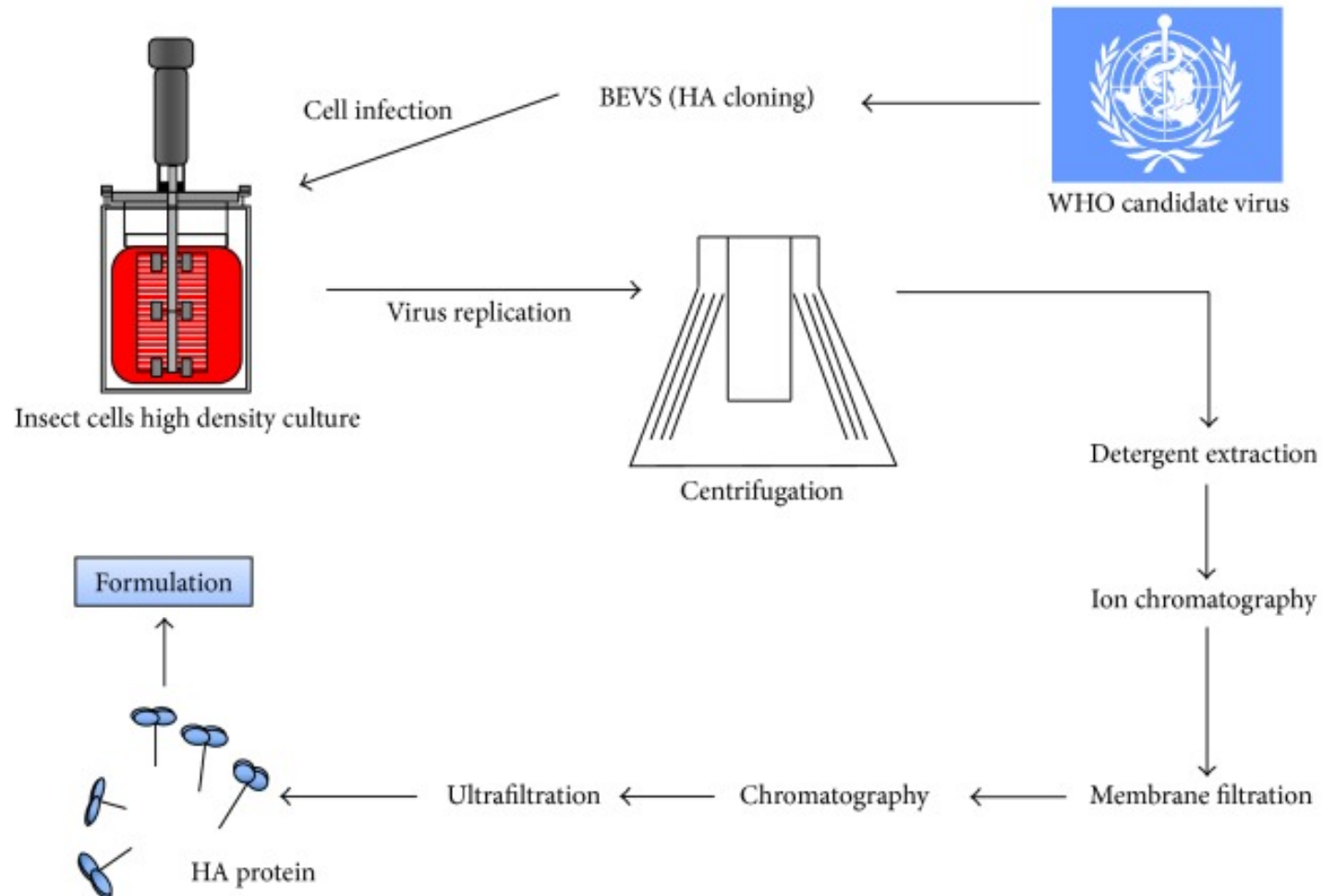
Nature Reviews | Drug Discovery



# Cell culture-based vaccines



# Recombinant vaccines





# Live-attenuated influenza vaccine

- Live but weakened (attenuated) virus
  - Virus has been changed so that it can only survive at colder temperatures
  - Causes asymptomatic infection in the nose but can't spread further
- Delivered as a nasal spray for otherwise healthy people 2-49 years
- Less effective than shots for several previous flu seasons and was not recommended for past 2 years, but for 2018-2019 it is once again considered an acceptable option

# Influenza vaccines

- Multiple options for different scenarios, patient populations
- Getting ANY vaccine far more important than the specific type!

**JUST DO IT**



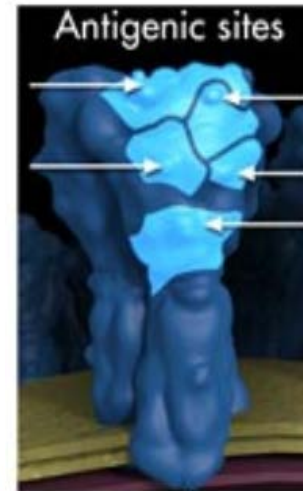
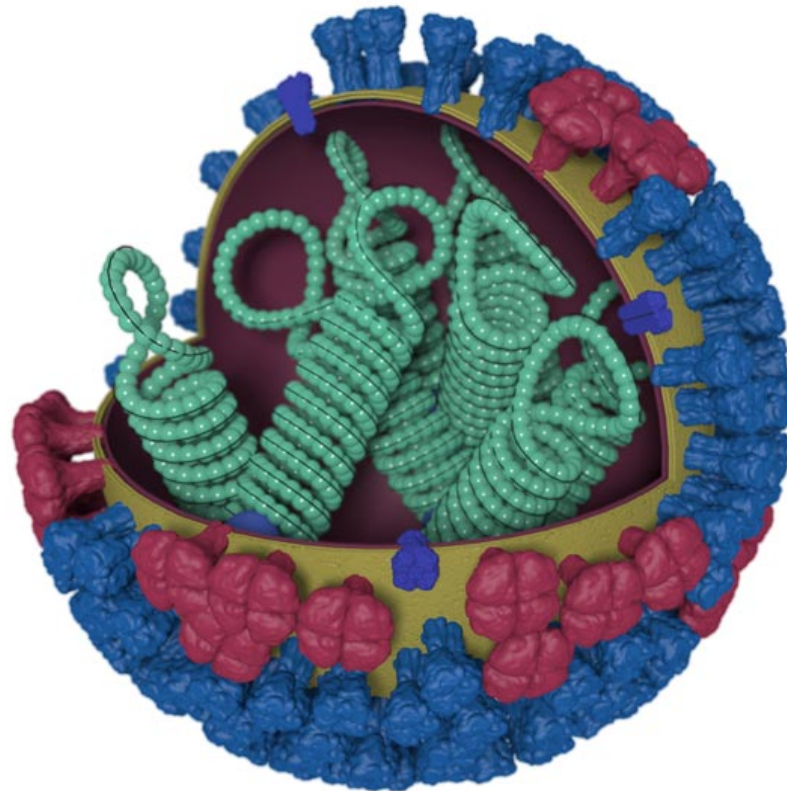


# Influenza vaccination: could it have helped?

- **80% of influenza deaths in children occur in children who were not vaccinated**

# Influenza vaccines: Is there a better way?

## AN INFLUENZA VIRUS



Hemagglutinin



Neuraminidase



# Universal influenza vaccine: the holy grail

- A flu vaccine that only needs to be given once and protects against all future flu infections
- Based on the idea that there must be *some* regions of the virus that are conserved across strains

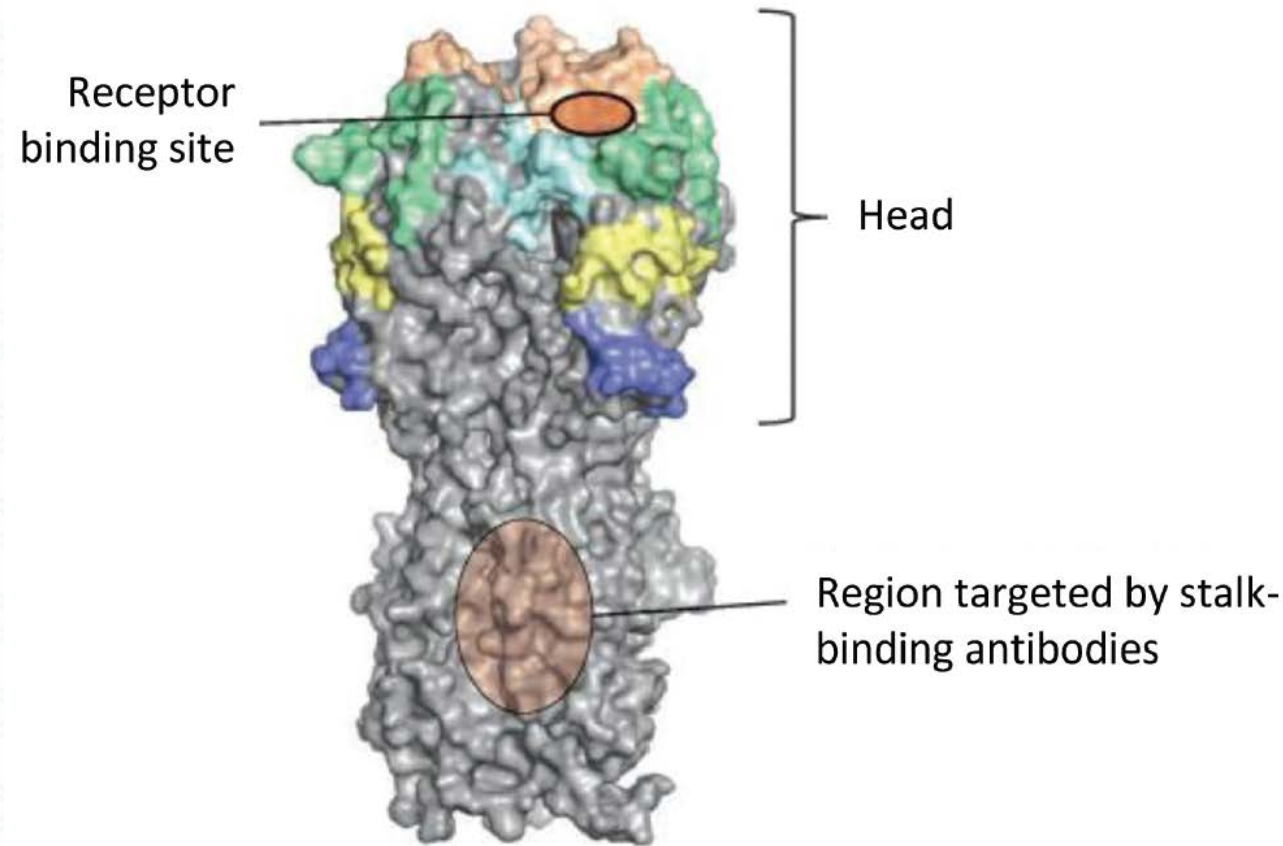


# Universal flu vaccine: possible targets

- HA stalk
- Globular HA head (conserved or optimized antigens)
- M2e channel
- Vaccines that stimulate cellular immune responses



# Universal influenza vaccine: targets



# Conclusions

- Influenza is a serious public health problem, in all populations
- Yearly epidemics interspersed with rare pandemics – get used to it!
- The best way to protect yourself and loved ones is yearly flu vaccine
- Flu vaccines are safe and effective, even if not as effective as we'd like



# For more information

- <https://www.cdc.gov/flu/index.htm>

# Thank you very much!

- Questions?