Introduction to the Immune System, Influenza Epidemics and Pandemics

What is the Purpose of the Immune System?

- ***Defense*** against pathogenic organisms - bacteria and viruses, some fungi & parasites
- ***Identification*** of self versus non-self cells - cancer

Pathogens

These are ***antigens*** – each can be recognized by the immune system

Figure 1-5a
Kuby IMMUNOLOGY, Sixth Edition

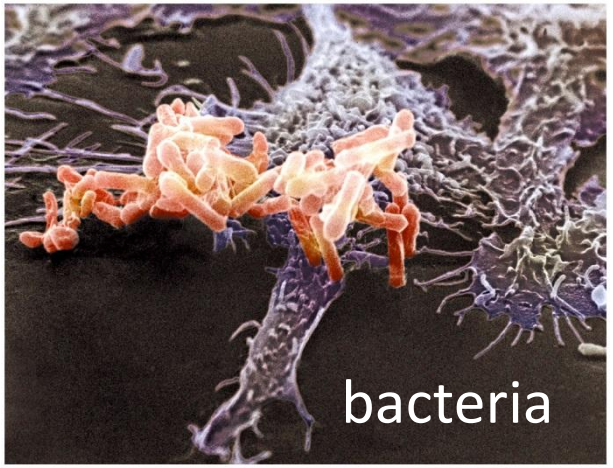

Figure 1-5b
Kuby IMMUNOLOGY, Sixth Edition

Figure 1-5c
Kuby IMMUNOLOGY, Sixth Edition

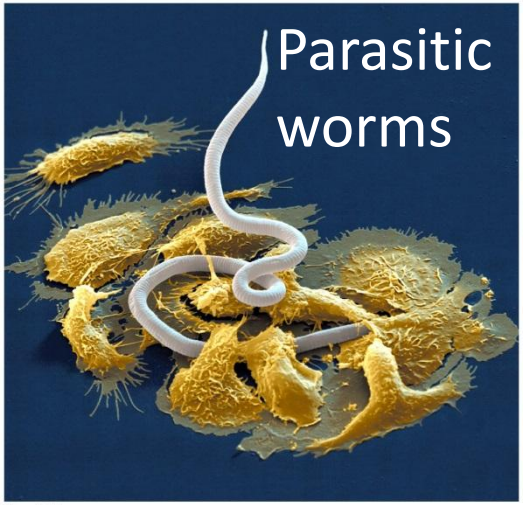

Figure 1-5d
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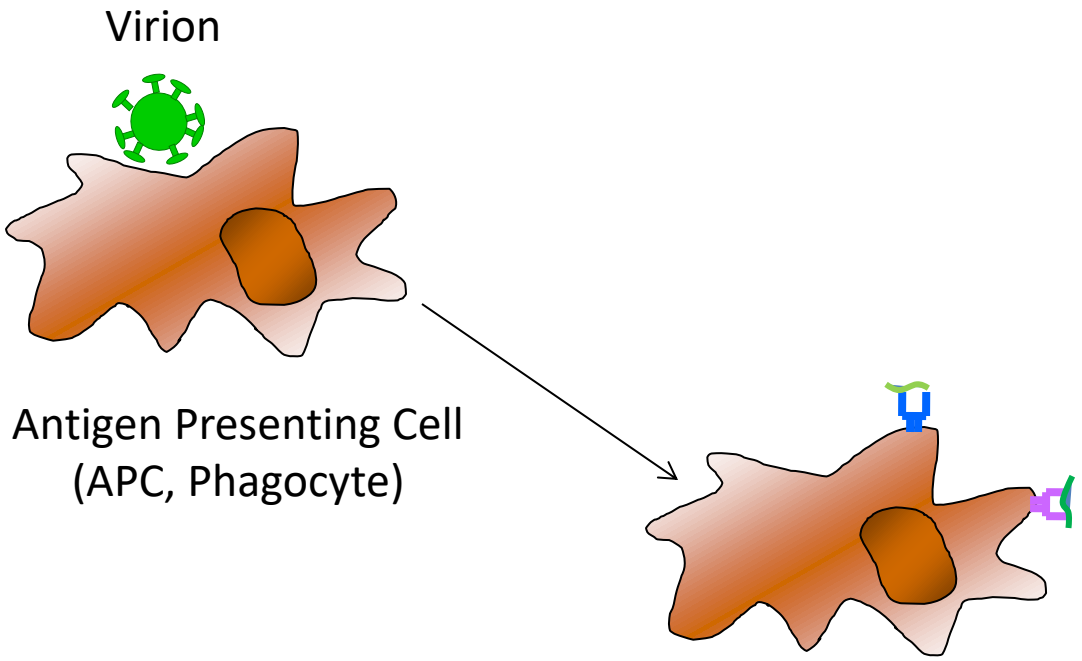
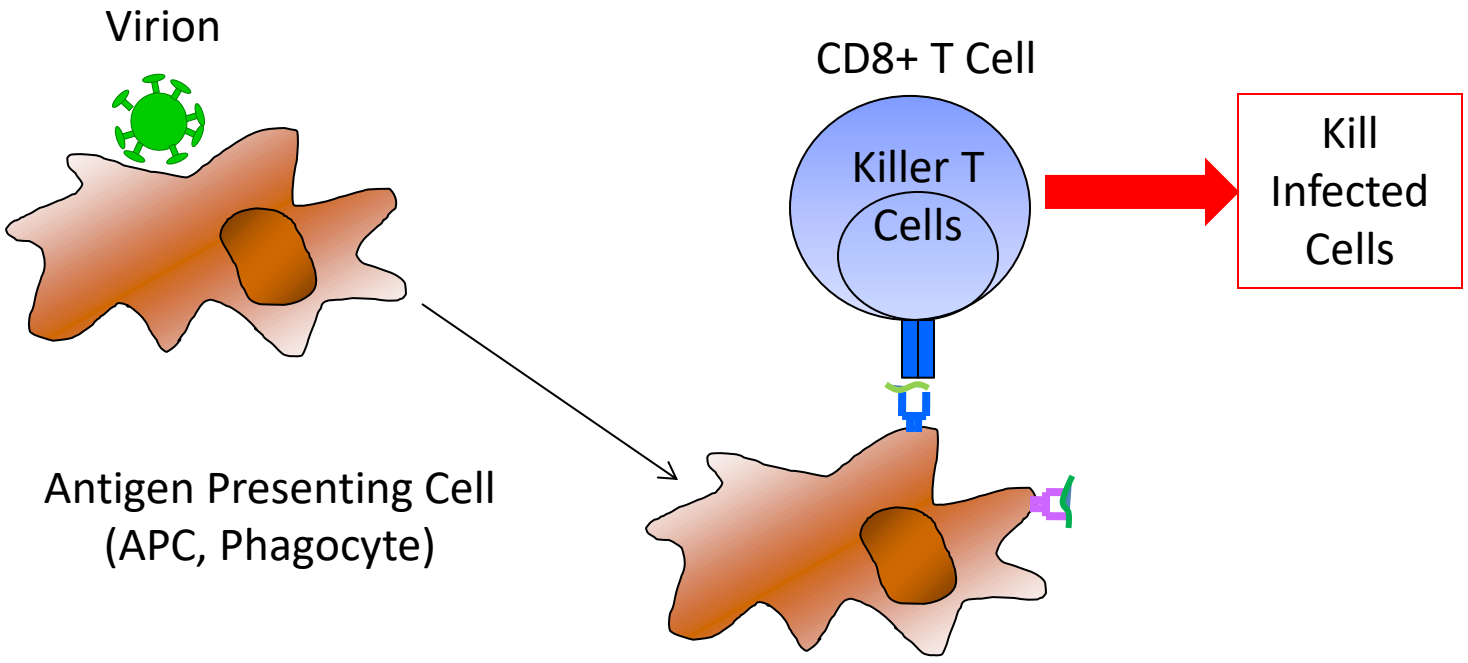
Immune Responses to Infection



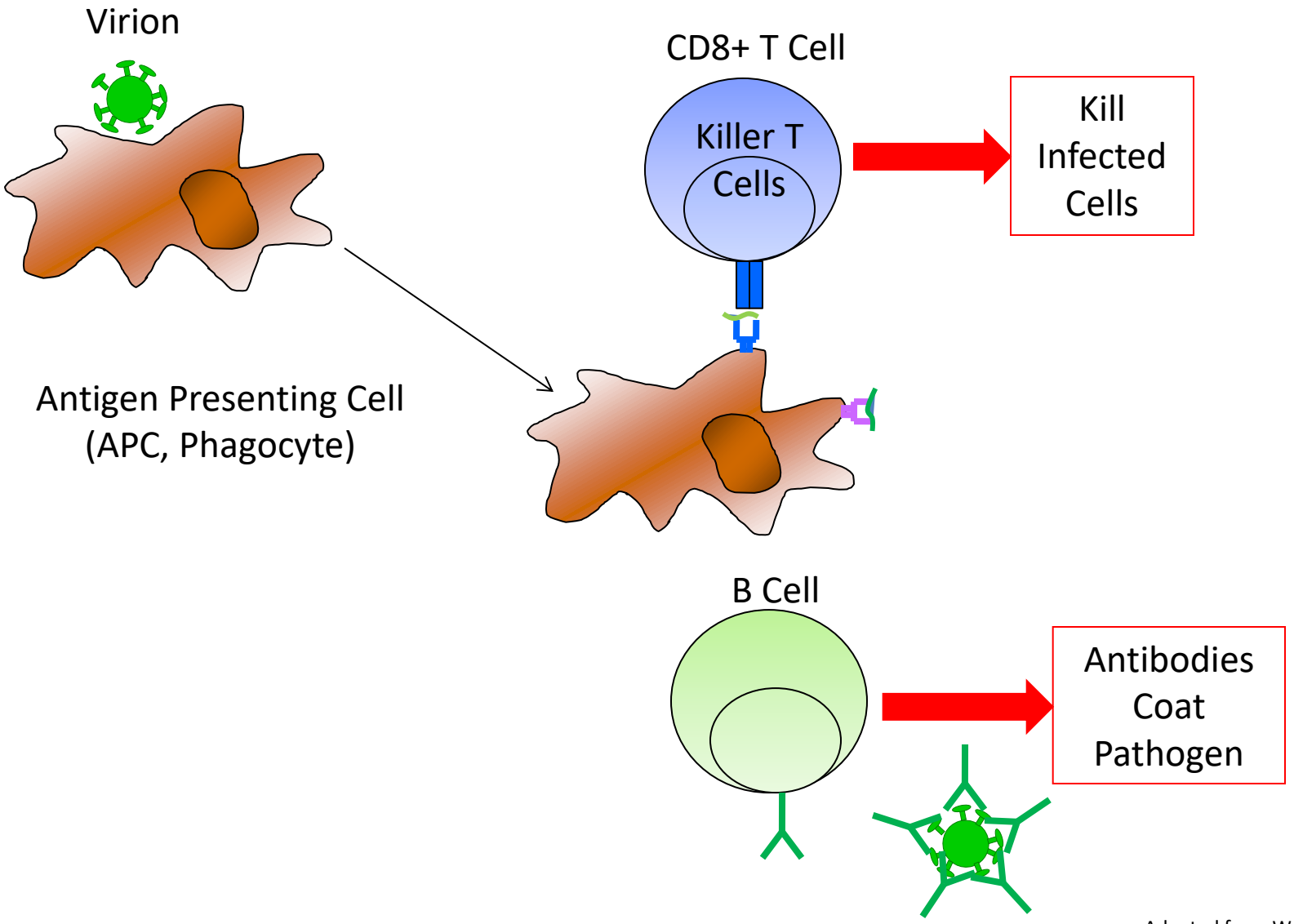
Adapted from Wendy Blay Puryear, Ph.D.

Immune Responses to Infection



Adapted from Wendy Blay Puryear, Ph.D.

Immune Responses to Infection



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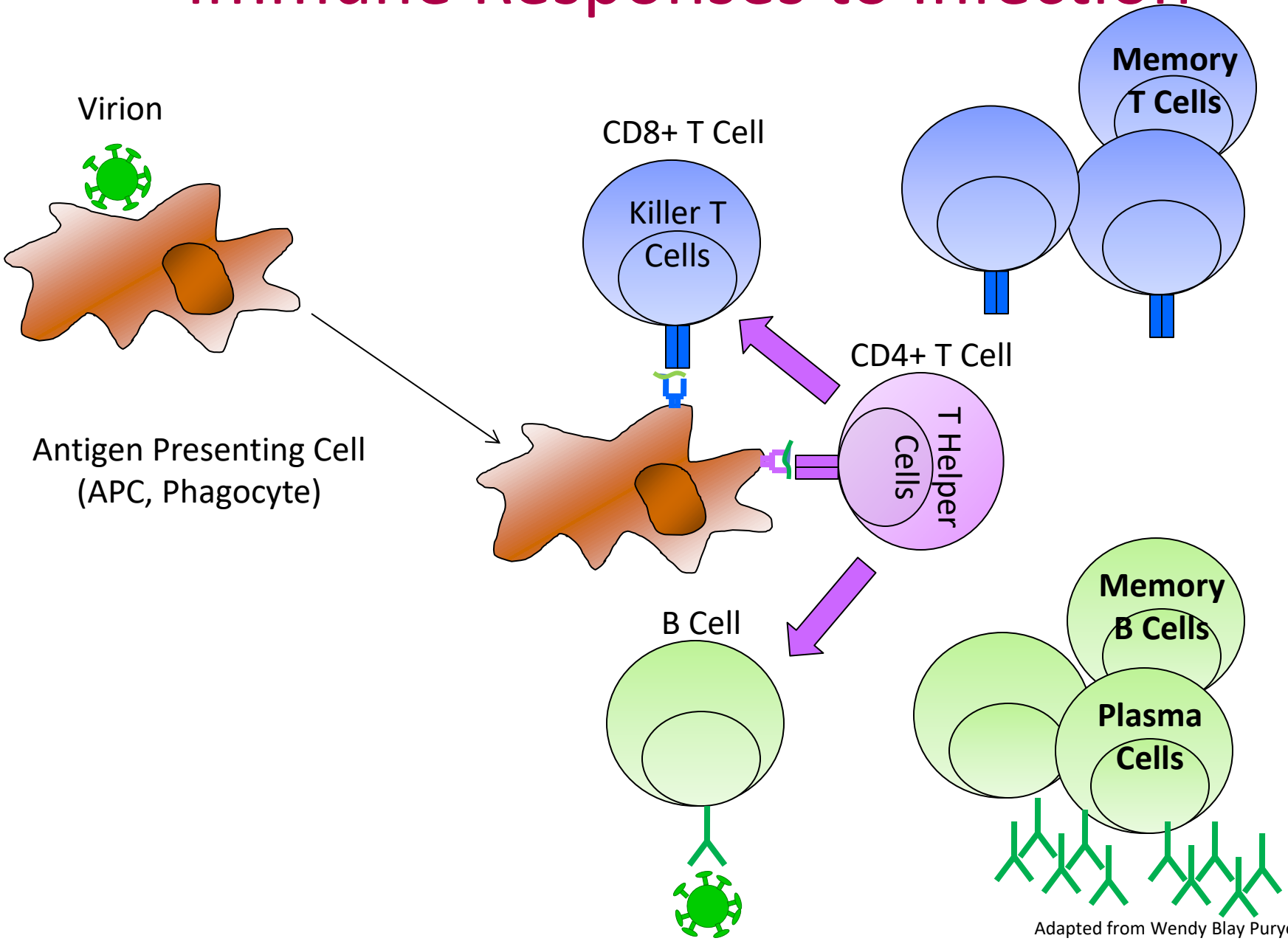
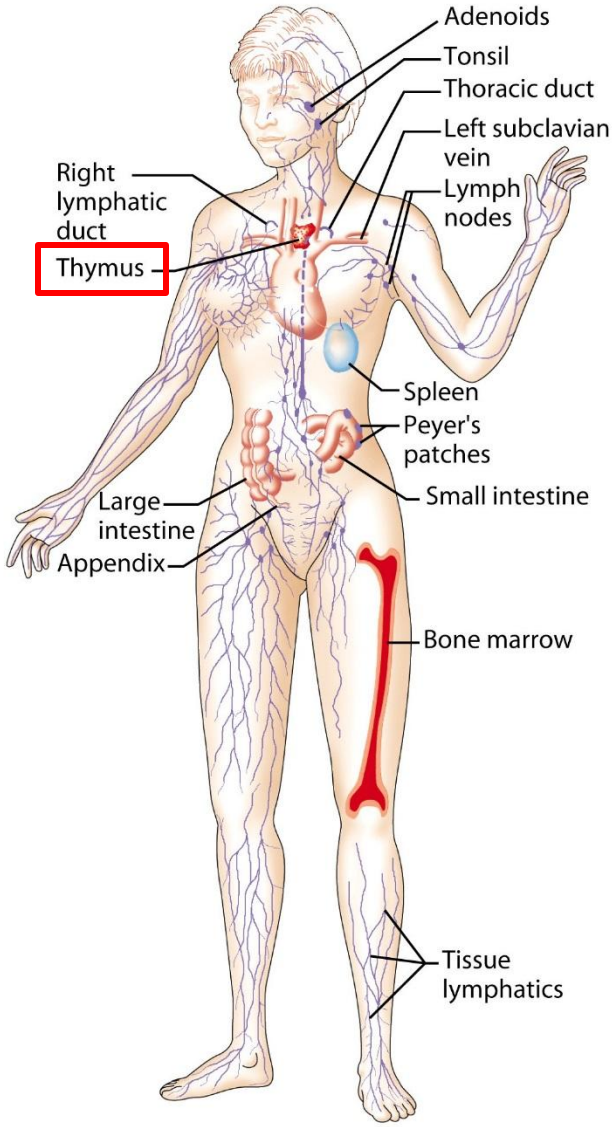
Immune Responses to Infection



Adapted from Wendy Blay Puryear, Ph.D.

Organs of the Immune System



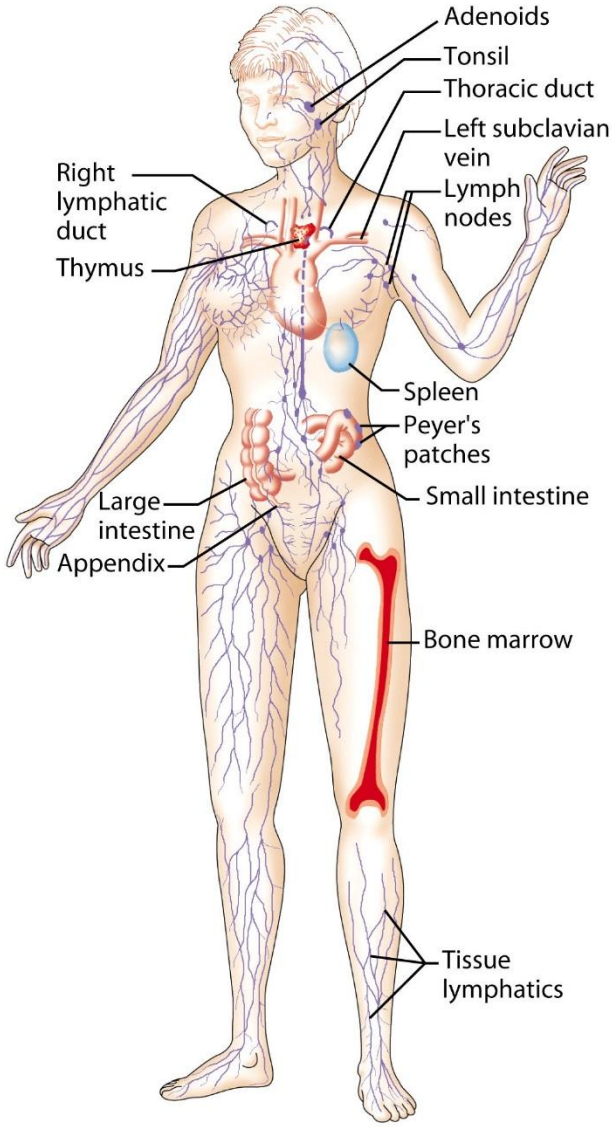
Primary Organs: Production of Cells

1 - **Bone Marrow** – production of all hematopoetic cells ("white blood cells").

- B cells
- T cells
- Other immune cells and red blood cells

2 – **Thymus** – T cells "mature"

Organs of the Immune System



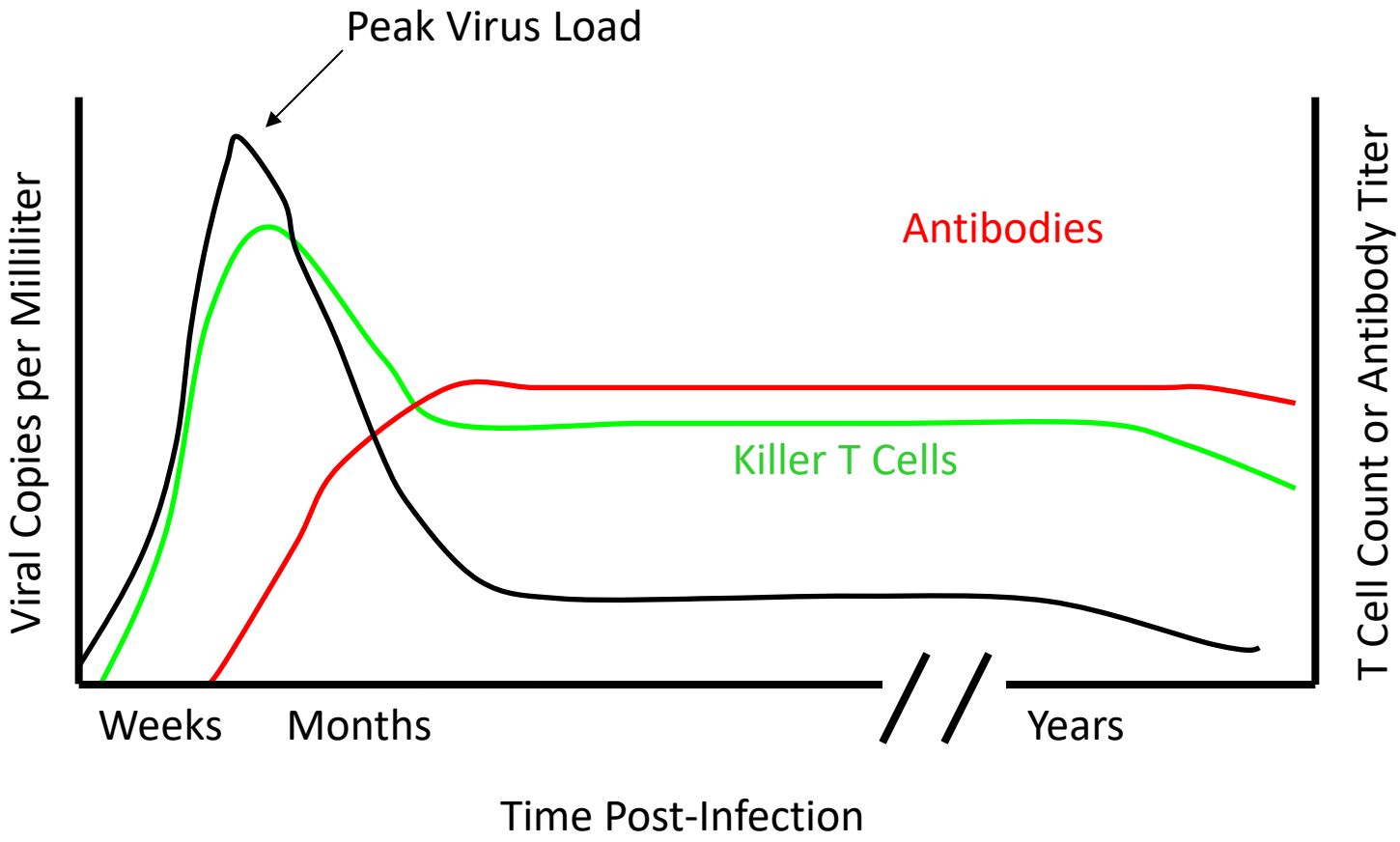
Secondary Organs: Initiation of the "Adaptive Immune Response" (response to a specific pathogen)

1 – **Lymph Nodes**

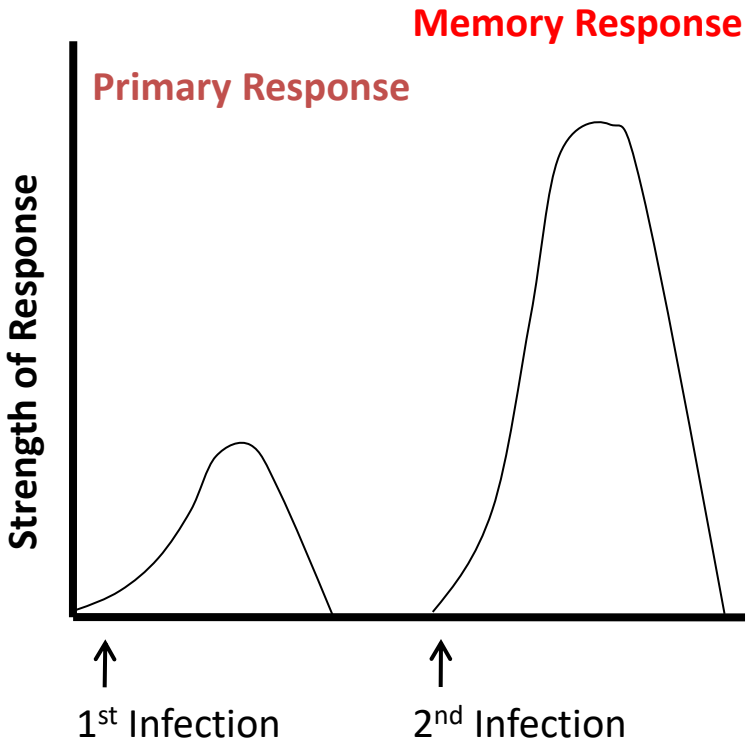
2 – **Spleen**

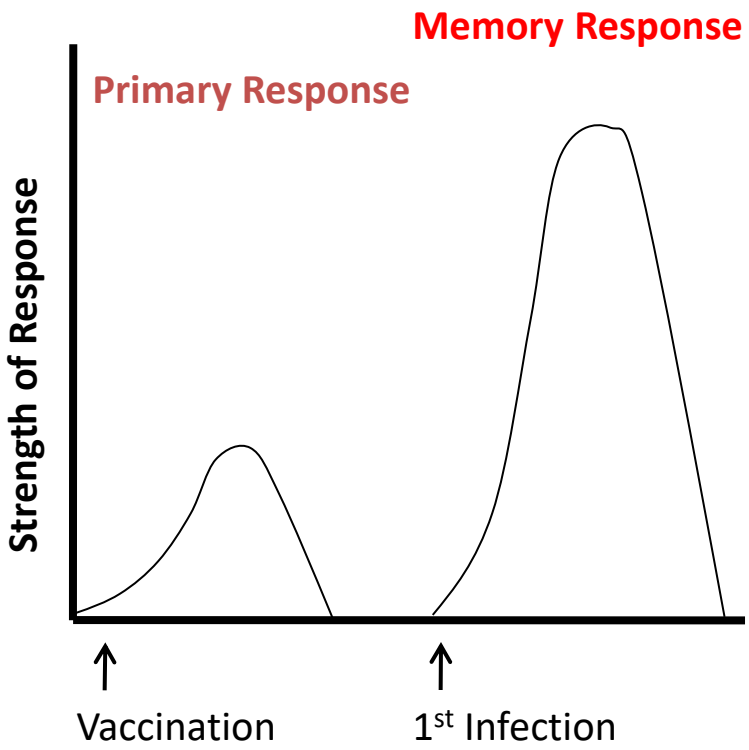
APCs interact with mature B and T cells to start adaptive immune response

How the Immune System Responds to Viral Infection



The Power of Immune Memory



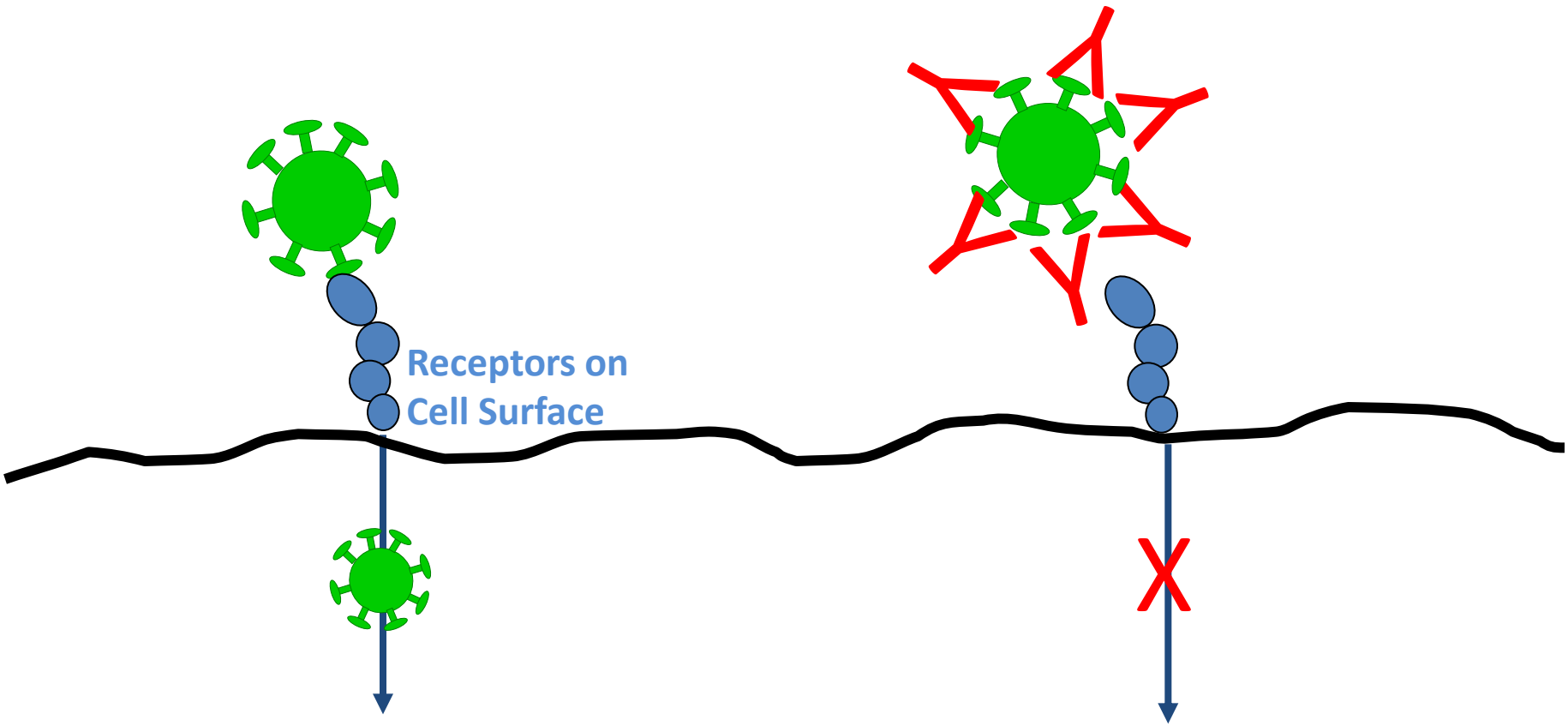


What are Antibodies?

Antibodies are Proteins Made by the Immune System to Fight Infection

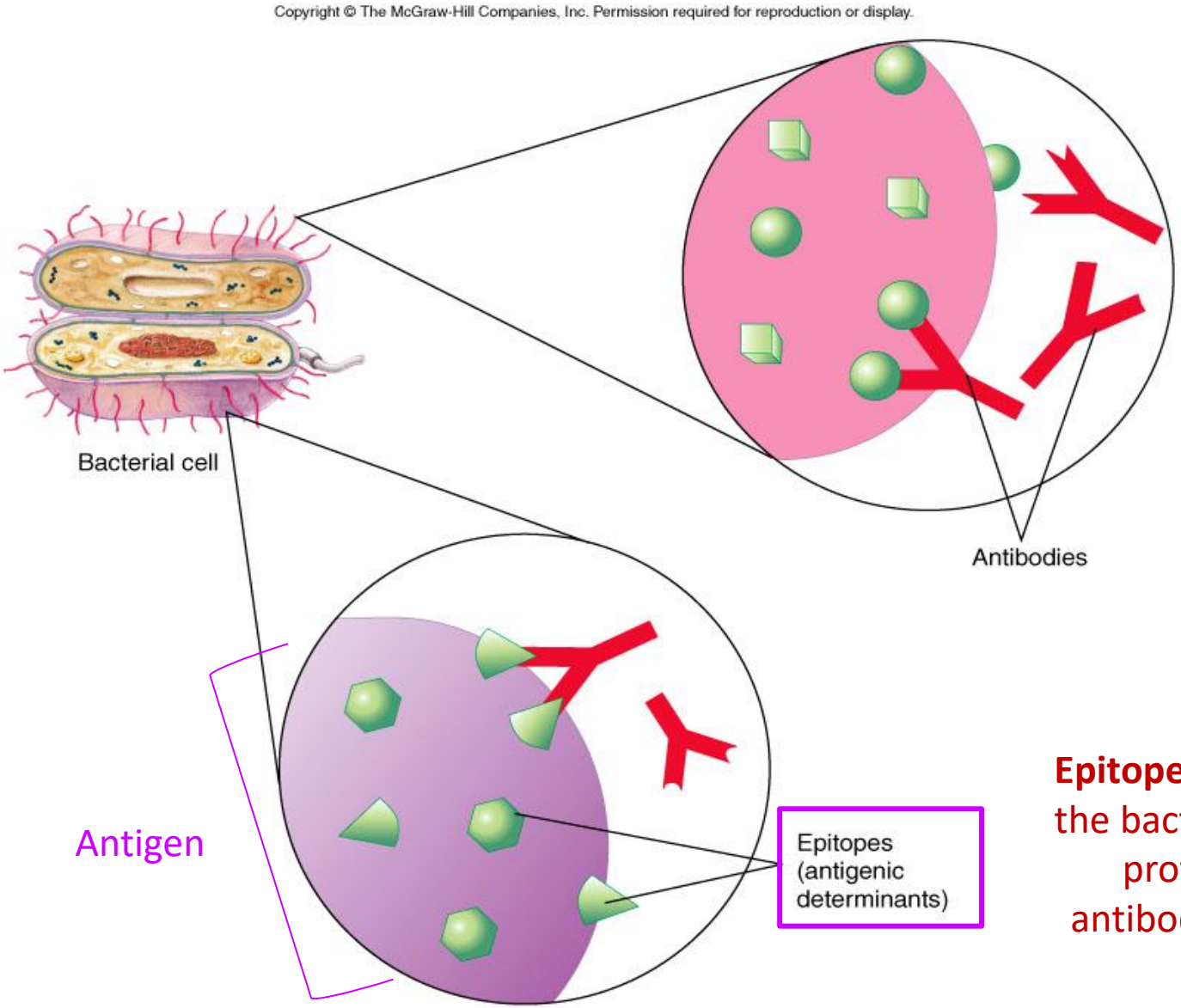
No Antibody:
Virus Enters Cell

Antibody Blocks Virus
from Entering your Cells



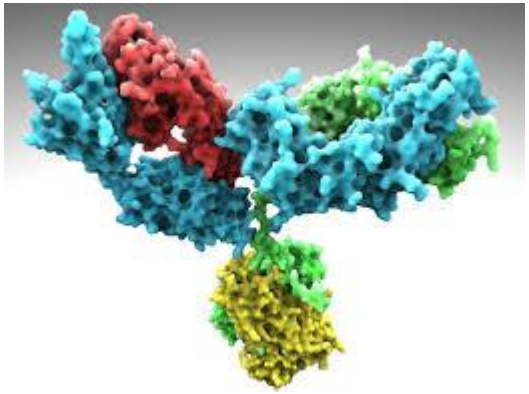
Adapted from Wendy Blay Puryear, Ph.D.

Antibodies Bind to Proteins

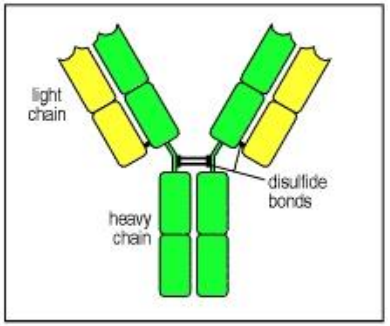


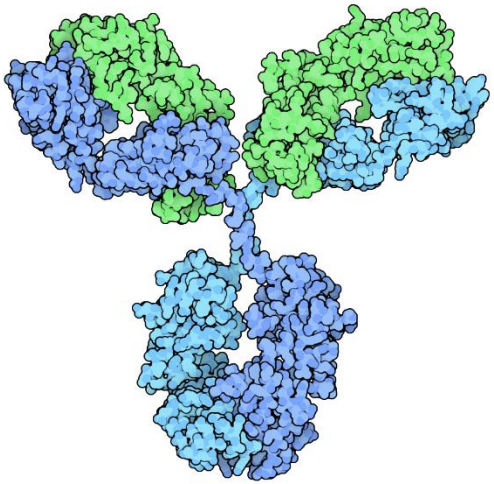
Epitope: The part of the bacterial or viral protein that antibodies bind to

What do Antibodies Look Like?



Y



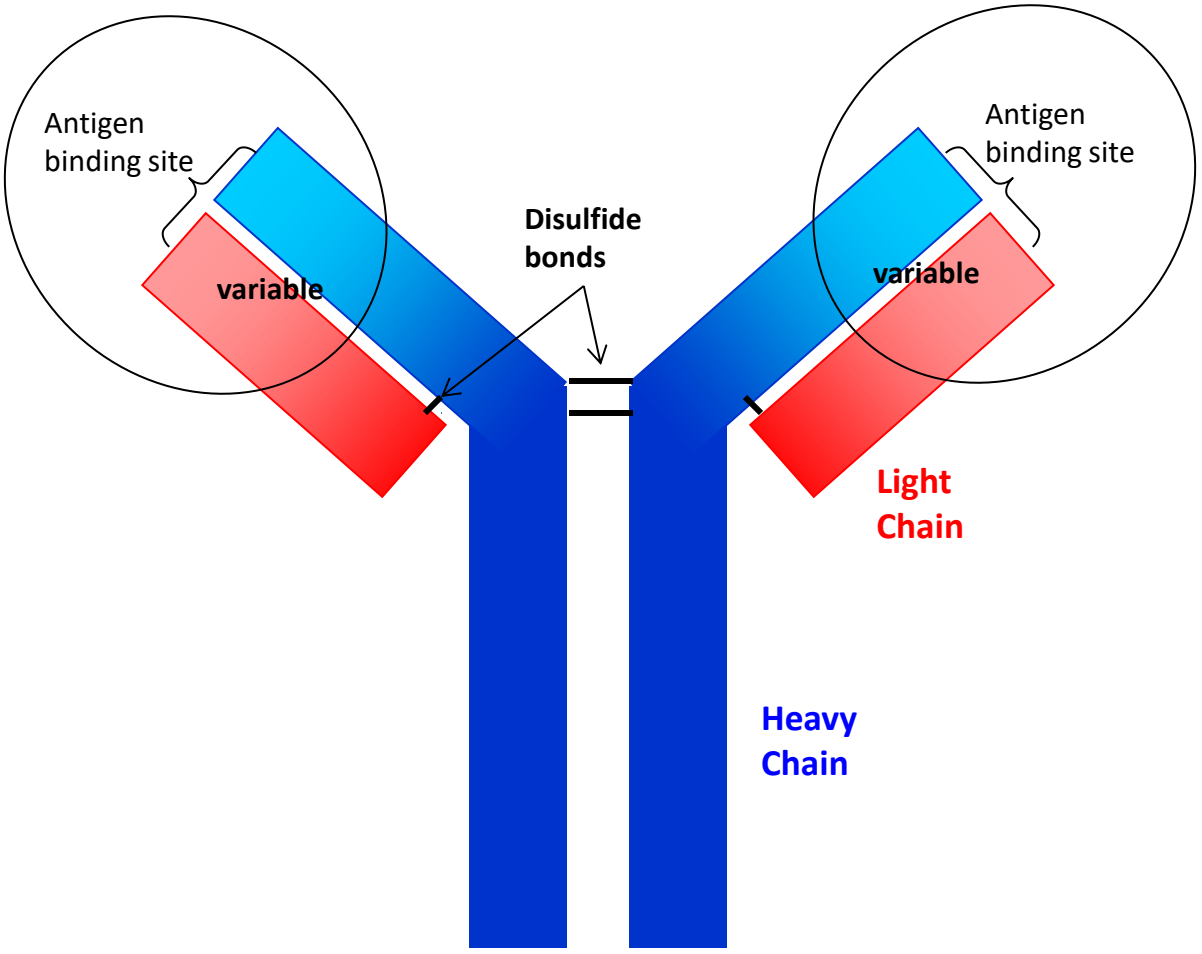


There are many kinds of antibodies, also called **Immunoglobins ("Ig").**

The most common is called "**IgG.**"

"IgM scheme". Licensed under CC BY-SA 2.5 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:IgM_scheme.svg#mediaviewer/File:IgM_scheme.svg
http://www.greatplainslaboratory.com/home/eng/total_igg_vs_igg4.asp
http://www.rcsb.org/pdb/101/motm.do?momID=136
http://www.scq.ubc.ca/mucosal-immunity-and-vaccines/
http://www.turbosquid.com/FullPreview/Index.cfm/ID/605294

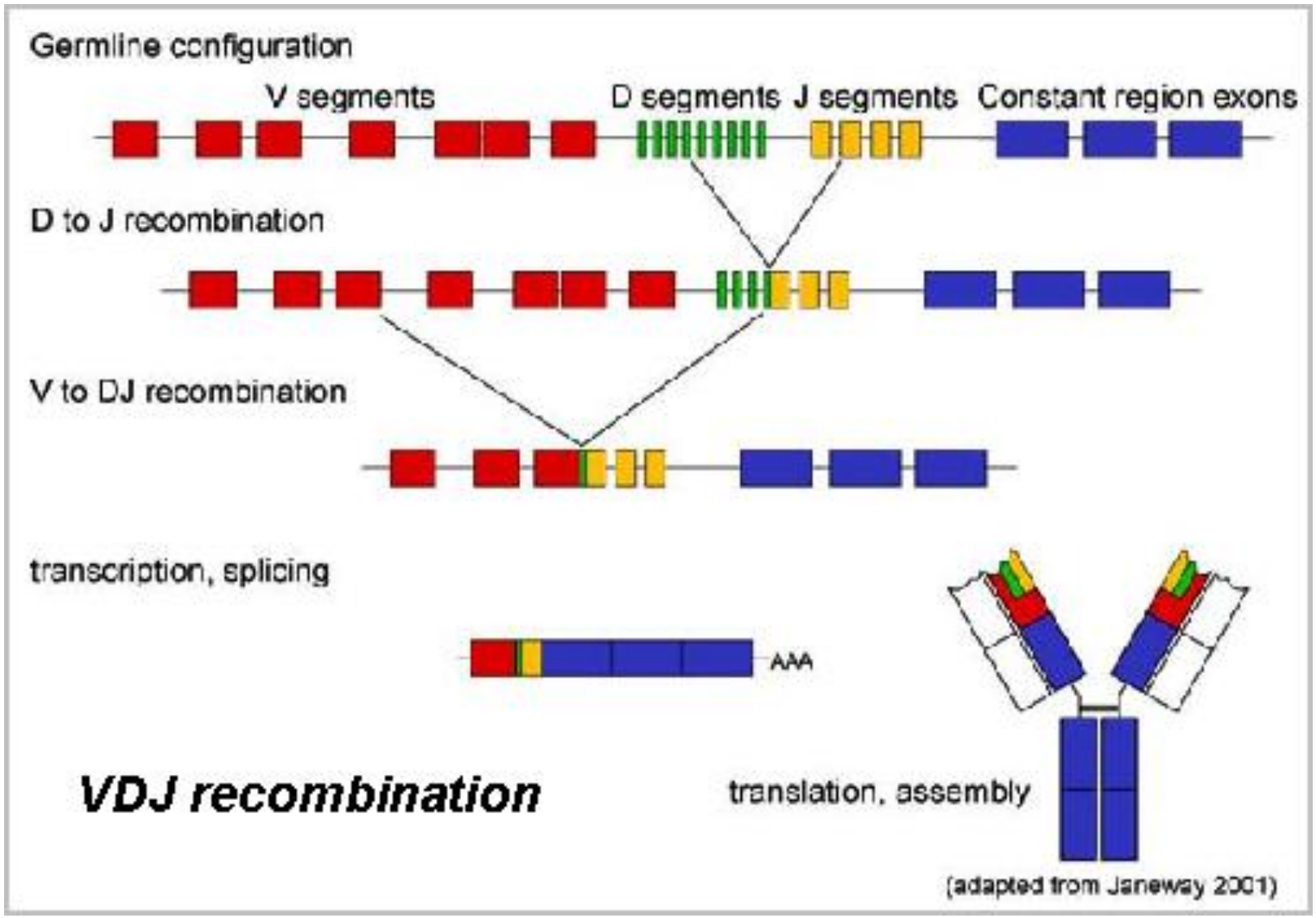
How do 2 genes create antibodies that can bind to any foreign object?



Isotypes:

- IgA
- IgD
- IgG
- IgE
- IgM

Antibody Diversity is Achieved via Genetic Recombination



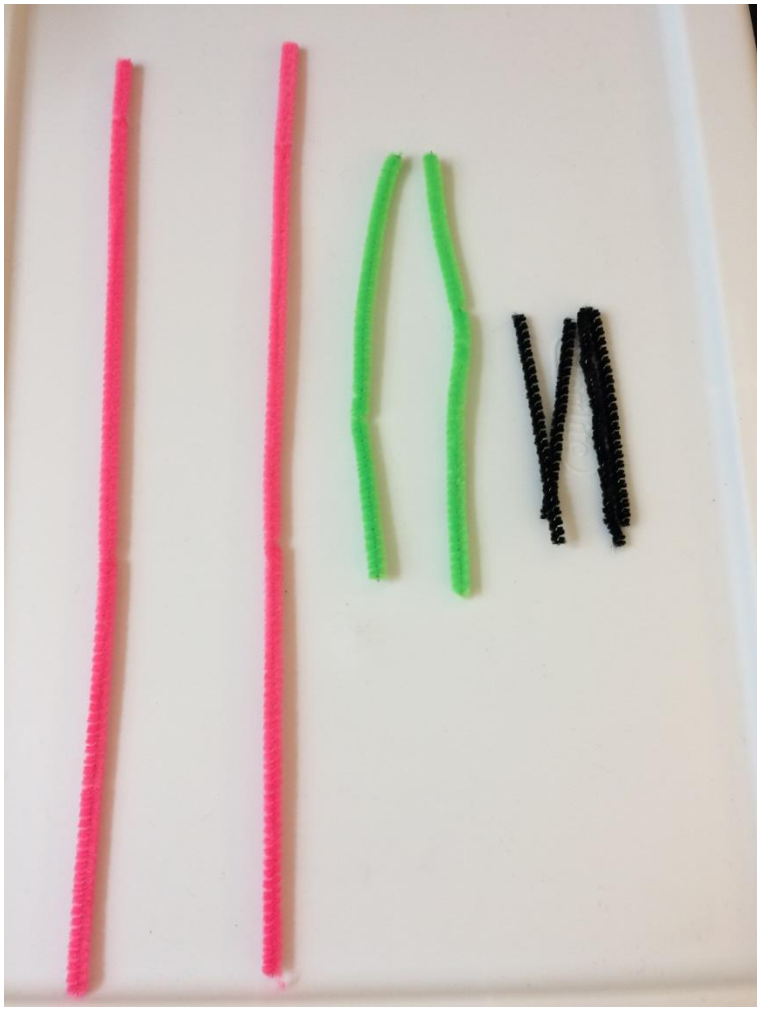
The Human Genome Contains Multiple Heavy and Light Chain Gene Segments

Number of functional gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	40	30	40
Diversity (D)	0	0	25
Joining (J)	5	4	6

Figure 4-3 Immunobiology, 7ed. (© Garland Science 2008)

Gather Your Materials



- 2 long chenille stems of the same color = 2 heavy chains
- 2 short chenille stems of the same color = 2 light chains
- 4 small black chenille stem pieces = disulfide bonds

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Disulfide Bonds on Heavy Chains

- Use two black ‘disulfide bonds’ to attach the two heavy chains
- Bend the two ‘arms’ of the antibody model apart

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Disulfide Bonds on Light Chains

- Attach each light chain to each heavy chain using 1 disulfide bond each

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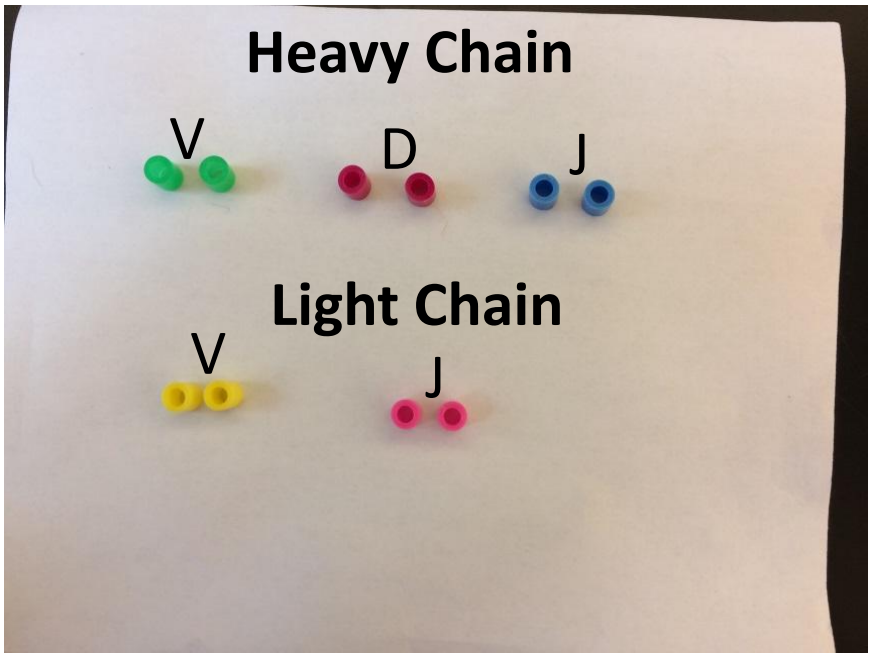
Increasing Antibody Diversity: V(D)J Regions



- **<u>Heavy Chains</u>**:
  - Choose 2 “V” beads
  - Choose 2 “D” beads
  - Choose 2 “J” beads
- **<u>Light Chains</u>**:
  - Choose 2 “V” beads
  - Choose 2 “J” beads
  - *Light chains don’t have D regions*

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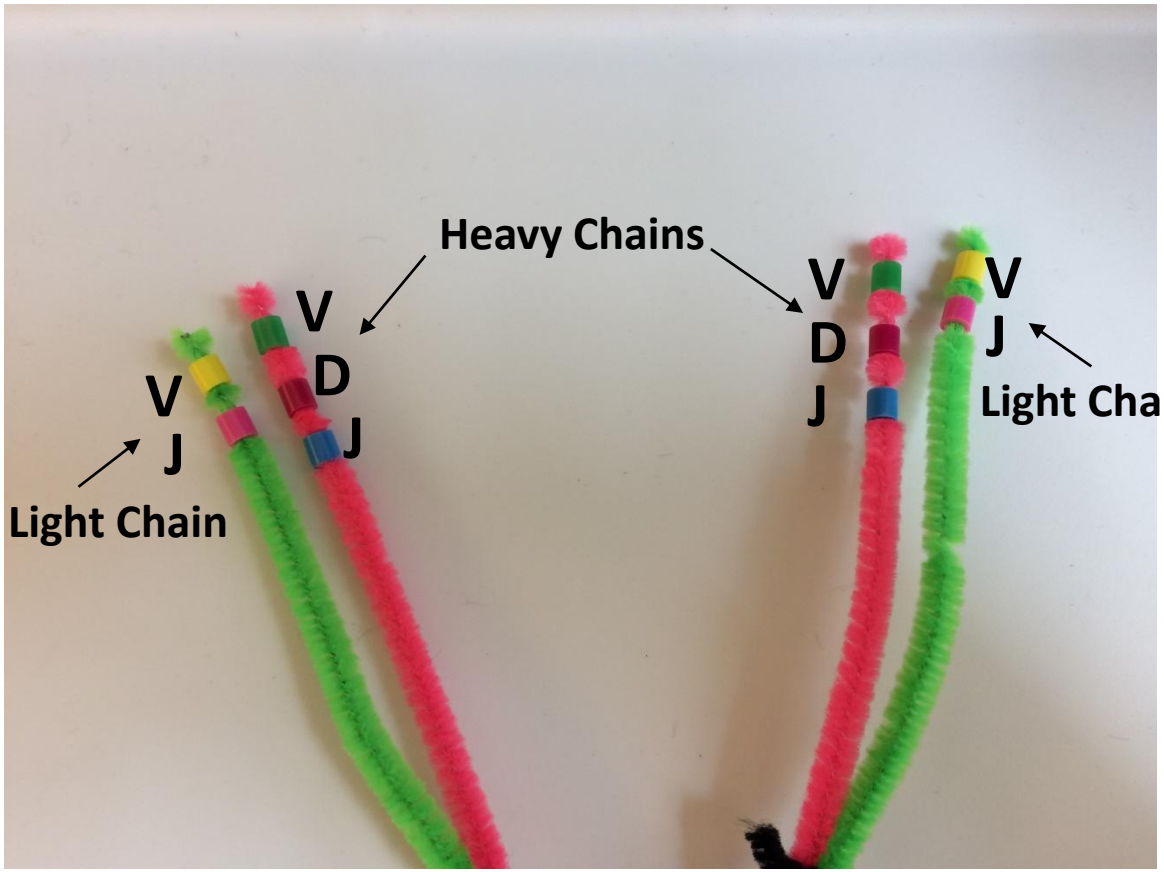
Increasing Antibody Diversity: V(D)J Regions



- Place the 3 V, D and J beads on each heavy chain
- Place the 2 V and J beads on each light chain

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Final Antibody Structure: Each One is Different!

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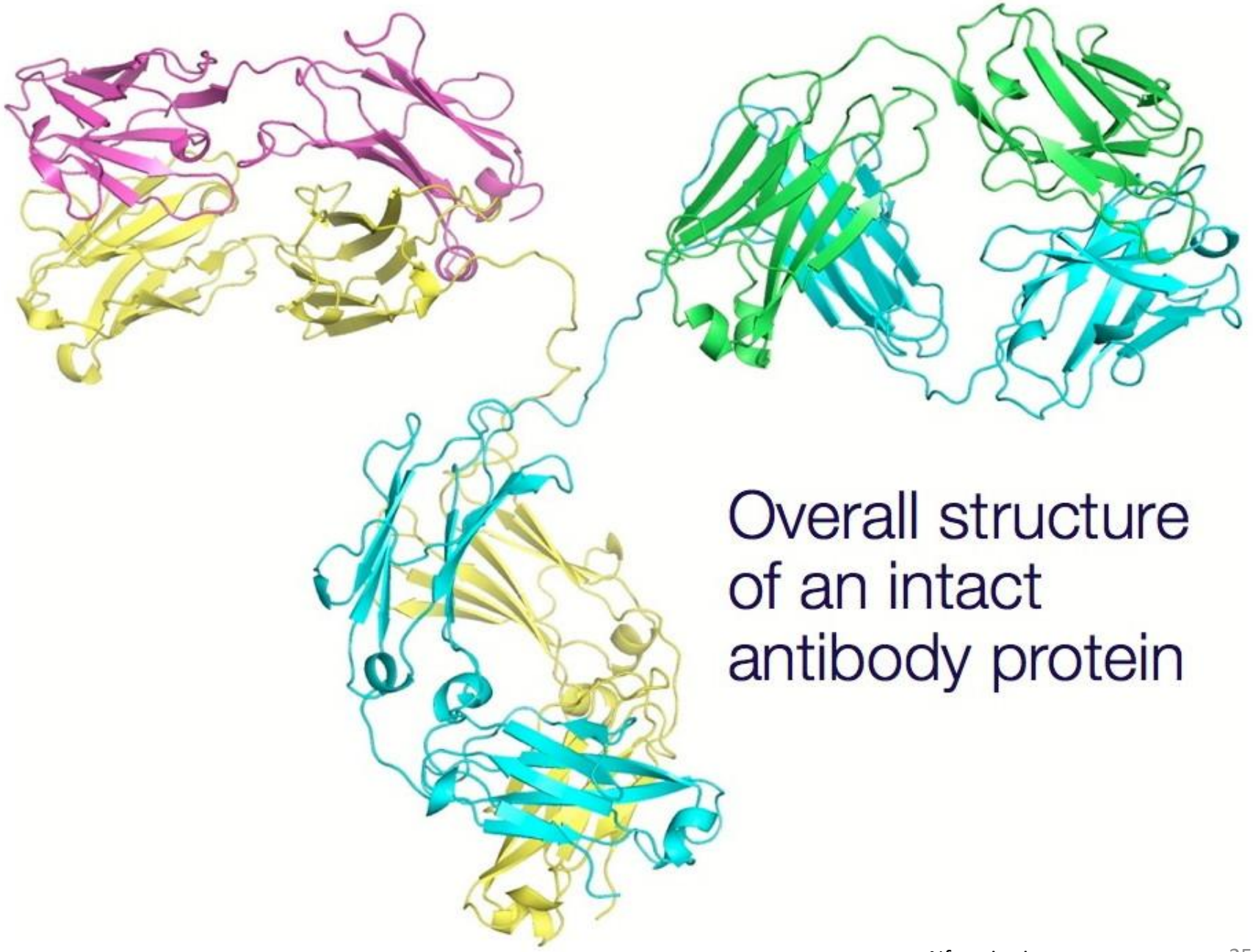


Overall structure of an intact antibody protein

Why Study Influenza?

- Fairly common infectious agent
  - Annual **prevalence** 1.5-70% ("**prevalence**" = how many people are infected at one time)
  - 3-5 million cases & 250,000-500,000 deaths worldwide
  - 36,000 deaths & 200,000 hospitalizations in US, mostly the very young & the elderly
- Risk of pandemic: ~3 / century, kills 2-5% of world population
- Need for effective vaccines & therapeutics
  - Current vaccines updated annually (there is no 'universal' vaccine)
  - Current therapeutics (Zanamivir / Ralenza & Oseltamivir / Tamiflu are modestly effective at limiting symptoms -> resistance)

Annual Economic Costs of Influenza

Table 1

Estimated annual influenza impacts on the entire US using population and costs of 2010

	Total	Lower 95%CI	Upper 95%CI
Number of cases (Million)	25.34	24.83	25.86
Direct costs (Millions $)	10,262.98	10,046.60	10,482.80
Indirect costs (Millions $)	18,853.66	18,321.81	19,439.80
Total economic costs (Millions $)	29,116.65	28,441.24	29,870.84

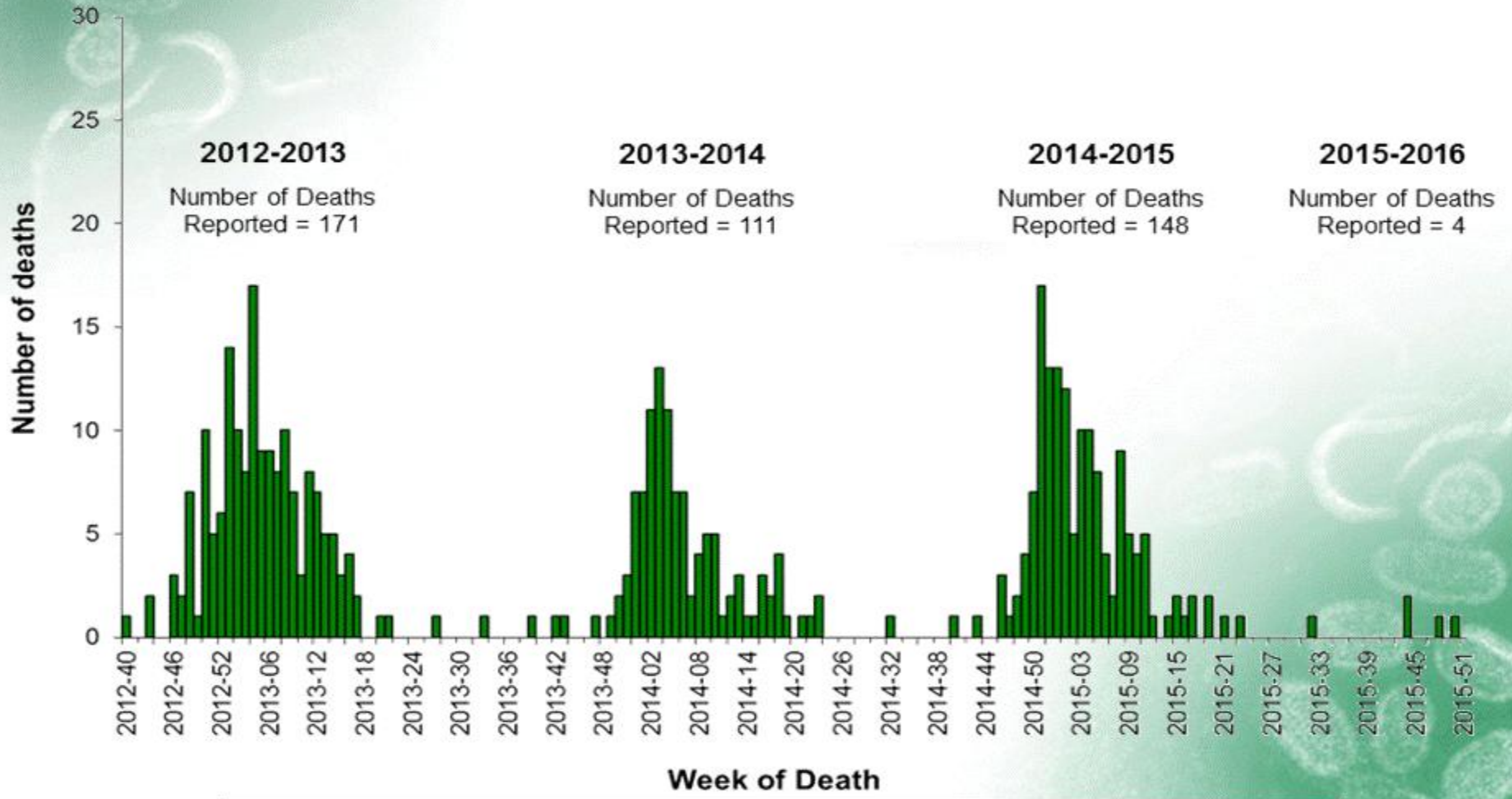
Source: Mao et al. 2012. Annual economic impacts of seasonal influenza on US counties: Spatial heterogeneity and patterns. *International Journal of Health Geography.* 11(16). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3479051/. Accessed September 17, 2018.

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

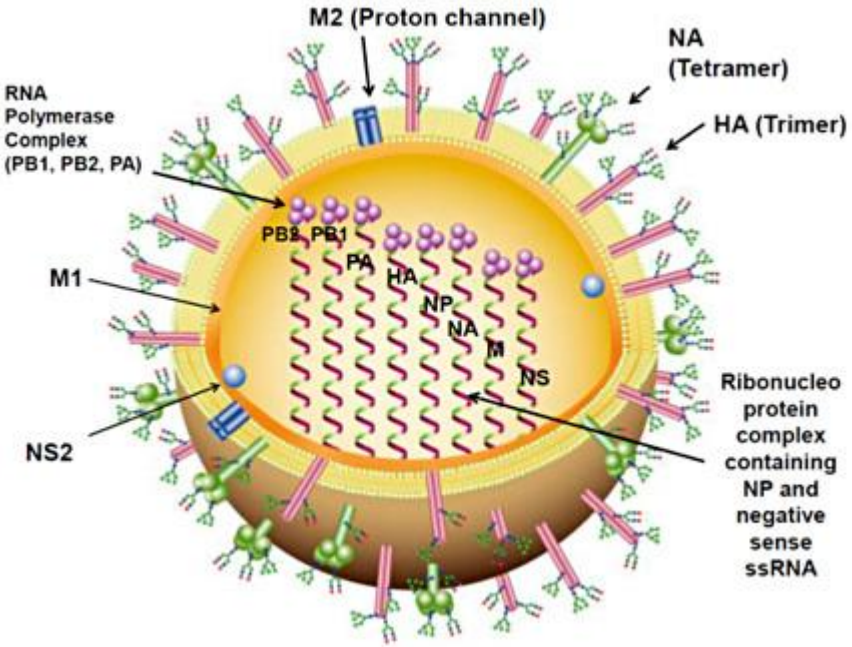
CDC

Number of Influenza-Associated Pediatric Deaths by Week of Death: 2012-2013 season to present



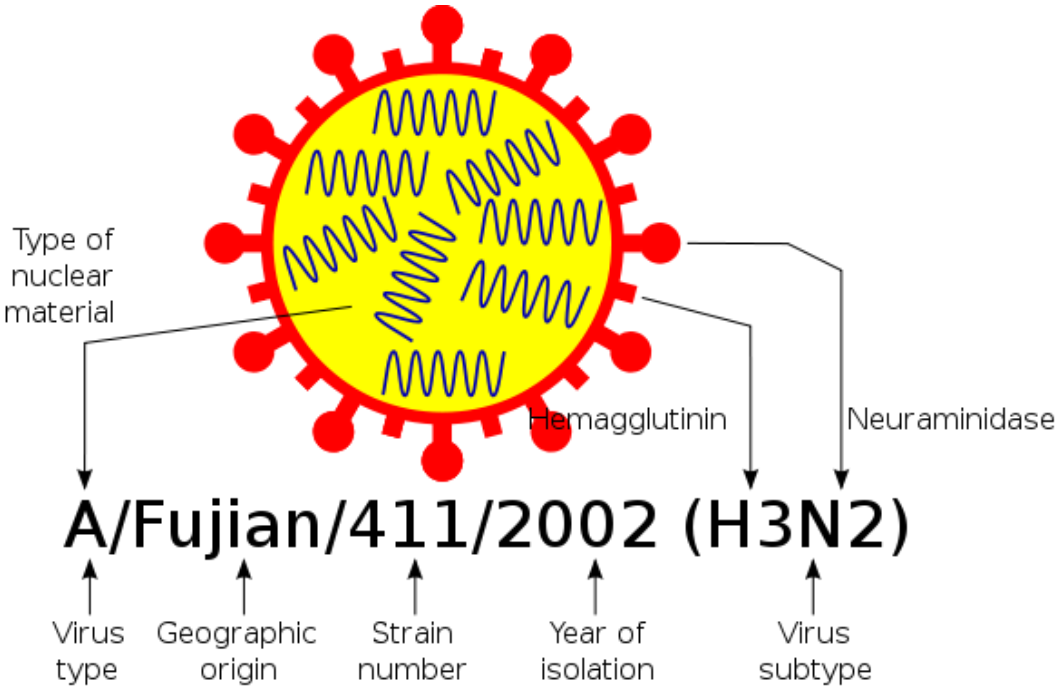
Viral Structure

- Surface proteins
  - Hemagglutinin: protein the virus uses to get into the cell
  - Neauraminidase: protein the virus uses to get out of the cell
  - M2 (Proton channel)
- "Shell" of the virus is made of M1 proteins
- Inside:
  - Other proteins & **8 RNA segments** (genome)



http://www.glycoforum.gr.jp/science/glycomicrobiology/GM10/GM10E.html

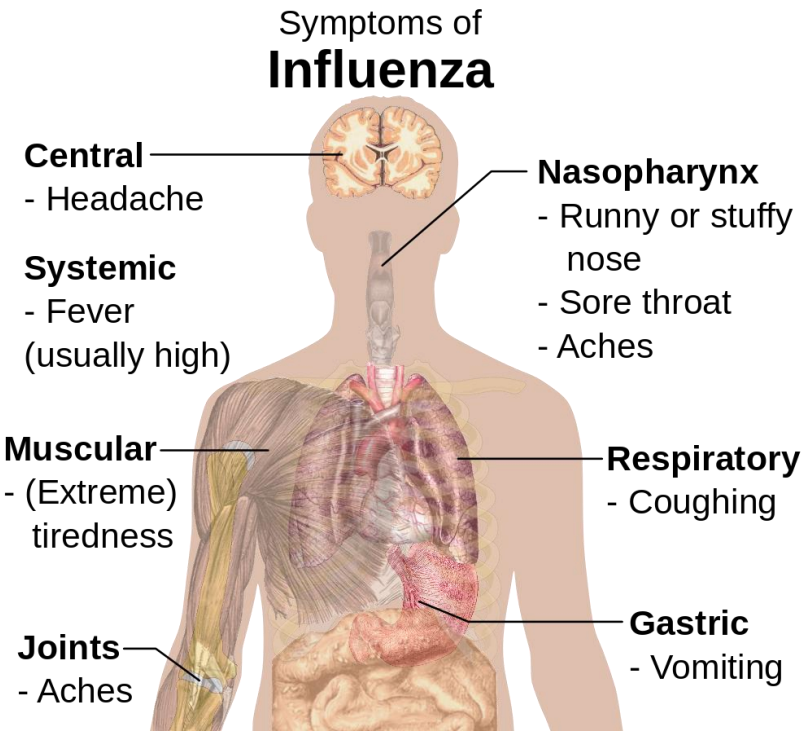
How Viruses are Named

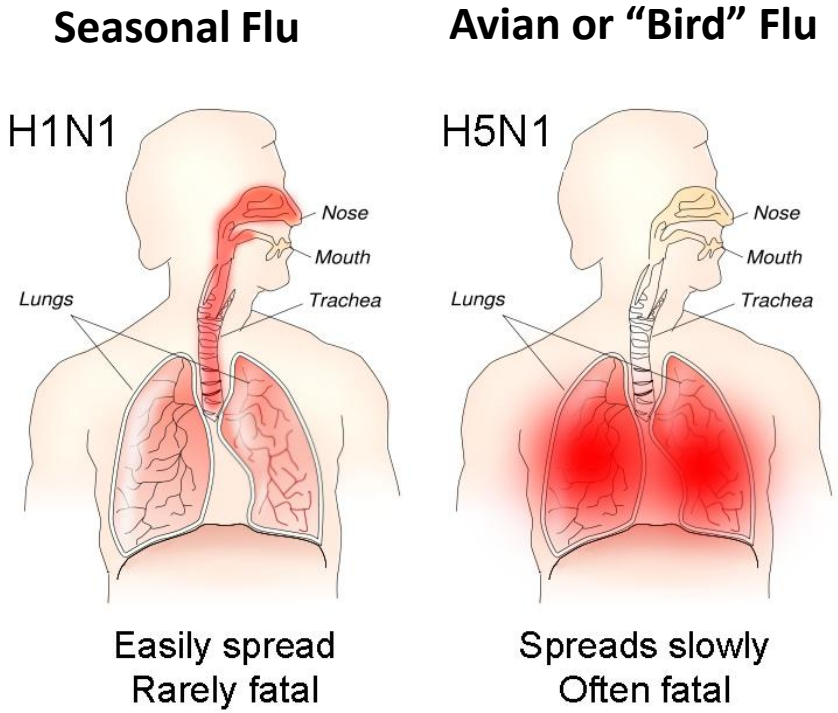


- H1 through H18
  - H1, H2 & H3 are most common in humans
- N1 through N11
  - N1 & N2 are most common in humans

- Different subtypes are ~50% the same
- Viruses within a subtype are ~90% the same

Pathogenesis of Influenza





"Symptoms of influenza" by Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". Wikiversity Journal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 20018762.

"H1N1 versus H5N1 pathology" by TimVickers - Own work. Licensed under Public Domain via Commons - https://commons.wikimedia.org/wiki/File:H1N1_versus_H5N1_pathology.png#/media/File:H1N1_versus_H5N1_pathology.png

Antibiotics Versus Antivirals

Antibiotics Treat Bacteria

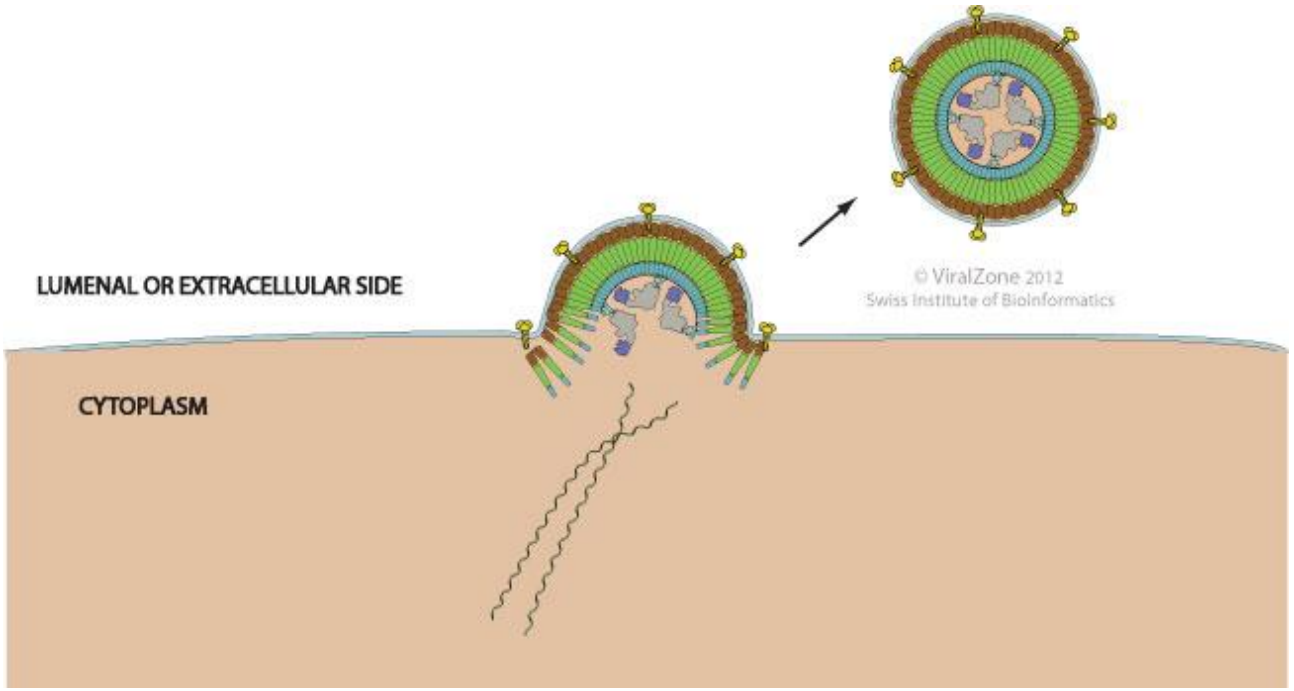
- Types of bacteria:
  - *Escherichia coli* (*E. coli*)
  - *Staphylococcus aureus*
  - *Mycobacterium tuberculosis* (MTb)
- How antibiotics work:
  - Classes of antibiotics work on multiple bacteria
  - Block things like:
    - Making a cell wall (penicillin)
    - Making bacterial proteins (streptomycin)

Antivirals Treat Viruses

- Types of Viruses:
  - Influenza
  - HIV
  - Zika
  - Ebola
- How antivirals work:
  - Specific to each virus
  - Block things like:
    - Getting in the cell
    - Getting out of a cell
    - Making more viral genetic material

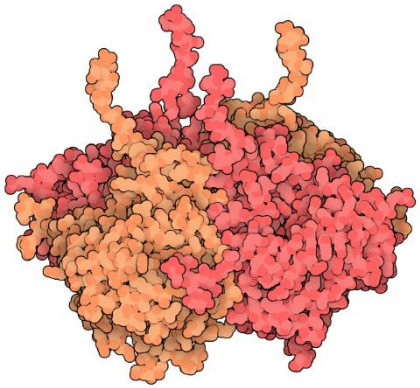
Viruses Use YOUR Cell Membranes!

<u>Budding</u> = A new virus forms at the cell membrane and "buds" off the surface, taking your cell membrane with it.

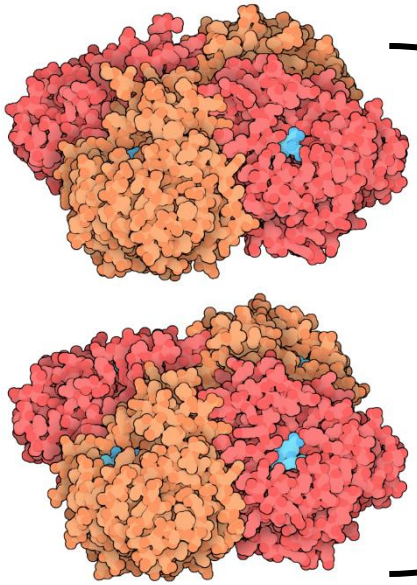


https://viralzone.expasy.org/1947?outline=all_by_protein

Antivirals Prevent Viral Budding

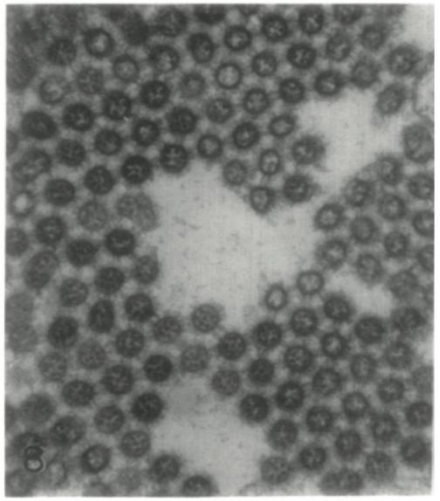


No antivirals



Treatment with Oseltamivir (Tamiflu)

Viruses treated with antivirals like Tamiflu can't bud off the plasma membrane – they're stuck there!



http://pdb101.rcsb.org/motm/113

http://www.mdpi.com/1999-4915/6/6/2465/htm

Antigenic Drift: Small Changes Over Time

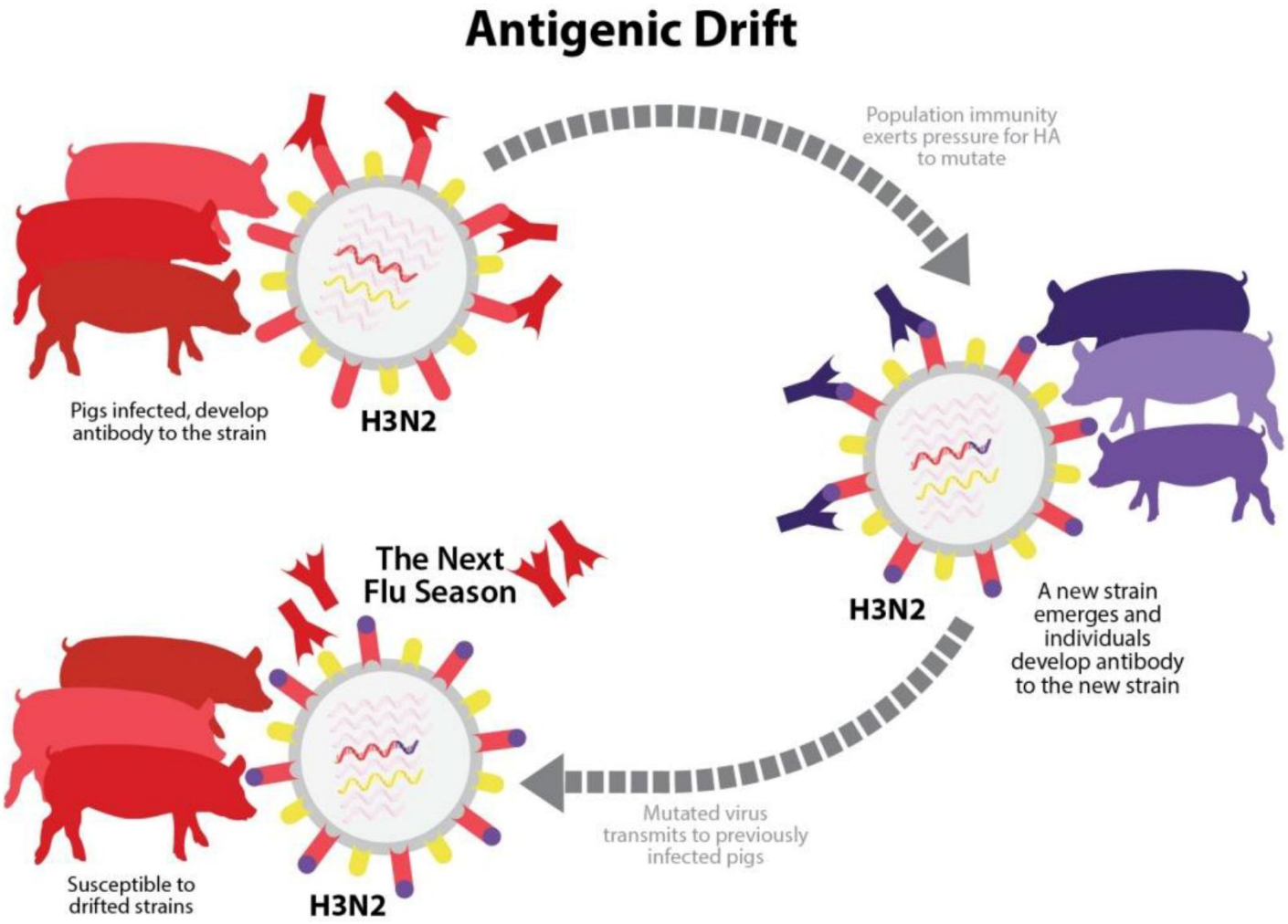
Every time the virus replicates, there are errors or mutations, ~1 per virus

```
Virus 1    ATGGCCAGTGACAGTCAAGTCAGTTGACATGACGTCA
Virus 2    ATGGCTAGTGACAGTCAAGTCAGTTGACATGACGTCA
Virus 3    ATGGCCAGTGACAGTCAGGTCAGTTGACATGACGTCA
Virus 4    ATGGCCAGTGTCAGTCAAGTCAGTTGACATGACGTCA
Virus 5    ATGGCCAGTGACAGTCAAGTCAGTTGACAAGACGTCA
```

What is a zoonotic disease?

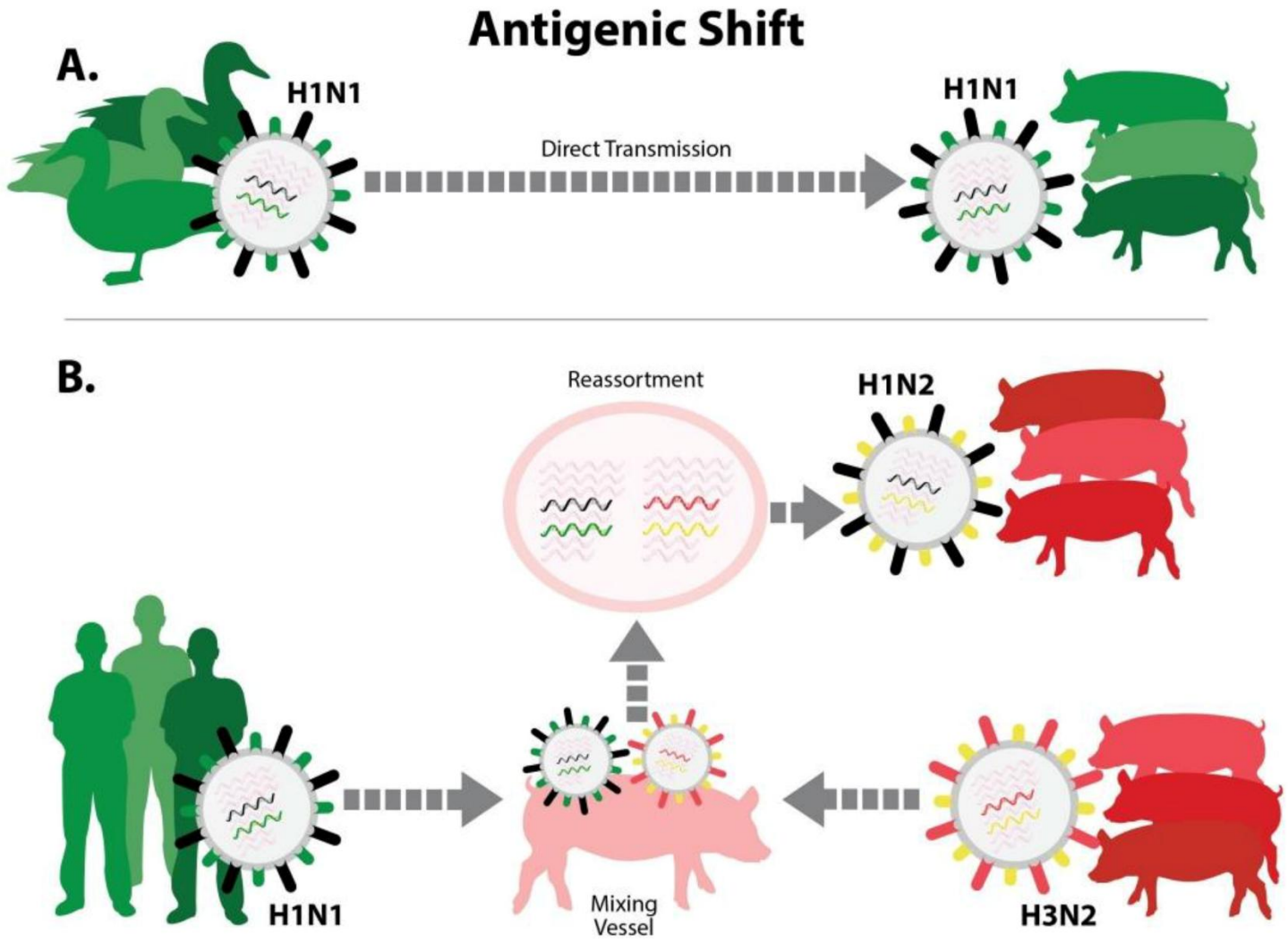
- Greek: *zoon* "animal" and *nosos* "ailment"
  - "are infectious diseases of animals (usually vertebrates), that can naturally be transmitted to humans." [Wikipedia]
- **Direct**: From animals to humans [influenza, rabies]
- **Indirect**: From **reservoir** animals to **vector** [such as ticks, mosquitos, fleas] to humans [malaria, Dengue, Chagas, West Nile fever, Lyme disease]

Antigenic Drift: Small Changes Over Time



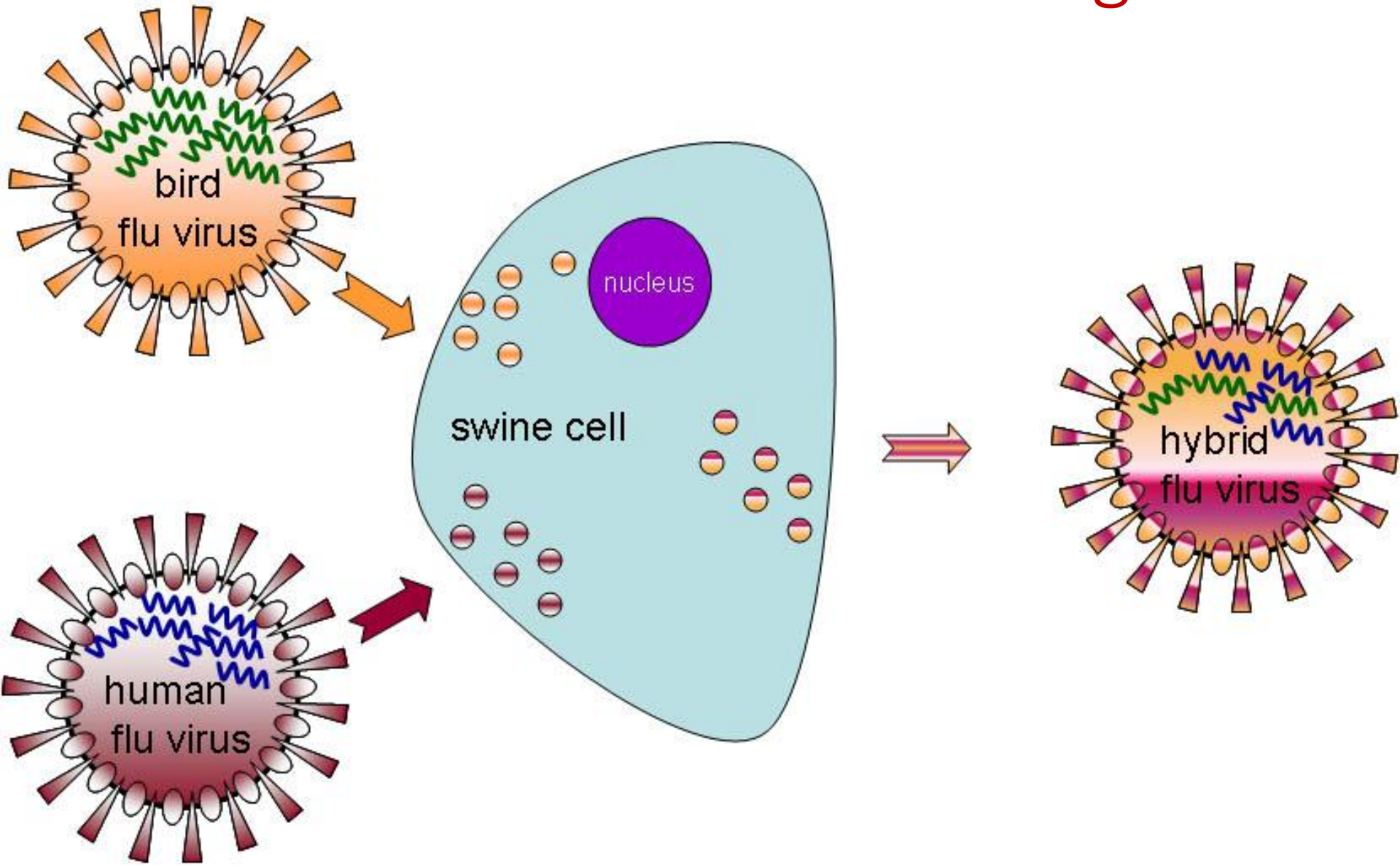
https://www.researchgate.net/publication/276264503_Optimal_Use_of_Vaccines_for_Control_of_Influenza_A_Virus_in_Swine/figures?lo=1&utm_source=google&utm_medium=organic

Antigenic Shift:
Big Changes in a Short Time

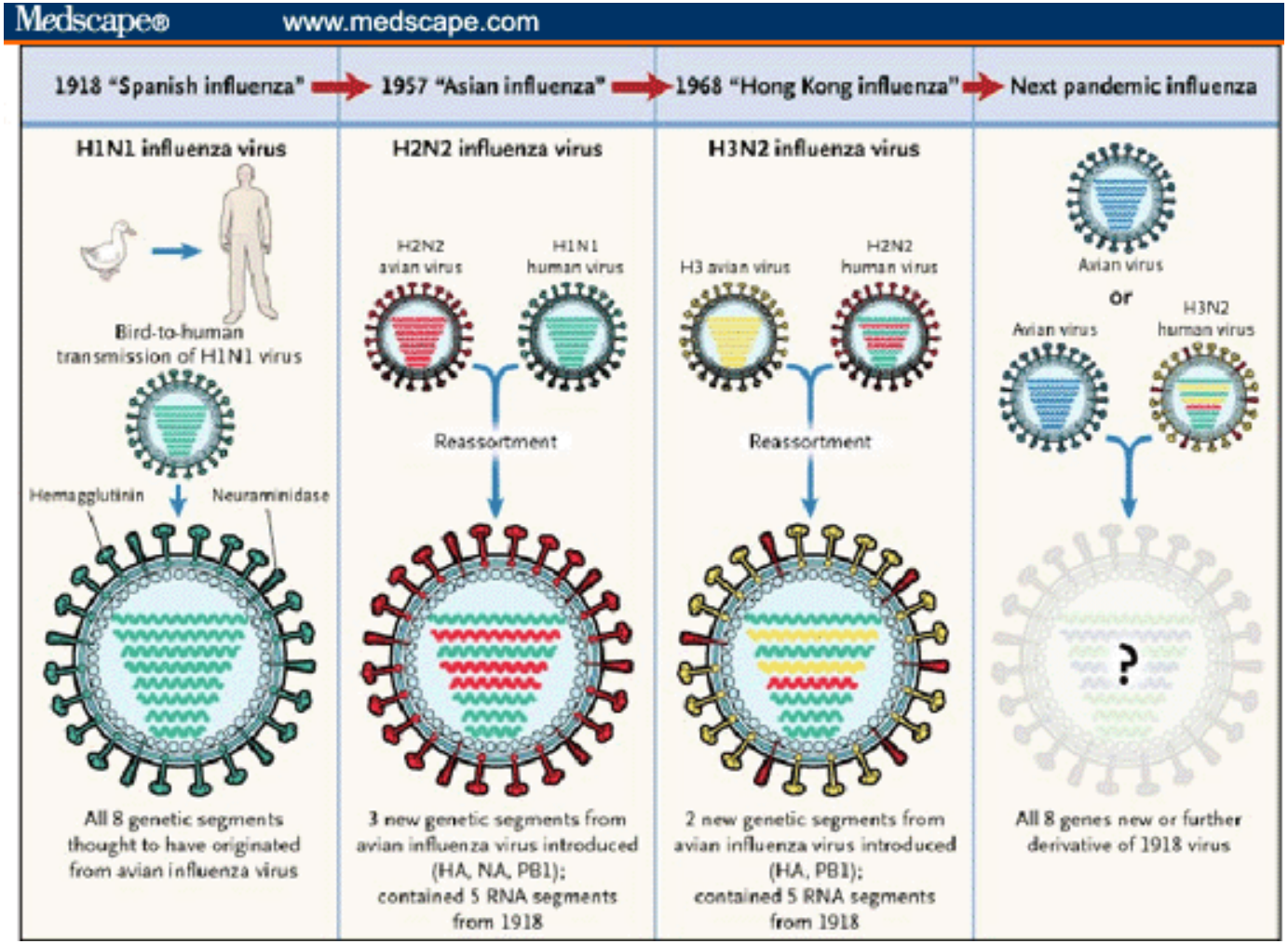


Antigenic Shift

Co-Infection of a Single Cell



The Major Influenza Pandemics of the 20th Century



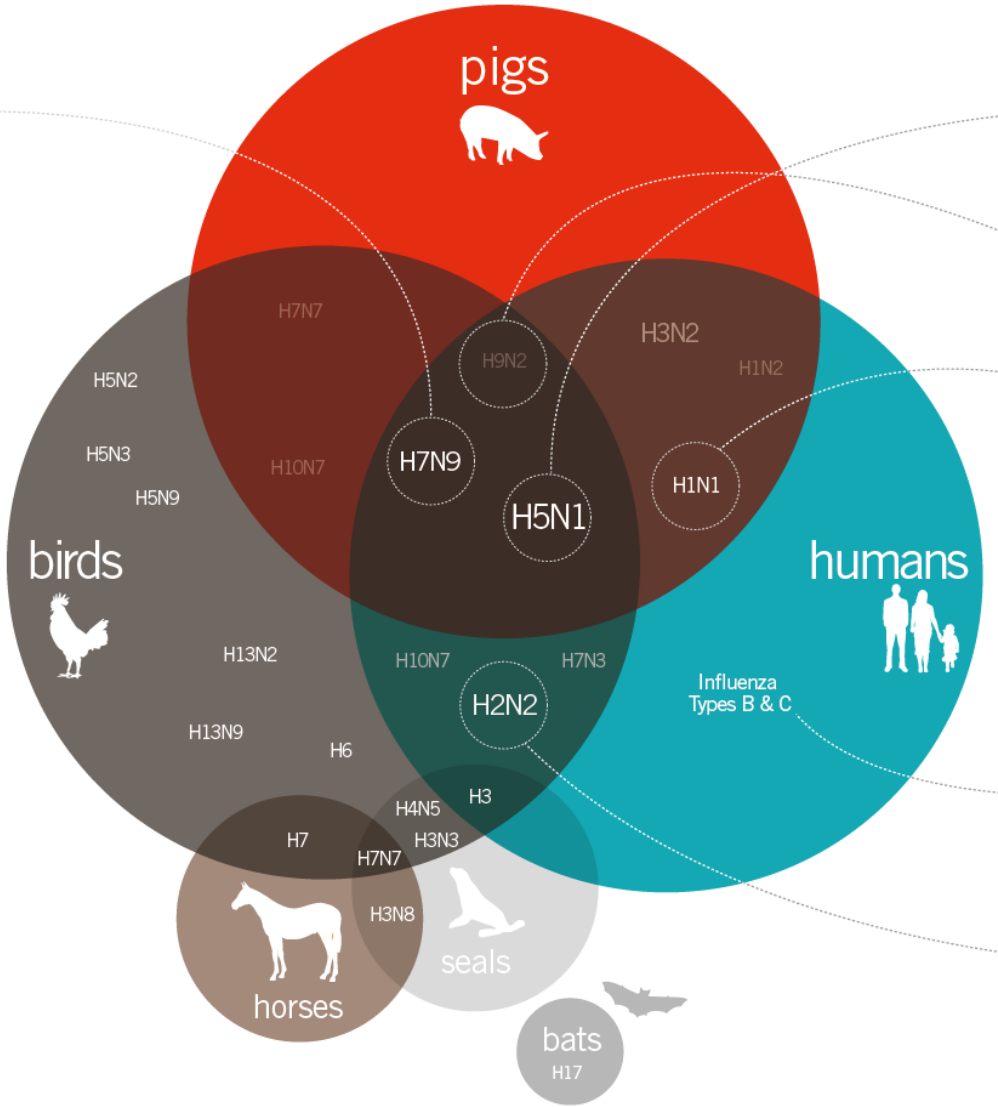
http://drainameducci.blogspot.com/2011/09/virology-antigenic-shift-vs-antigenic.html

Influ-Venn-Za

Who can catch which flu?

Pigs often a source of flu pandemics as they can be infected by bird, human & swine flus.

Worse-case, they act as a bridge for newly evolved virus strains to cross from birds to humans.



April 22nd 2013 - suspected mutation of an avian virus emerged outside Shanghai, China. Human fatality rate is unknown but out of 101 people infected, 20 have died.

The "Bird Flu" most mentioned in the media. Kills 60% of humans it infects. But direct human-to-human transmission has not been reported.

Lesser known "bird flu" endemic in poultry in Eurasia. Rarely seen in humans.

The most common variant of "Swine Flu". As "Spanish Flu" it killed 50-100 million people in 1918. The 2009-10 pandemic killed 15,000 worldwide.

Influenza Type A is divided into H & N strains (i.e. H1N1) referring to different combinations of:

H = hemagglutinin (binds to cells)

N = neuraminidase (surface enzyme)

"Common flu"only found in humans. Less harmful than type A. Does not cause pandemics.

Caused "Asian Flu" pandemic in 1957 then disappeared from human population. Still circulates in birds.

text SIZE
= human fatality rate

LIGHT TEXT
= rarely infects humans

Concept & Design: David McCandless
Research: Ella Hollowood // Additional design:Phillipa Thomas
Version 1.21 / April 2013

informationisbeautiful.net

Sources: Centres for Disease Control, WHO
data: http://bit.ly/KIB_influenza

Epidemiology Teams

- Epidemic = presence of disease *in one place*.
  - "Epi-" from the Greek "upon" or "on" the "-demos" or "people"
- - logy = the study of
- Epidemiology = "the branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health."
- Pandemic = epidemic over a large area, often world-wide
  - "Pan" from the Greek meaning "all" of the "-demos" or "people"

Epidemiological Investigation

- Each lab group will be assigned four patient samples to analyze
- **Methods used**:
  - Enzyme-Linked Immunosorbent Assay (**ELISA**) – To test for the presence of anti-influenza antibodies
  - Polymerase Chain Reaction (**PCR**) – To test for the presence of the influenza virus
- Why is it good to have multiple methods to diagnose disease?
- What are some factors to consider when determining which method(s) to use?