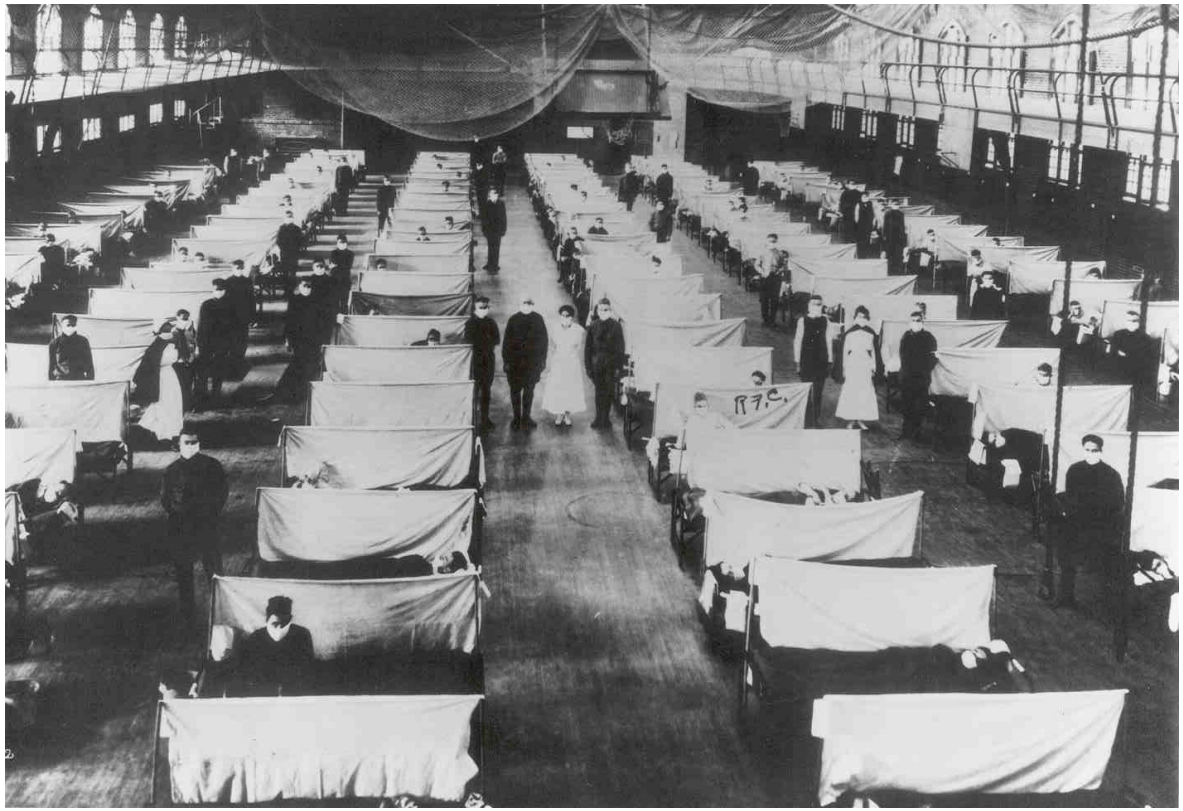
Viruses: Hacking the Host

SITN

Cole Peters

Joe Timpona

The “Grippe” of Influenza on the world



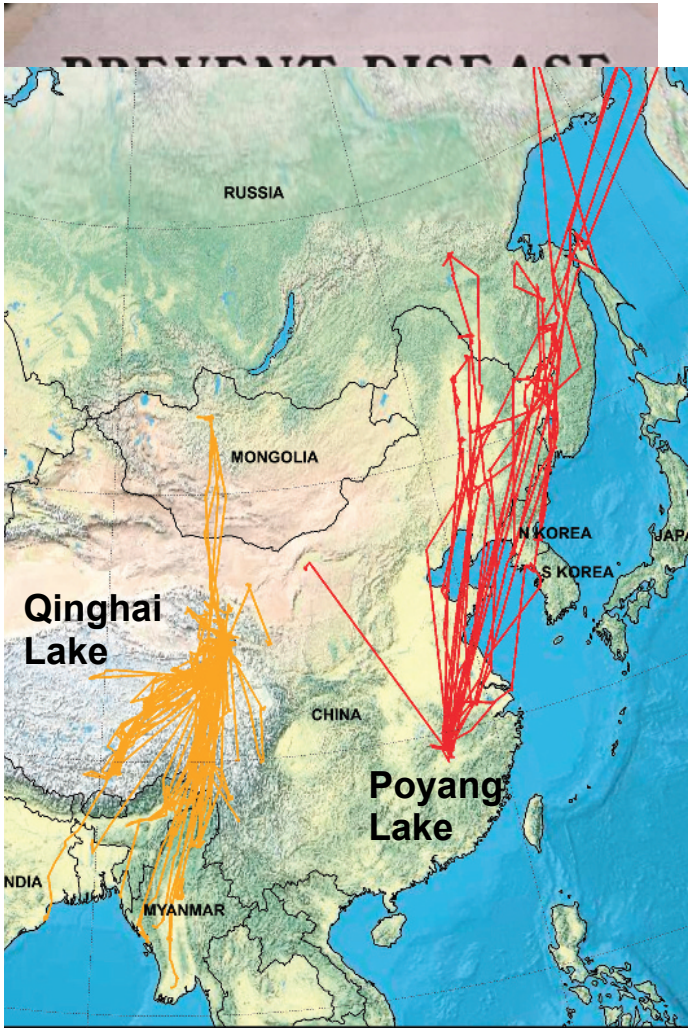
Fort Riley, Kansas

"The 1918 has gone: a year momentous as the termination of the most cruel war in the annals of the human race... Medical science for four and one-half years devoted itself to putting men on the firing line and keeping them there. Now it must turn with its whole might to combating the greatest enemy of all--infectious disease."

-Journal of the American Medical Association, 28 December 1918

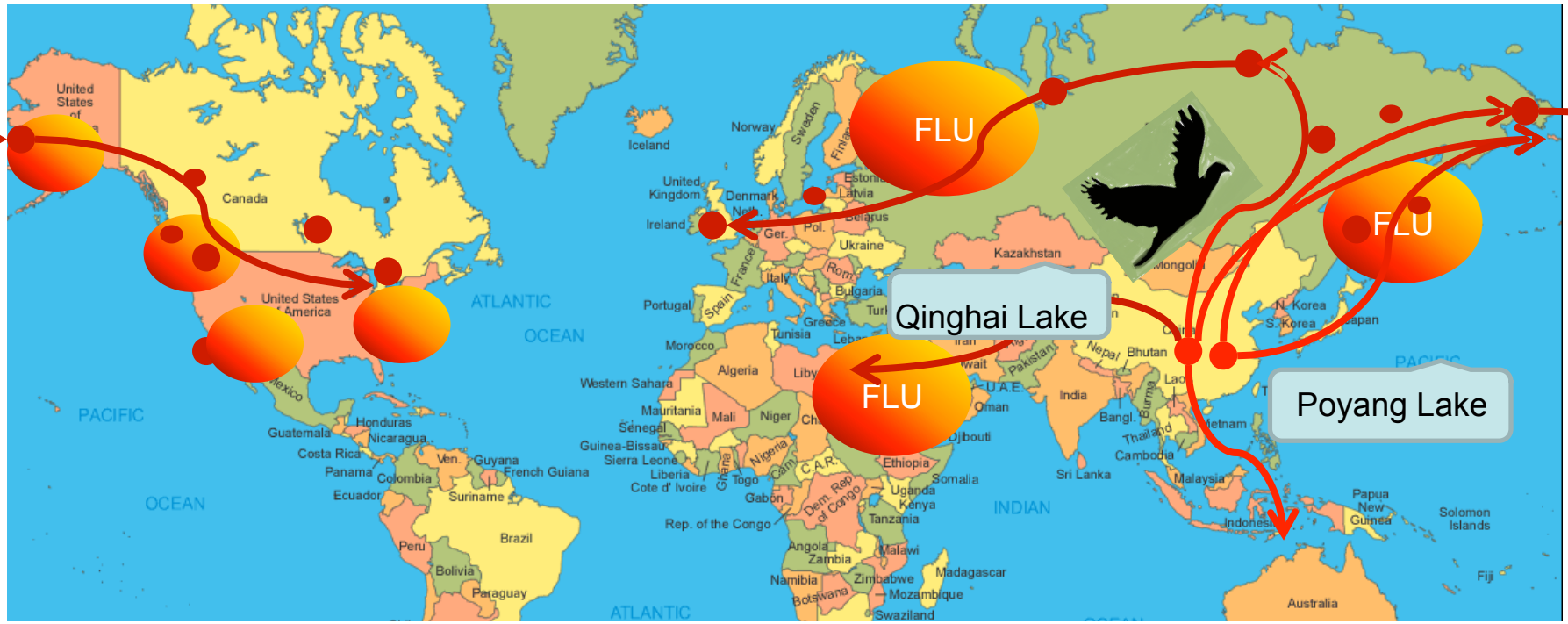
The pandemic of 1918–19 killed between 20 and 40 million people worldwide. World War I combat deaths numbered 8-13 million.

How can we prevent the next worldwide flu pandemic?



- The 1918-1919 Pandemic just stopped, there was no cure, or even a reason for the disease.
- Influenza Virus (the virus that causes the flu) was not isolated until 1933.
- Studying a virus can allow us to predict where it is going to strike next and how to cure it.
- Qinghai (H5N1) and Poyang Lakes (H1N1) in China were determined to be sites of high flu speciation.

World Wide Avian Influenza Migration



Avian Influenza must MUTATE to infect humans!

The US CDC has characterized ***2,083 DIFFERENT influenza viruses*** present in the United States since October 1, 2014.

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Outline

Part I:

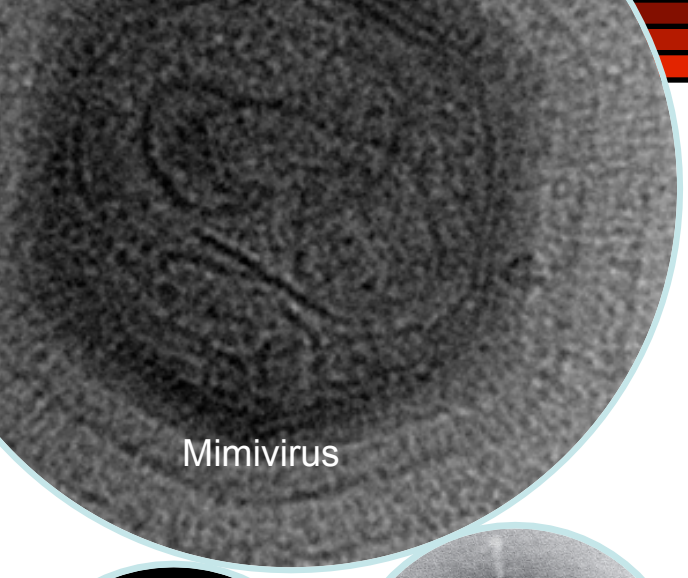
What is a virus?
Virus Diversity

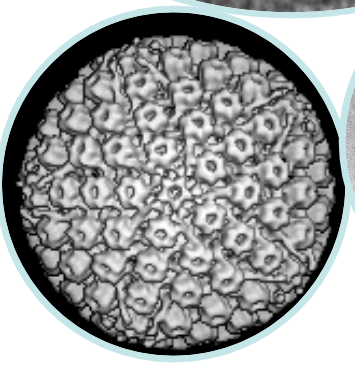
Part II:

Where do viruses come from?
Zoonosis
How can we keep track of emerging viruses?

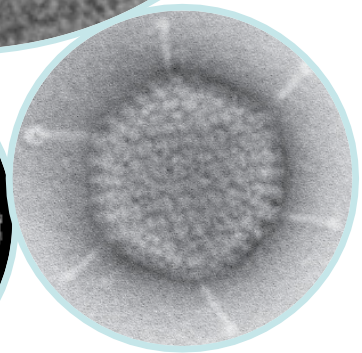
What is a Virus?

A virus is a packet of protein encapsulated DNA or RNA that MUST infect a cell to make more viruses.

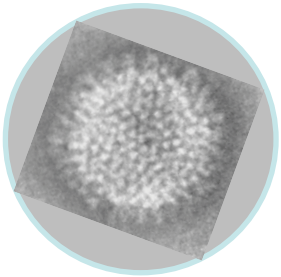




Herpes Simplex Virus-1

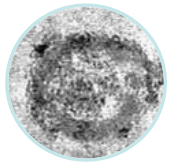


Adenovirus

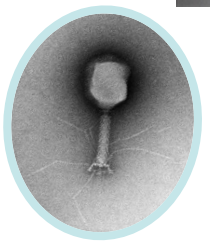


Influenza A Virus

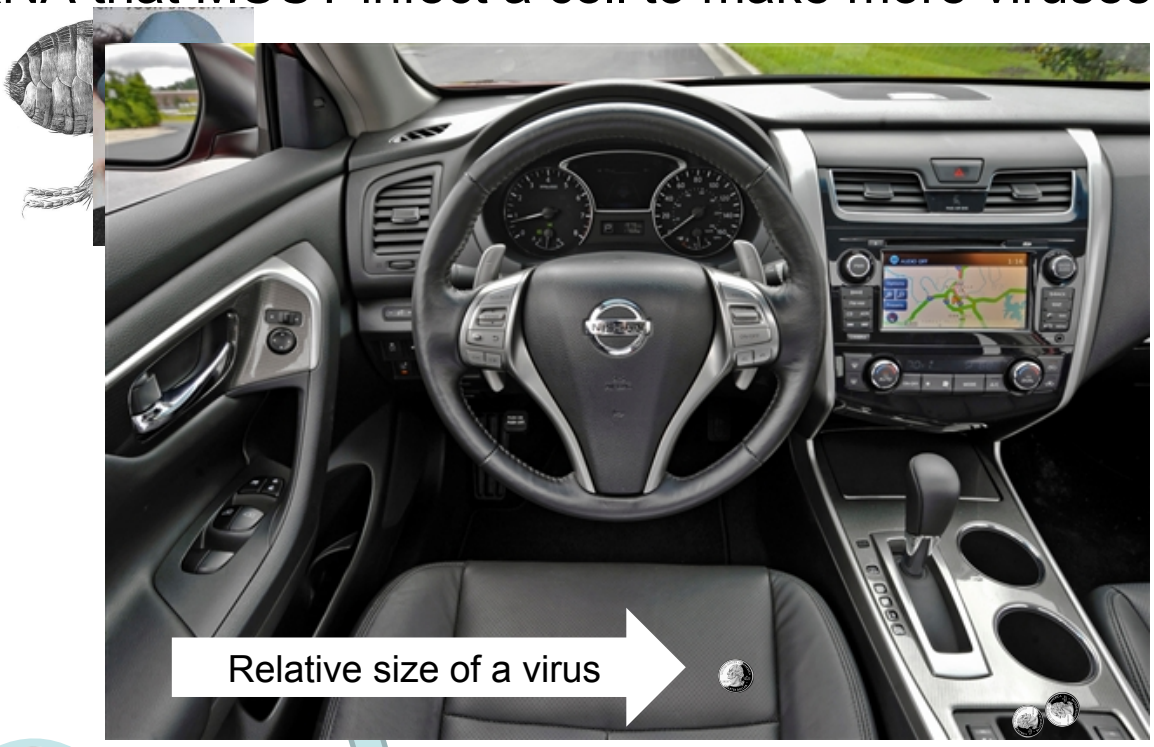
Gary Whitaker

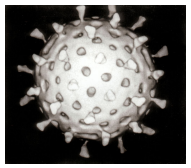


Hepatitis C Virus



T4 Bacteriophage
(Bacteria Infecting Virus)





(Graham Colm)

Most viruses are ~200 nanometers in diameter. **A virus is ~10,000 times smaller than a flea and 100x smaller than a cell!**

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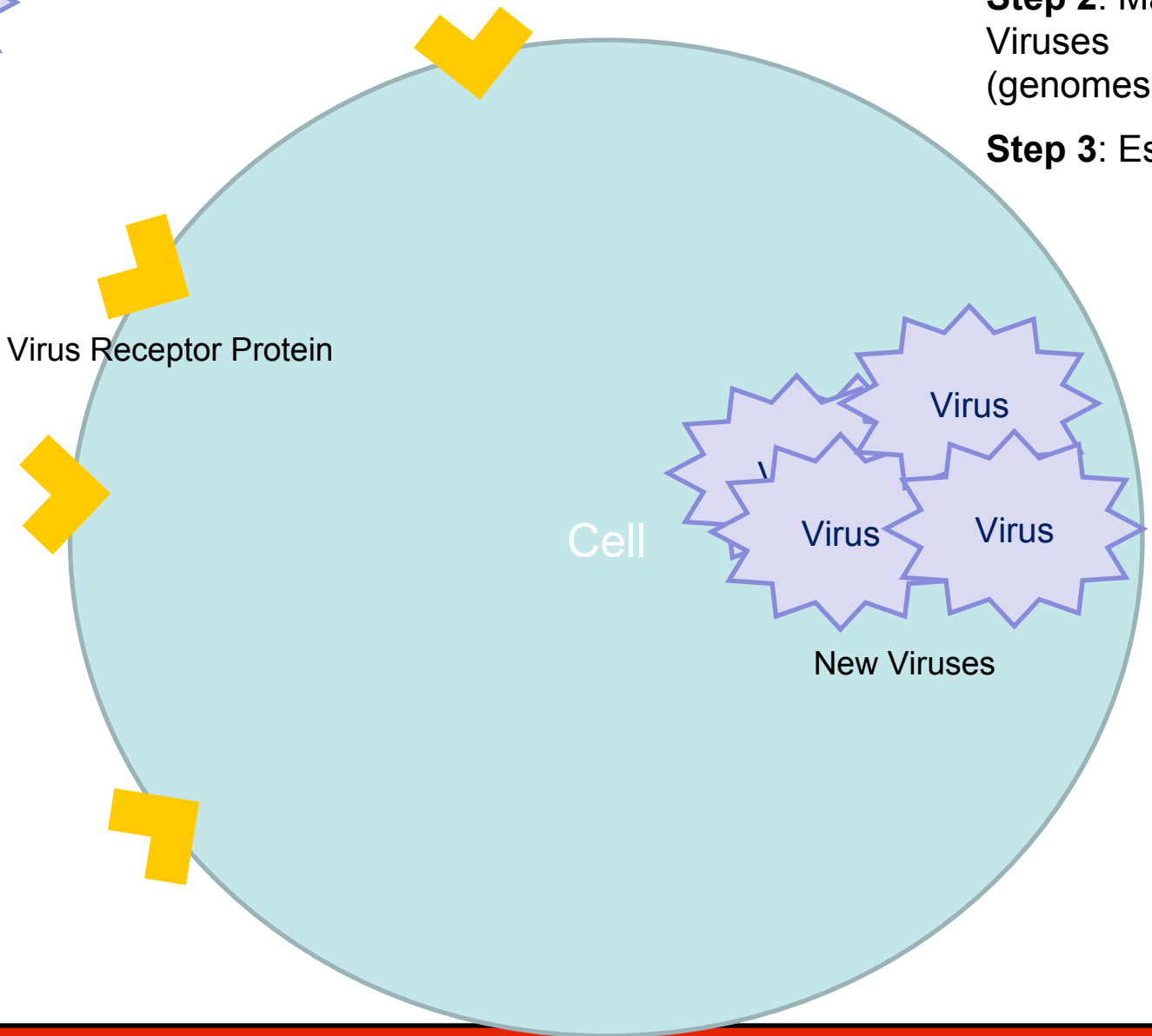
A day in the life (of a virus)

Step 1: Get into a cell.
Step 2: Make more Viruses
(genomes and proteins)

Step 3: Escape



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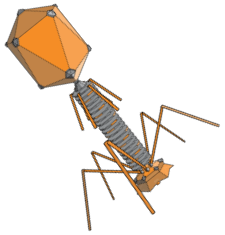
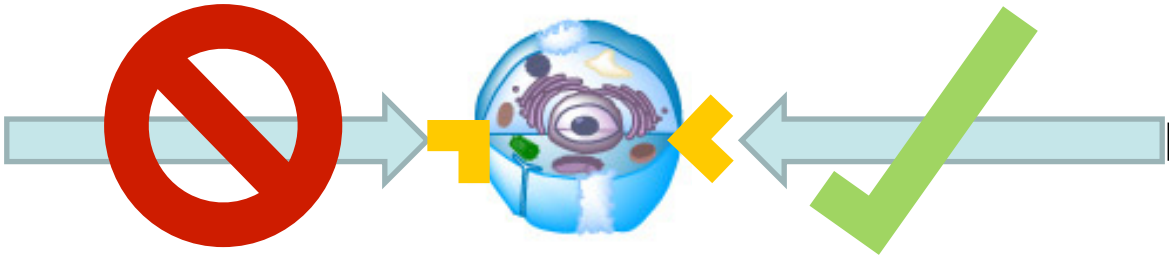
Can any virus infect any cell?

Tropism: A cell must have a specific protein(s) in order for a virus to get inside the cell.

- Not all Viruses are able to infect the same cells.
- Not all cells can be infected within an organism.

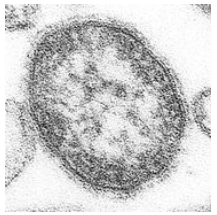
Bacteriophage

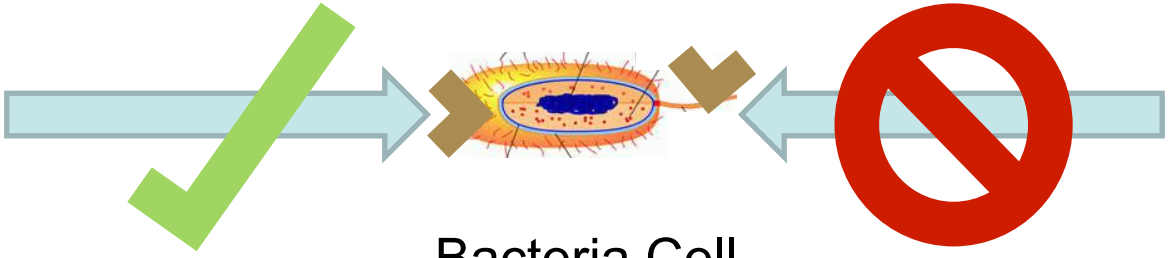




Human Cell

Measles Virus





Bacteria Cell

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Viruses are VERY diverse

Viruses are broken into 7 defined Orders and then into several distinct families.

Defined Virus Orders						
Caudovirales	*Herpesvirales*	*Ligamen-virales*	*Mono-negavirales*	*Nidovirales*	*Picornavirales*	*Tymovirales*
Families						
Siphoviridae	*Alloherpesviridae*	*Lipothrixviridae*	*Bornaviridae*	*Arteriviridae*	*Dicistroviridae*	*Alphaflexiviridae*
Myoviridae	*Herpesviridae*	*Rudiviridae*	*Filoviridae*	*Coronaviridae*	*Iflaviridae*	*Betaflexiviridae*
Podoviridae	*Malacoh...*			*Mesoniviridae*	*Marnaviridae*	*Gammaflexiviridae*
				Roniviridae	*Picornaviridae*	*Tymoviridae*
					Secoviridae	

Academy Award Winning Actor Vin Diesel

Within each family are several species of virus, and within a species are tens to thousands of strains!

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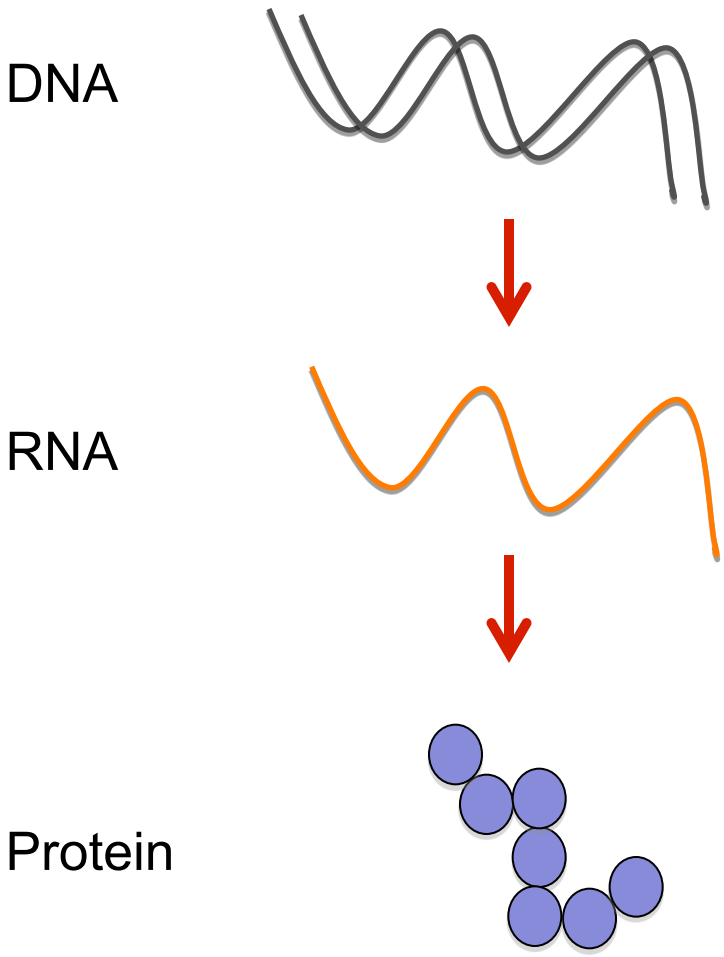
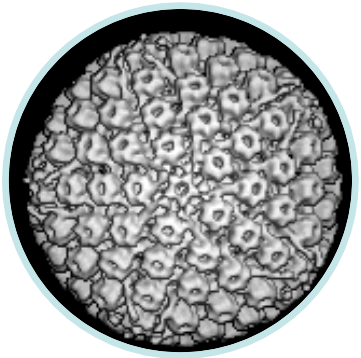
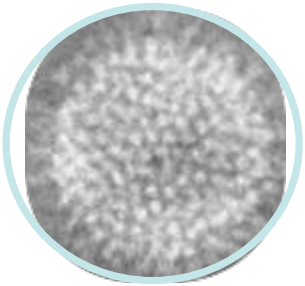
Central Dogma of Molecular Biology



Virus Groups



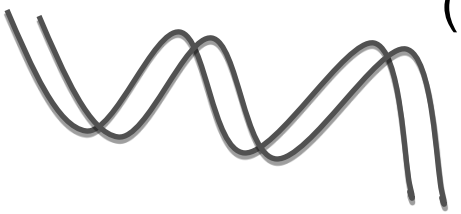
Herpes Simplex Virus-1

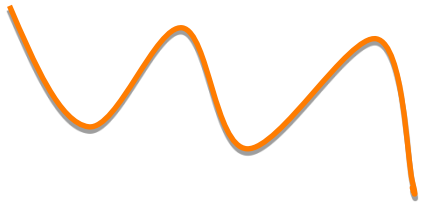


Influenza A Virus

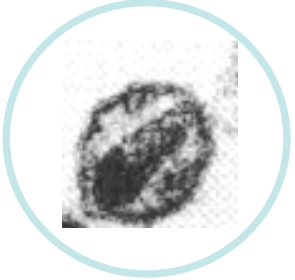
Reverse Transcriptase
(protein)

Viral DNA



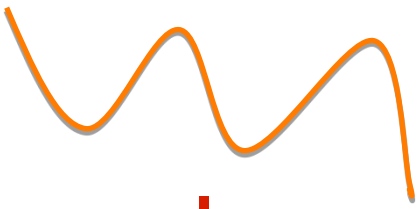


Viral RNA

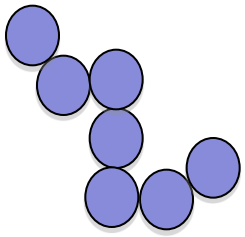


Human Immunodeficiency Virus

Viral RNA



Viral Proteins



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Summary

1. Viruses are tiny particles of encapsulated genetic material.
2. Viruses require a cell to make more viruses, but can only infect certain cells, and only make new viruses in certain cells.
3. Viruses are diverse! There are thousands of new species of virus found every year, and countless strains!

Questions?

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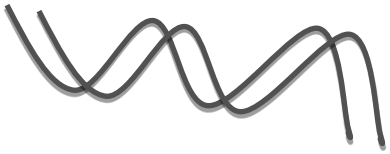
Viruses in focus

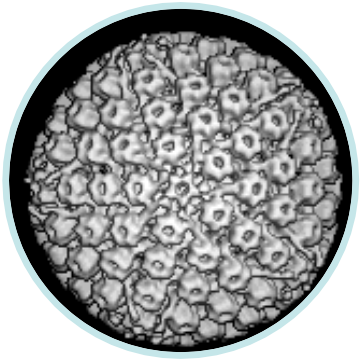
DNA Viruses:

-DNA Genome



-Don't mutate as often as RNA viruses

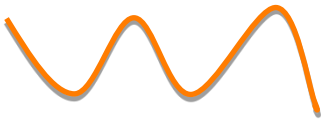
-Larger viruses



Herpes Simplex Virus-1

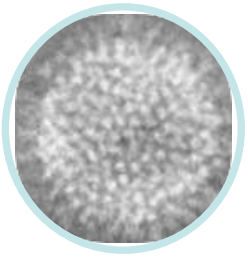
RNA Viruses:

-RNA Genome



-Mutate more often than DNA viruses

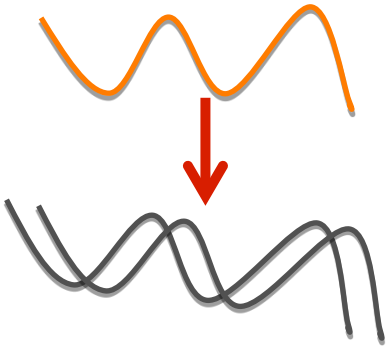
-Smaller Viruses

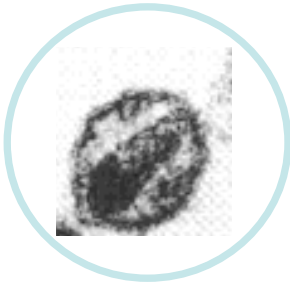


Influenza A Virus

Retroviruses:

-Turns its RNA Genome into DNA





Human Immunodeficiency Virus

Herpes Simplex Virus-1 (HSV-1)

• *It's definitely Herpes*… 60-88% of the USA has it in their blood/cells/tissues.

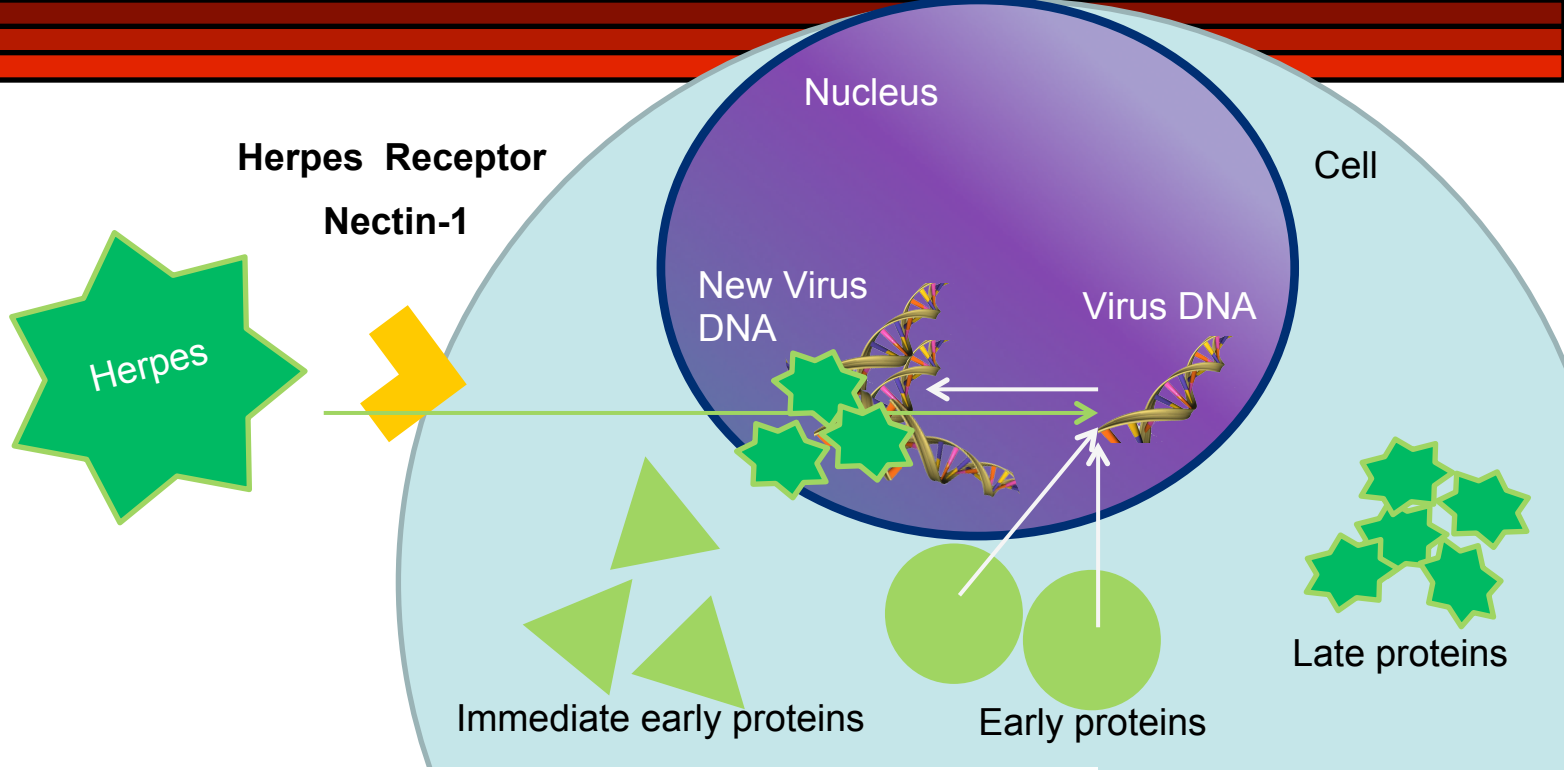
• HSV-1 can cause genital and mouth sores.

•HSV-1 can be dangerous/lethal

Herpes Keratitis- Infection of the eye which can lead to blindness.

Herpes Encephalitis- Infection of the brain which can cause encephalitis and death.


HSV-1 mainly infects neurons



The Herpes Simplex Virus-1 Lifecycle (3 major steps)

1. HSV-1 enters the cell and makes its **Immediate early proteins** which allow the virus to make **Early proteins**.
2. The **Early proteins make more virus DNA**.
3. The **new virus DNA is packaged** in the **Late proteins to form new viruses**, which leave the cell.

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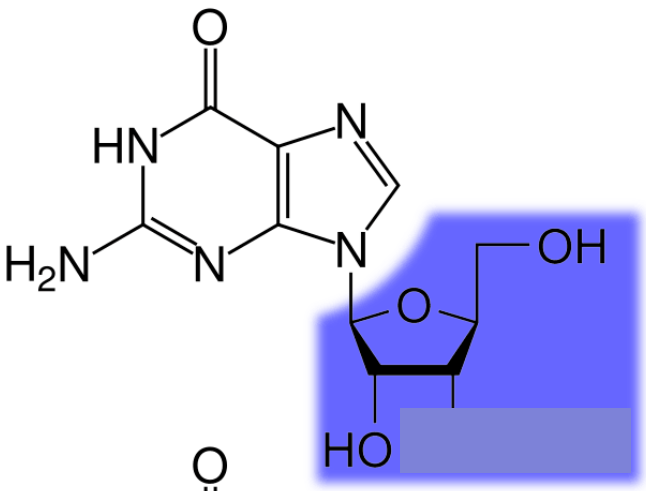
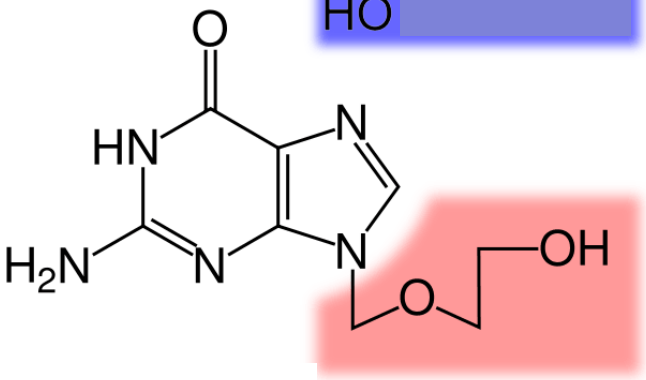
What makes Herpes Simplex Virus-1 dangerous?

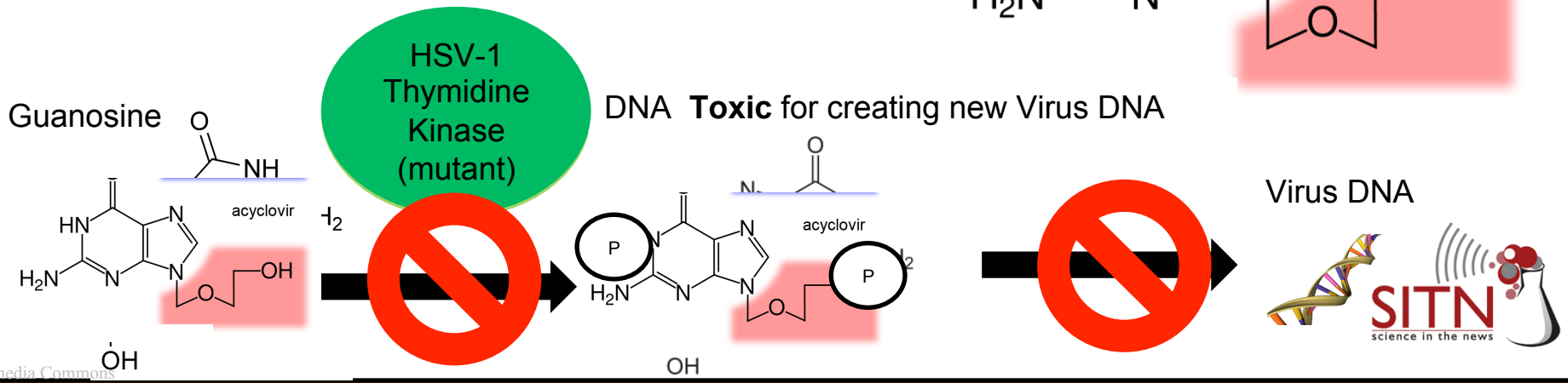
- HSV-1 Thymidine Kinase (TK) is an Early protein that helps to make DNA for the virus.
- Aciclovir fools the HSV-1 TK into making a toxic nucleotide which stops HSV-1 from making new virus DNA.
- HSV-1 can mutate its TK gene to become resistant to this drug by changing one part of the TK protein.

Guanosine (DNA)



Aciclovir (Mimic)



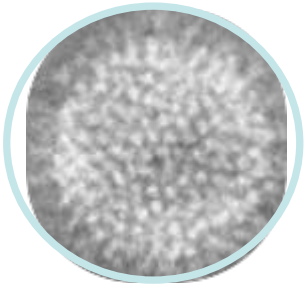


RNA Viruses:

-RNA Genome

-Mutate more often than DNA viruses

-Usually replicate in a cell's cytoplasm



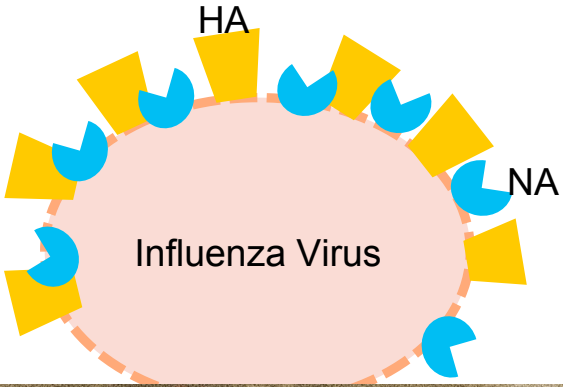
Influenza A Virus

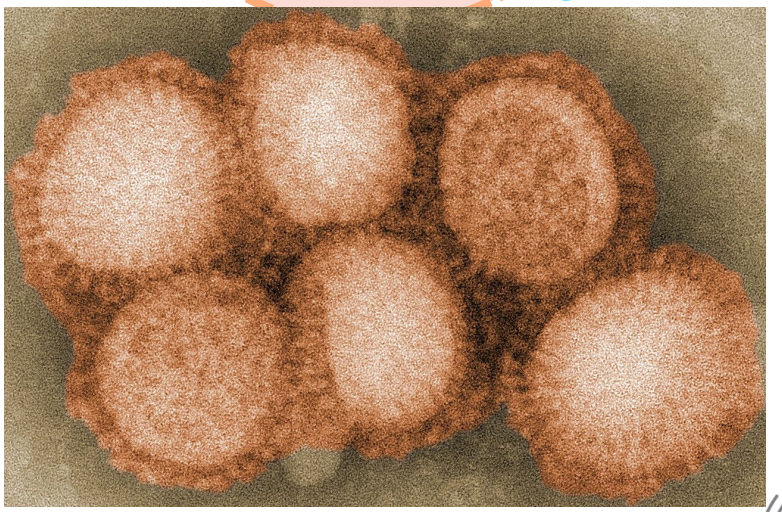
Influenza A Virus (IAV)

- Causes the Flu, which infects millions of people each year, and countless aquatic birds.
- Flu virus is typed by its hemagglutinin (HA)

And neuraminidase (NA) surface proteins (ie: H1N1= a flu with HA-1 + NA-1).

- The Flu virus has 8 distinct genomic RNAs and can mix and match with other flu viruses to create new species/strains of virus.





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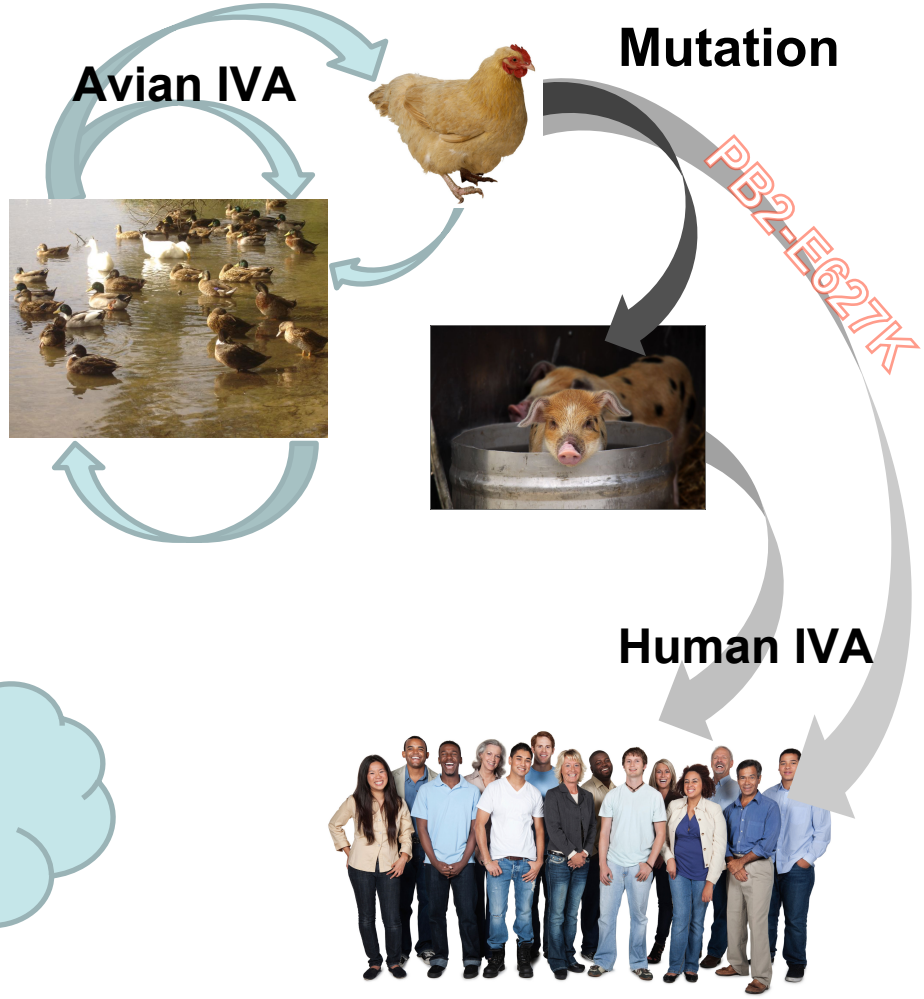
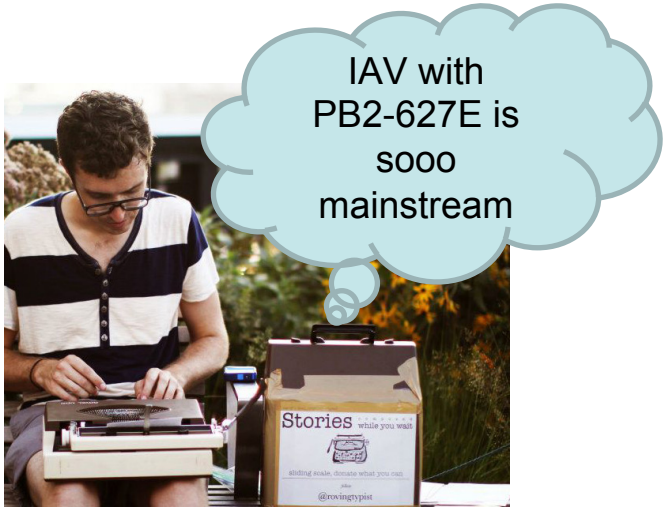
IVA jumps the fowl

- The Flu virus proteins PB2/PB1/PA are responsible for making new flu RNAs.

- A single mutation in PB2 can allow IVA to jump from birds to humans.

- The pandemic flu of 1918-1919 had this same mutation!





Retroviruses:

-Turns its RNA Genome into DNA

-To make new viruses they must insert their genome into the host cell's DNA. **They can only make more virus once they do this!**

Human Immunodeficiency Virus

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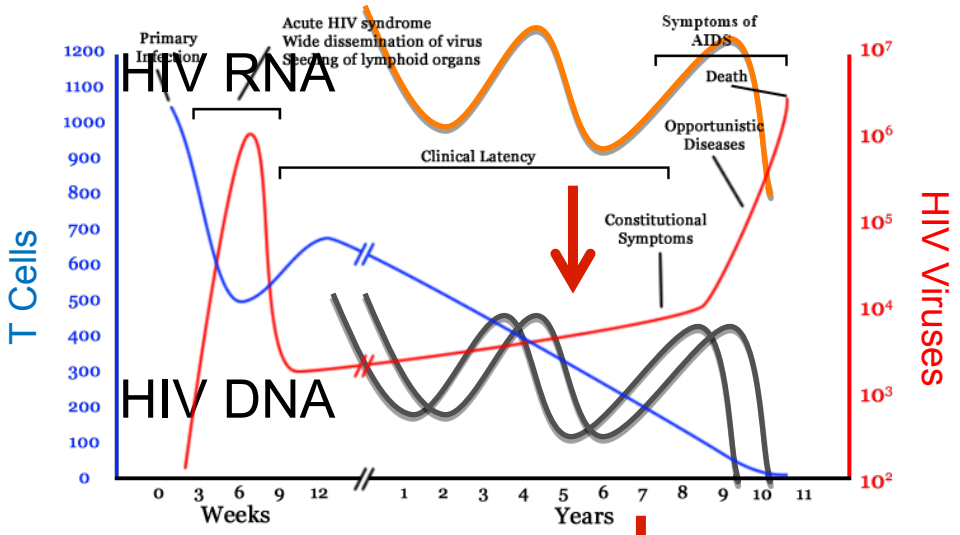
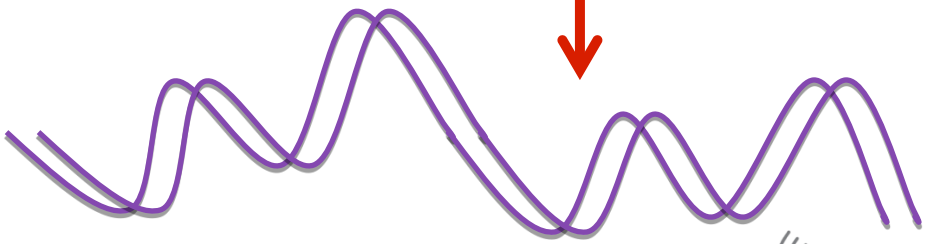
Human Immunodeficiency Virus (HIV)

- HIV uses a protein called Reverse Transcriptase to turn its RNA genome into DNA.

- HIV DNA cannot make any mRNA or new HIV viruses until it integrates (inserts itself) into the host's DNA.

- Once integrated HIV can rapidly produce more HIV viruses or 'hide' inside the host DNA (Clinical Latency).





Host DNA

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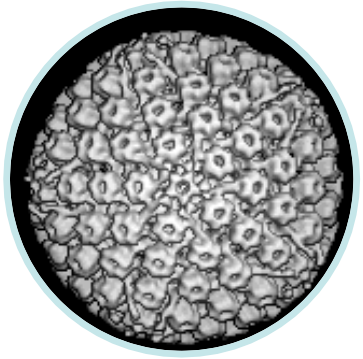
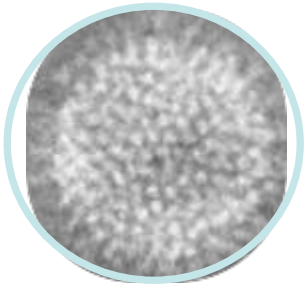
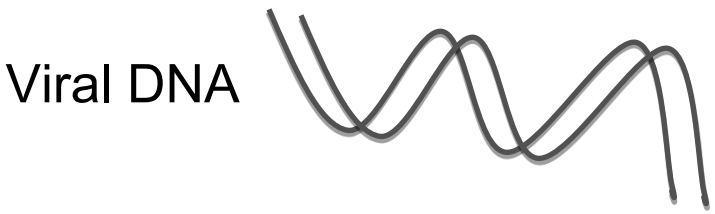
Summary

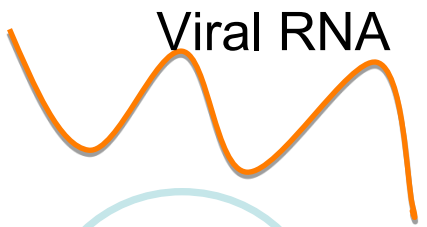


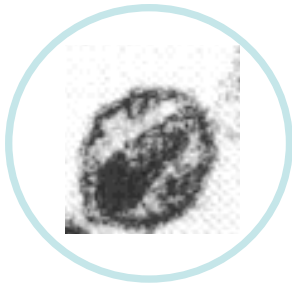
Herpes Simplex Virus-1



Influenza A Virus

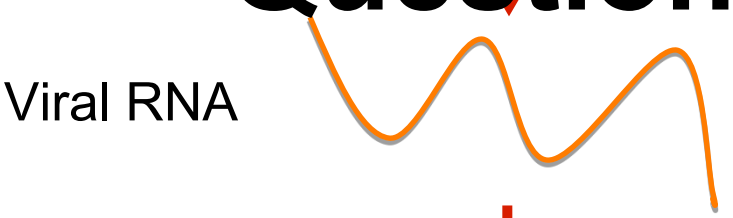


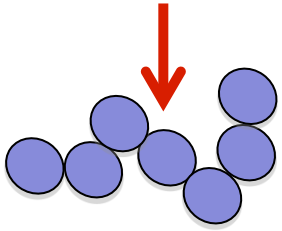




Human Immunodeficiency Virus

Questions?





- We can target a virus with drugs that stop it from replicating its genome.
- Viruses mutate to overcome drugs and our own defenses.
- A virus normally only infects a specific host but can mutate to jump to another host.

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Where do viruses that infect humans come from?

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2014-2015 Ebola Outbreak

- So far: 27,181 cases
- **11,162 deaths**

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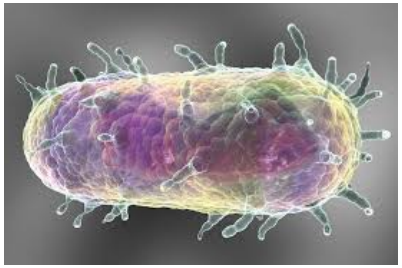
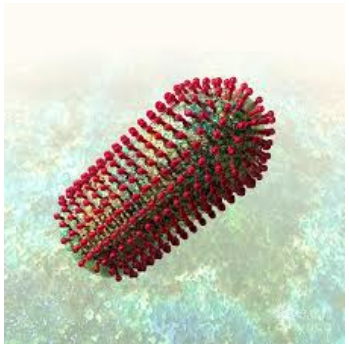
Zoonosis

- An animal infection transmissible to humans
  - Everything comes from somewhere



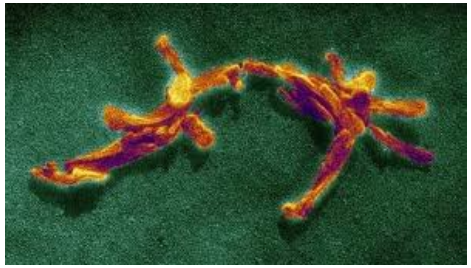
Bubonic Plague



Rabies virus

Ebola virus

Lyme Disease



Mad Cow Disease

Wikipedia.org

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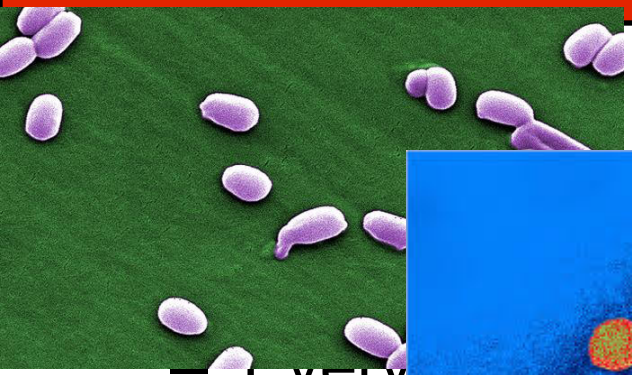
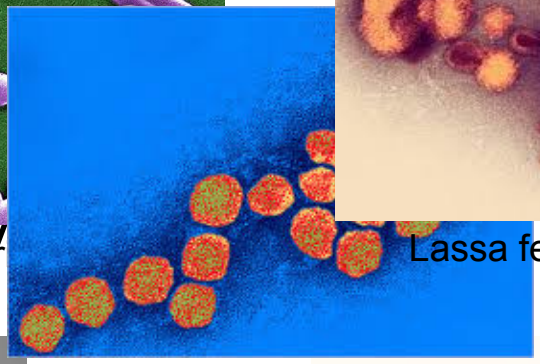
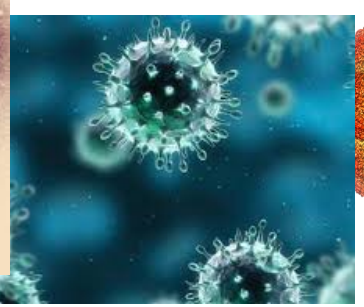


Anthrax bacter

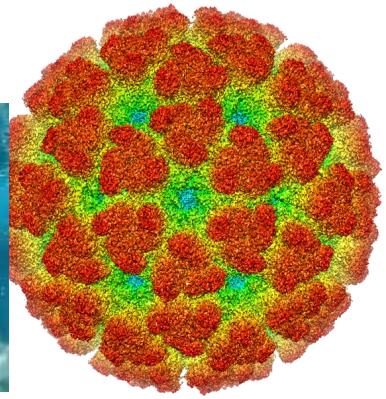


West Nile virus

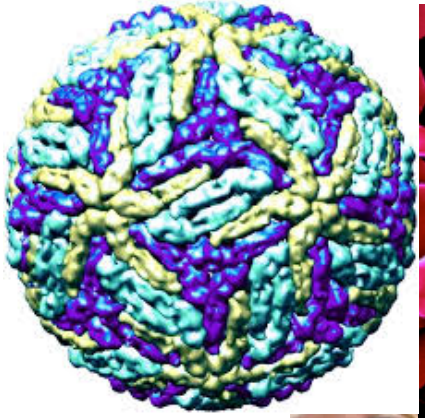
Lassa fever virus



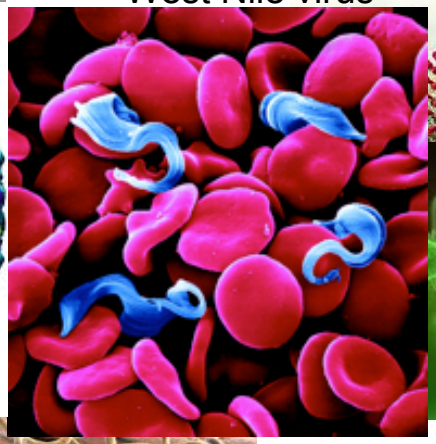
MERS



Chikungunya virus

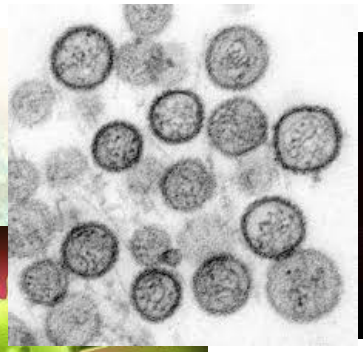


Dengue virus

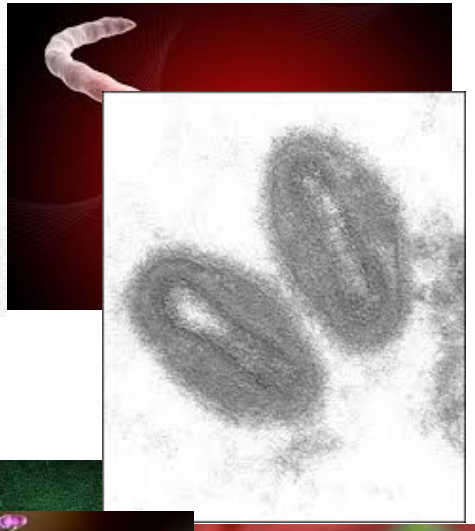


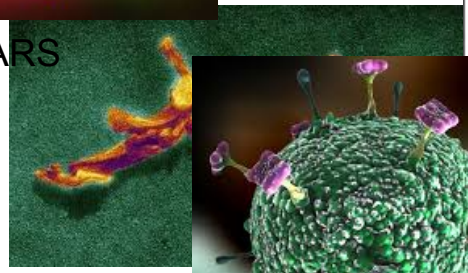
Sleeping sickness

SARS

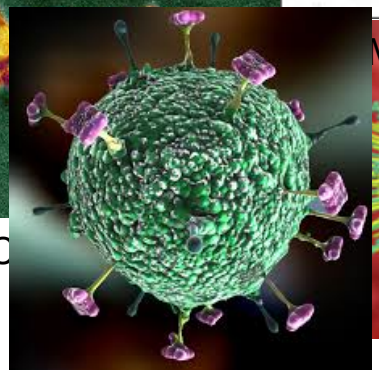


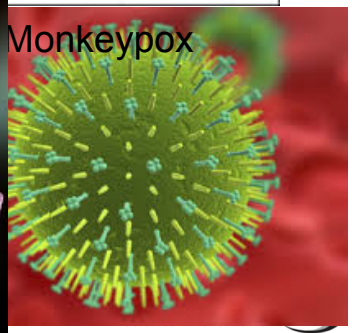
Hantaan virus





Mad C





Monkeypox

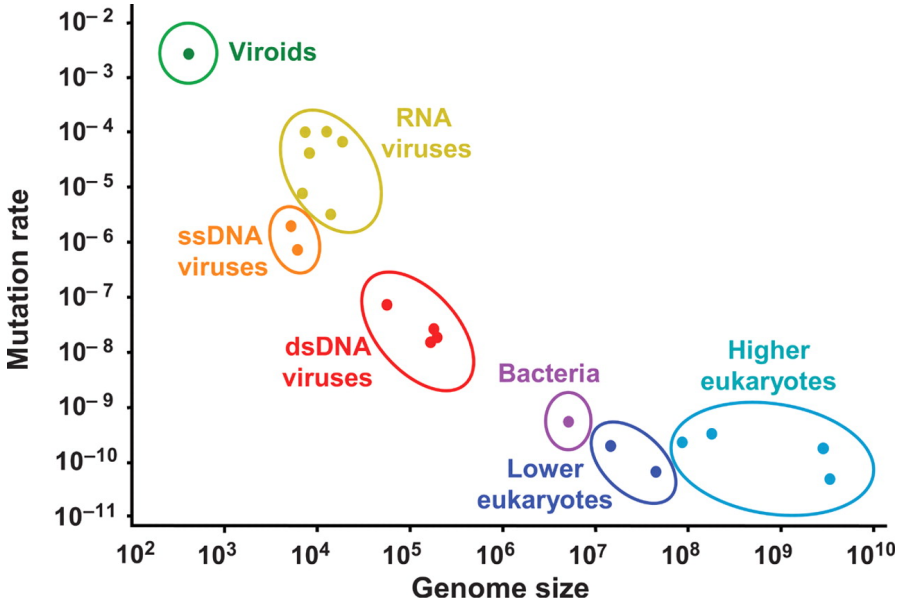
Machupo virus

Marburg virus

Influenza virus

Viruses are the most problematic

- Viruses evolve quickly

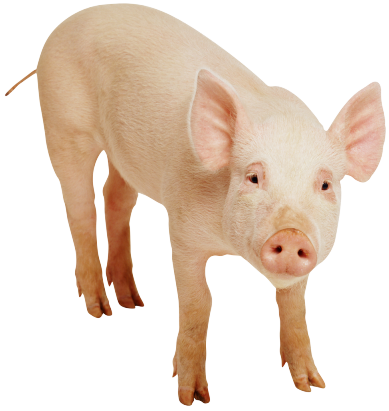


- Unaffected by antibiotics
  - No broad-spectrum antivirals

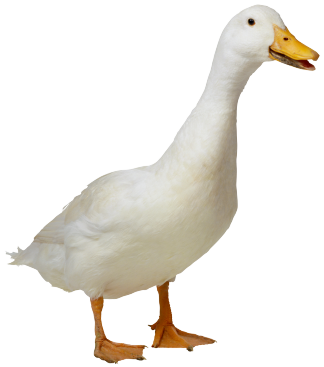
- Can inflict high rates of fatality
  - Rabies is 100% fatal in humans if not treated

Zoonotic pathogens “hide” between outbreaks

- Zoonotic viruses hide in reservoir hosts (also known as natural reservoirs)
  - Chronically carry the pathogen
  - Not harmed by it



Swine flu

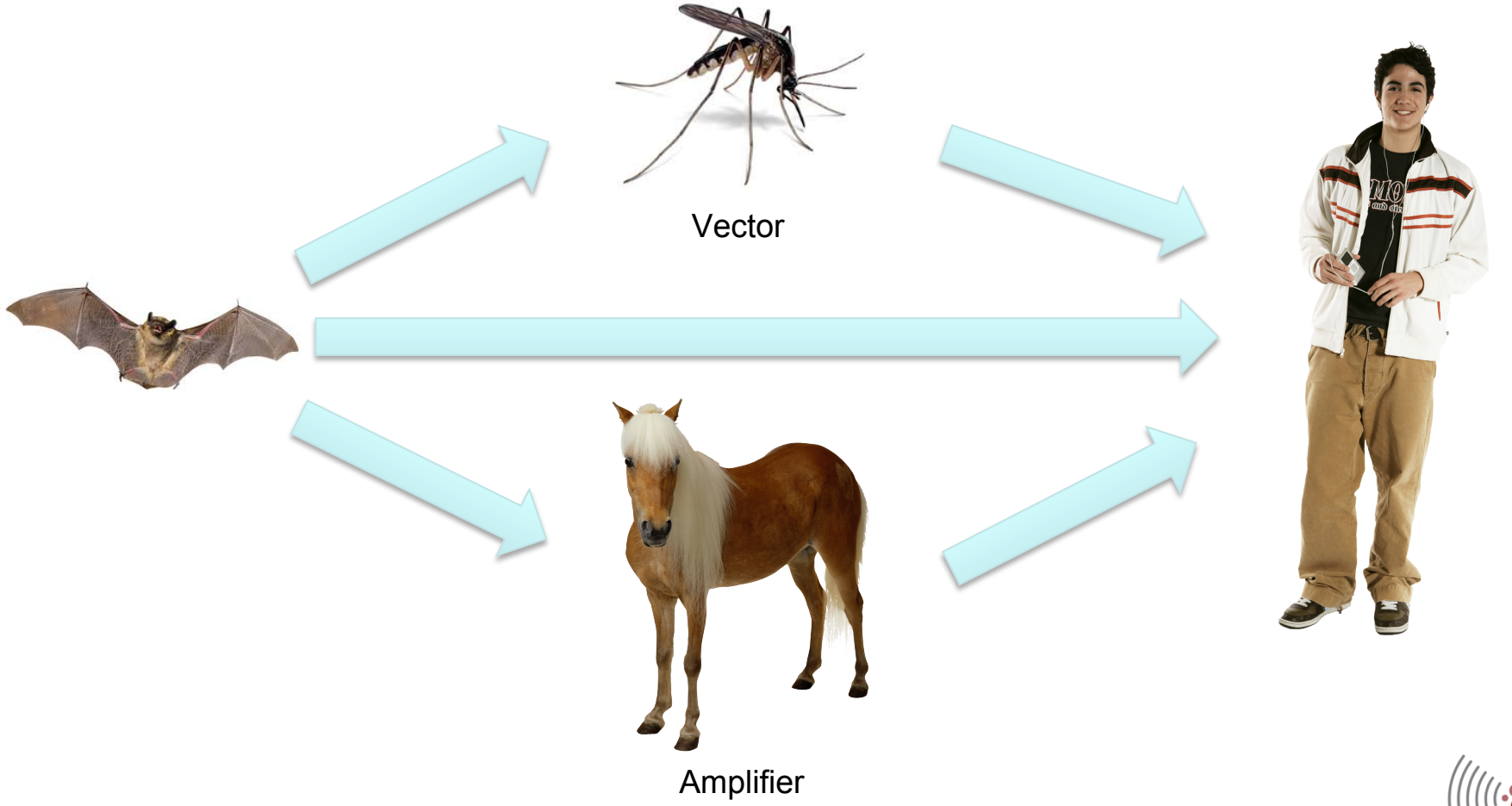


West Nile virus

Rabies
Nipah
Hendra
Marburg
SARS
More…

Wikipedia.org

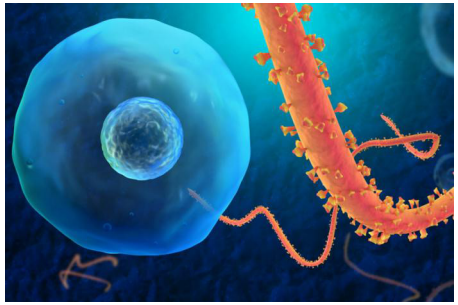
The path to humans is not always simple



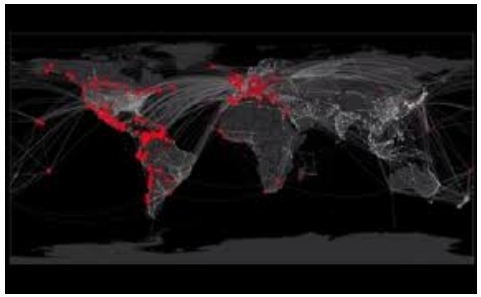
Variables that affect spillover potential

Exposure

Infection



Spread



Wikipedia.org

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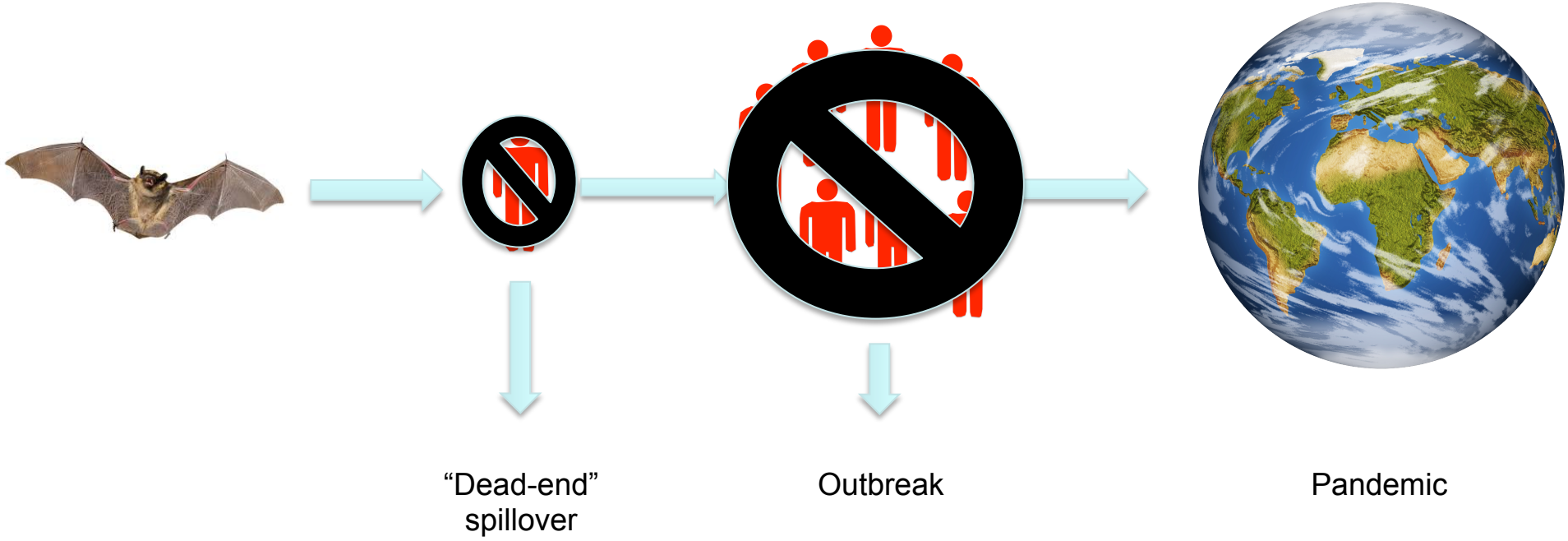
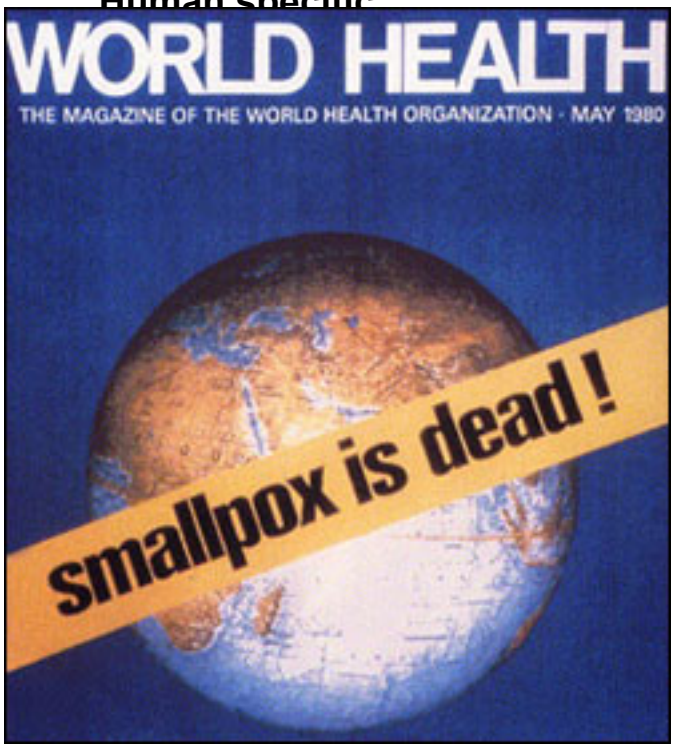
Different fates for a spillover



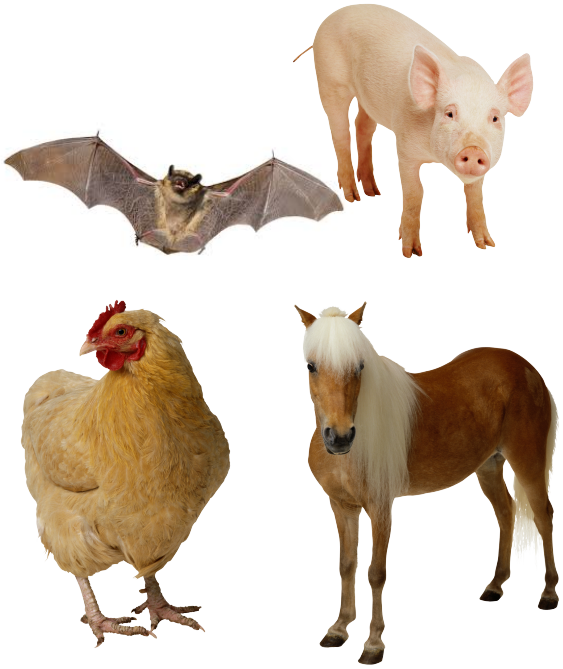
Zoonotic viruses are difficult to eliminate

Human specific



Smallpox virus
Varicella Zoster
Polio virus

Spillover (Zoonosis)



Ebola virus
Influenza A virus
West Nile virus
Rabies virus

Who.org

Tracking spillovers is key to prevention

Time.com

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Finding a Natural Reservoir for a virus

Gold Standard:

- –Find live virus/pathogen in the suspected animal.
- –Find virus' genome.
- –Find antibodies against the virus within animal reservoir.

Wikipedia.org

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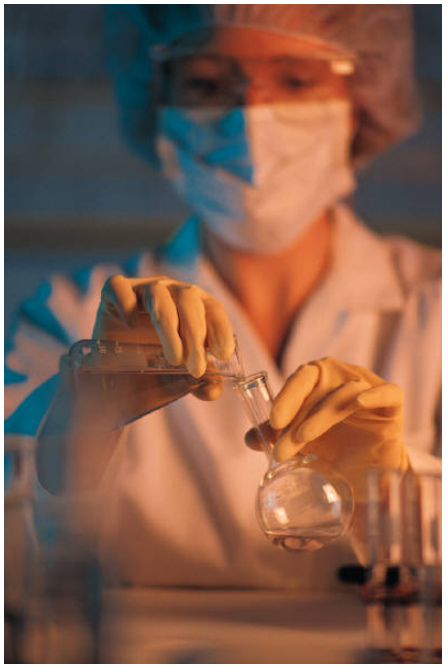
Key points

- Most emerging diseases come from animals
- Viruses are the most problematic
- Many factors influence whether a virus will spill over in to humans
- Tracking spillovers and finding natural reservoirs is key to prevention and preparedness



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Thank you!

SITN DayCon would like to acknowledge the following organizations for their generous support of our event.

The Harvard Graduate School of Arts and Sciences (GSAS)
Integrated Life Sciences (HILS)

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The nonprofit plasmid repository