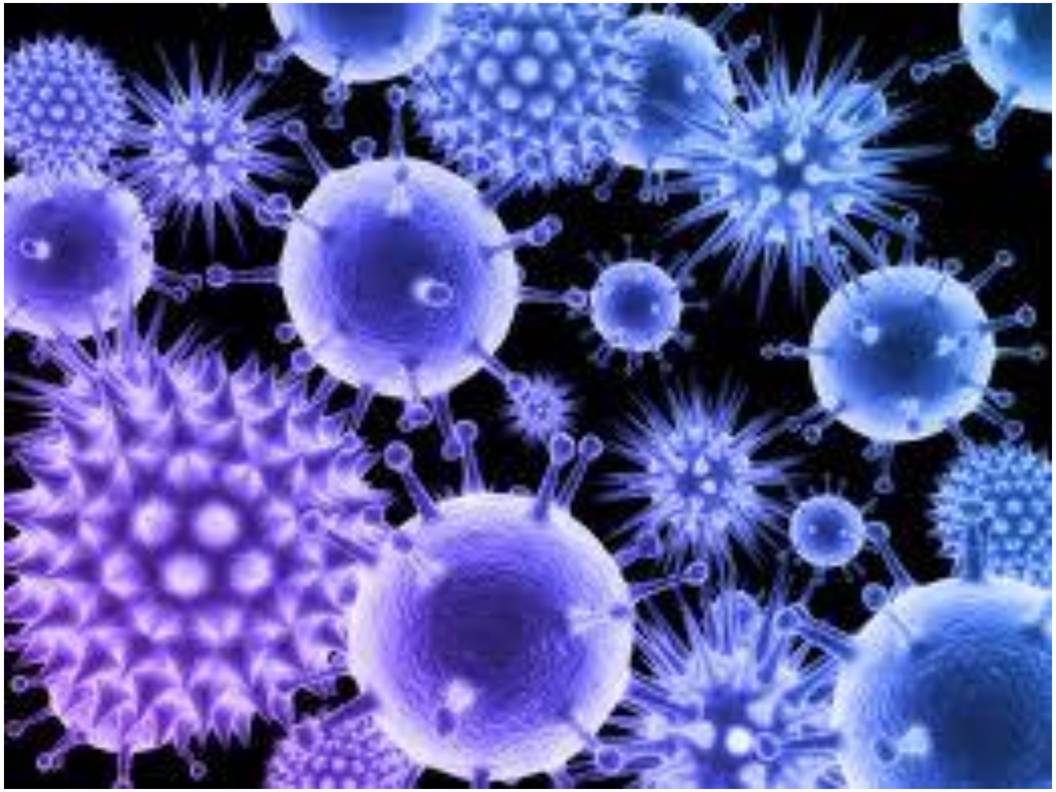
Chapter 27



Viruses

http://onlyhdwallpapers.com/high-definition-wallpaper/viruses-you-now-all-have-swine-flu-high-resolution-desktop-hd-wallpaper-297337/

Nature of Viruses

- All viruses have same basic structure
  - Nucleic acid core surrounded by **capsid**
    - Can be DNA or RNA
    - Circular or linear
    - Single or double stranded
  - No cytoplasm – not a cell
    - No ribosomes

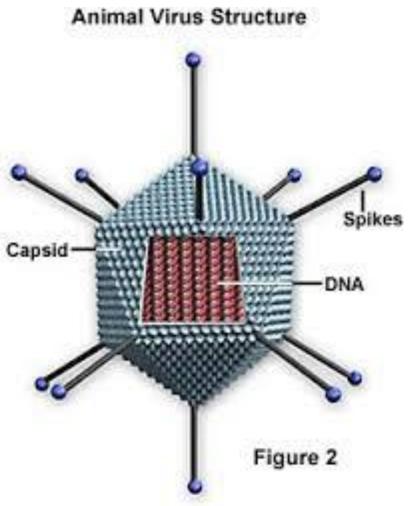
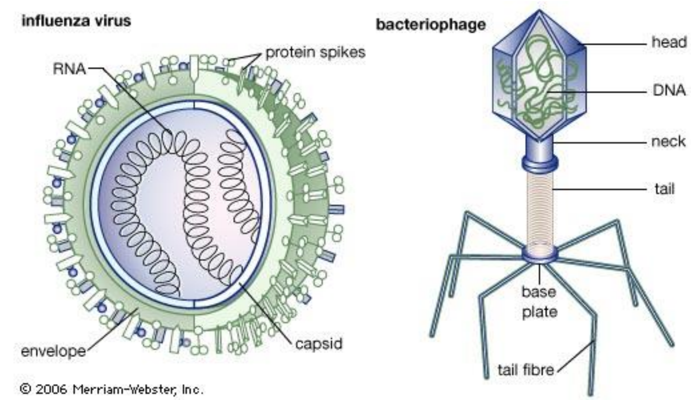


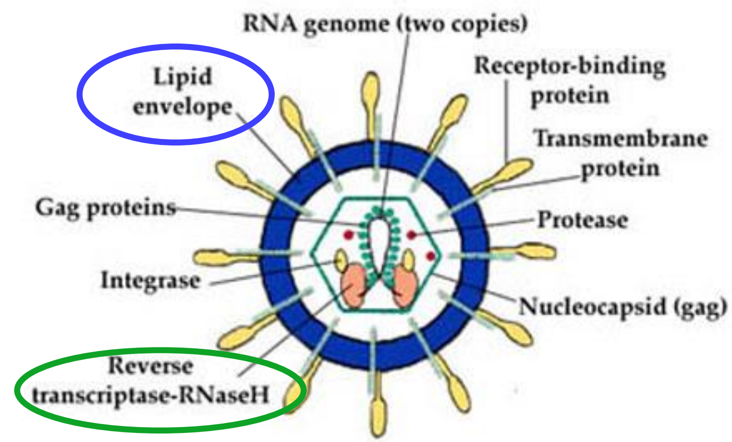
Figure 2

- Classified by genome, in part
  - RNA viruses, DNA viruses, or retroviruses

http://www.biologyjunction.com/virus_notes_b1.htm

- **Virion** - single virus particle outside of a cell
  - Not alive or dead
  - Relies on living cells for replication
- **Capsid** - nearly all viruses form a protein sheath around their nucleic acid core
  - Composed of repeats of 1 to a few proteins
- Some viruses store specialized enzymes not found in host
  – Example is Reverse transcriptase not found in host
- Many animal viruses have an **envelope**
  - Derived from host cell membrane with viral proteins

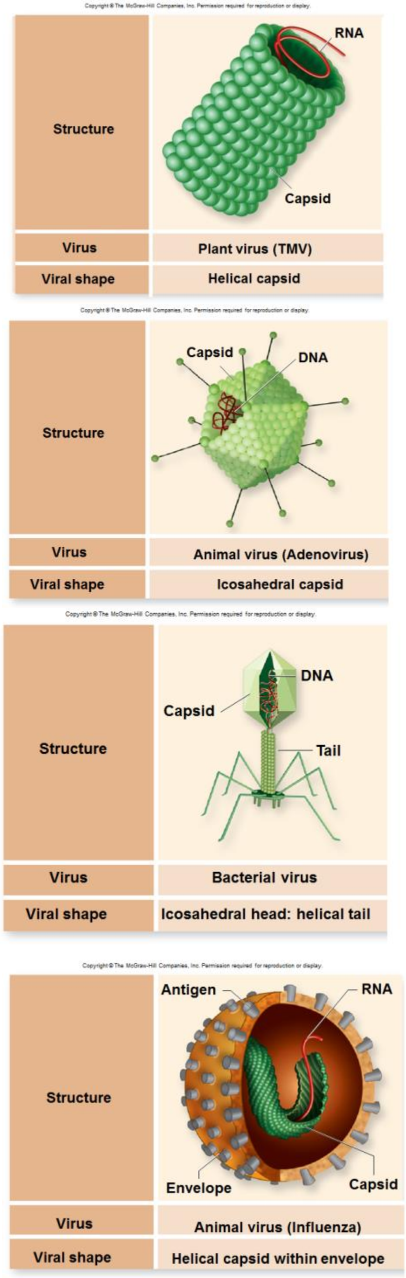




Structure of a retrovirus

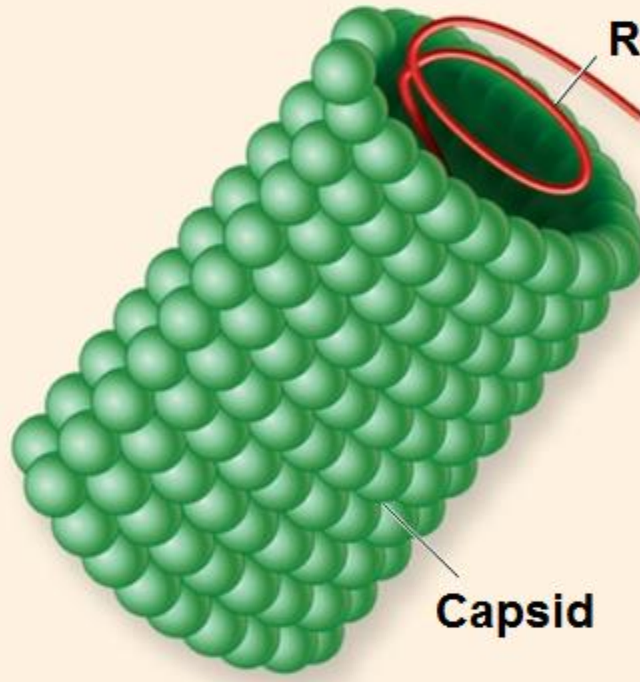
Viral Shapes

- Most viruses come in two simple shapes
    - **Helical** – TMV, rodlike or threadlike
    - **Icosahedral** – soccer ball shape
- Some viruses are more complex
    - **T-even bacteriophages** – 2 fold symmetry
        - Bacteriophages are viruses that infect bacteria
    - **Poxviruses** – multilayered capsid
- Enveloped viruses are polymorphic

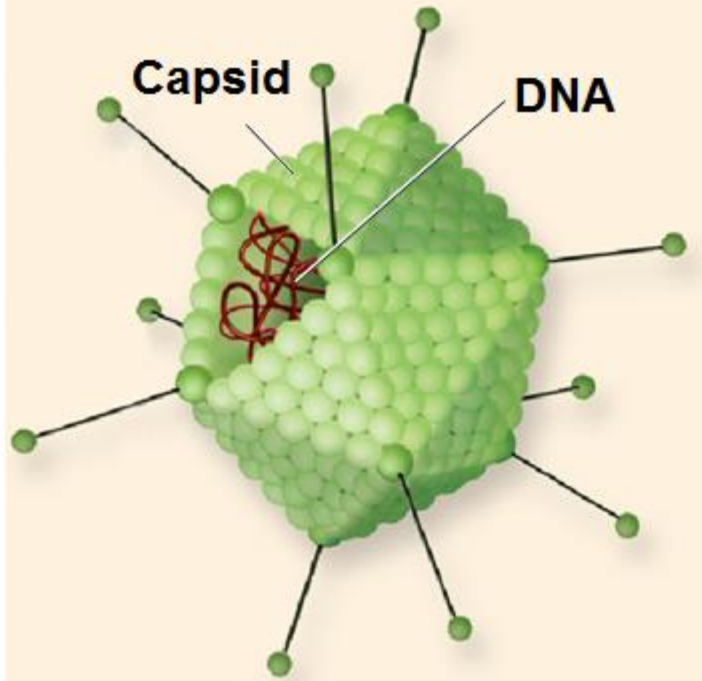


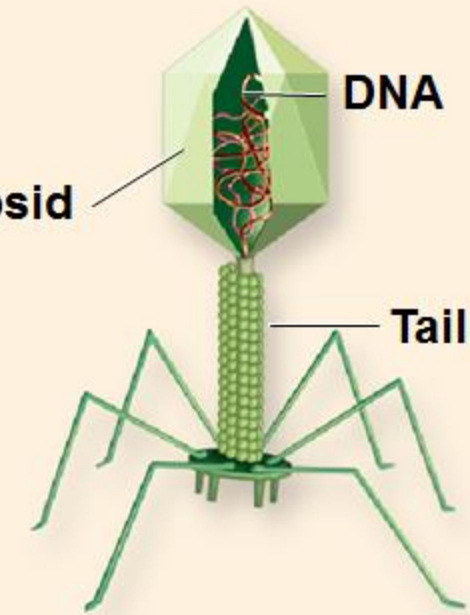
Envelope is derived from host cell membrane 8

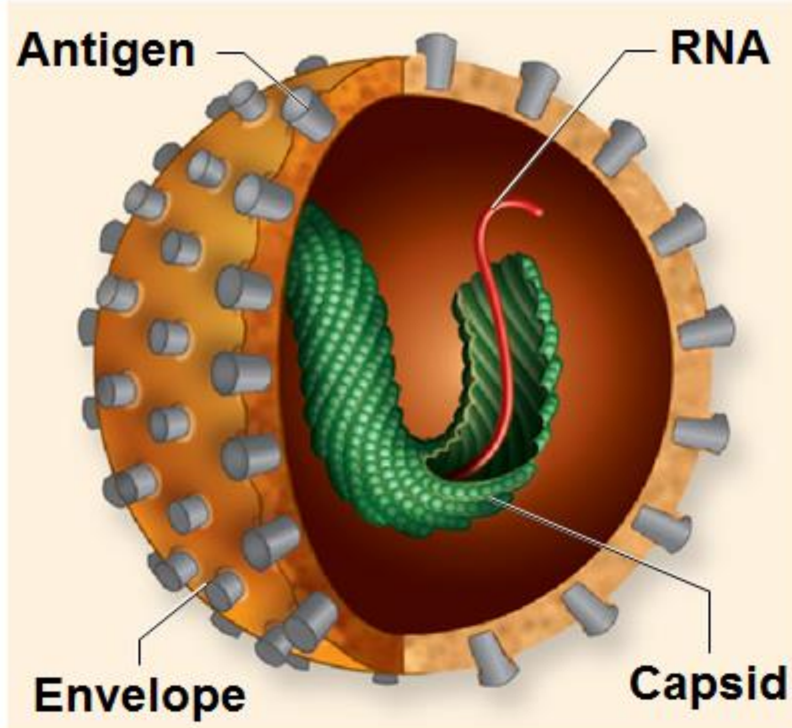
Structure



Virus	**Plant virus (TMV)**
Viral shape	**Helical capsid**

Structure	
Virus	Animal virus (Adenovirus)
Viral shape	Icosahedral capsid

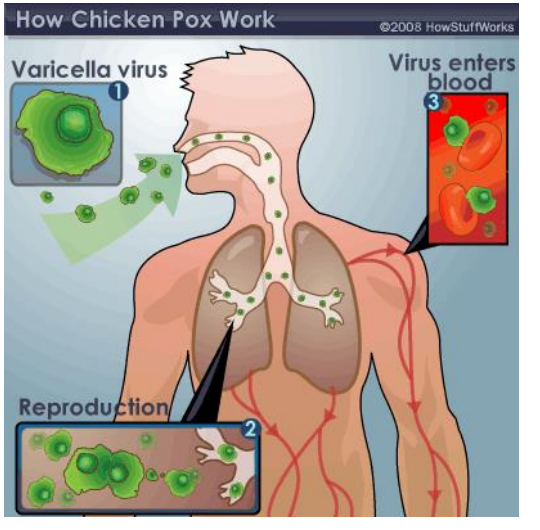
Structure	
Virus	Bacterial virus
Viral shape	Icosahedral head: helical tail

Structure	
Virus	**Animal virus (Influenza)**
Viral shape	**Helical capsid within envelope**

Envelope is derived from host cell membrane

Viral hosts

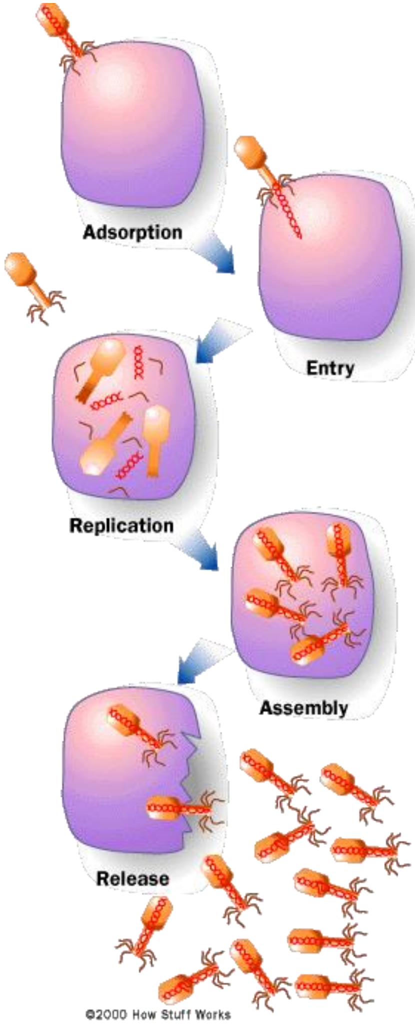
- Viruses are ***obligate intracellular parasites*** in every kind of organism investigated
  - Bacteria to multicellular eukaryotes
- **Host range** – types of organisms infected
  - Each type of virus has a limited host range
  - **Tissue tropism** – inside a host the virus may only infect certain tissues
- Viruses can remain dormant or latent for years
  - Chicken pox can reemerge as shingles
- More kinds of viruses exist than organisms



http://health.howstuffworks.com/skin-care/problems/medical/chicken-pox1.htm

Viral Replication

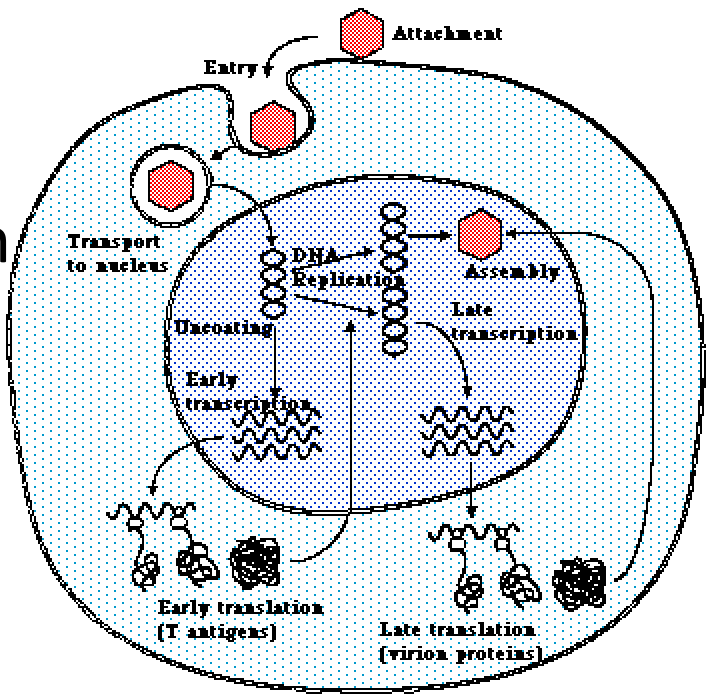
- Infecting virus can be thought of as a set of instructions
- Viral genome uses host cell's "machinery" into making more viruses
- Viruses can only reproduce inside cells
  - Outside, they are metabolically inert virions



http://science.howstuffworks.com/life/cellular-microscopic/virus-human2.htm

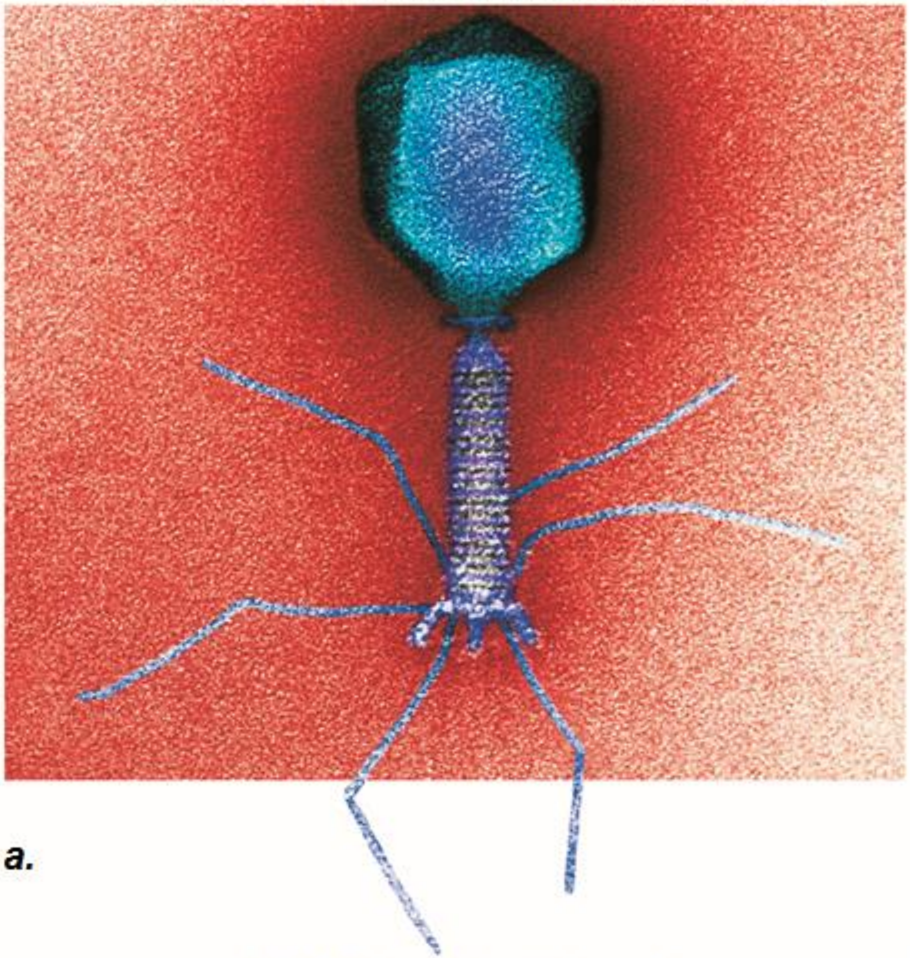
- Viruses lack their own ribosomes and enzymes for protein and nucleic acid synthesis
- Virus hijacks the cell's transcription and translation machineries to express
  - **Early genes** – neutralize defenses, breaks down host DNA
  - **Middle genes** – mobilizes transcription/translation
  - **Late genes** – assembles and releases viruses

- End result is assembly and release of viruses



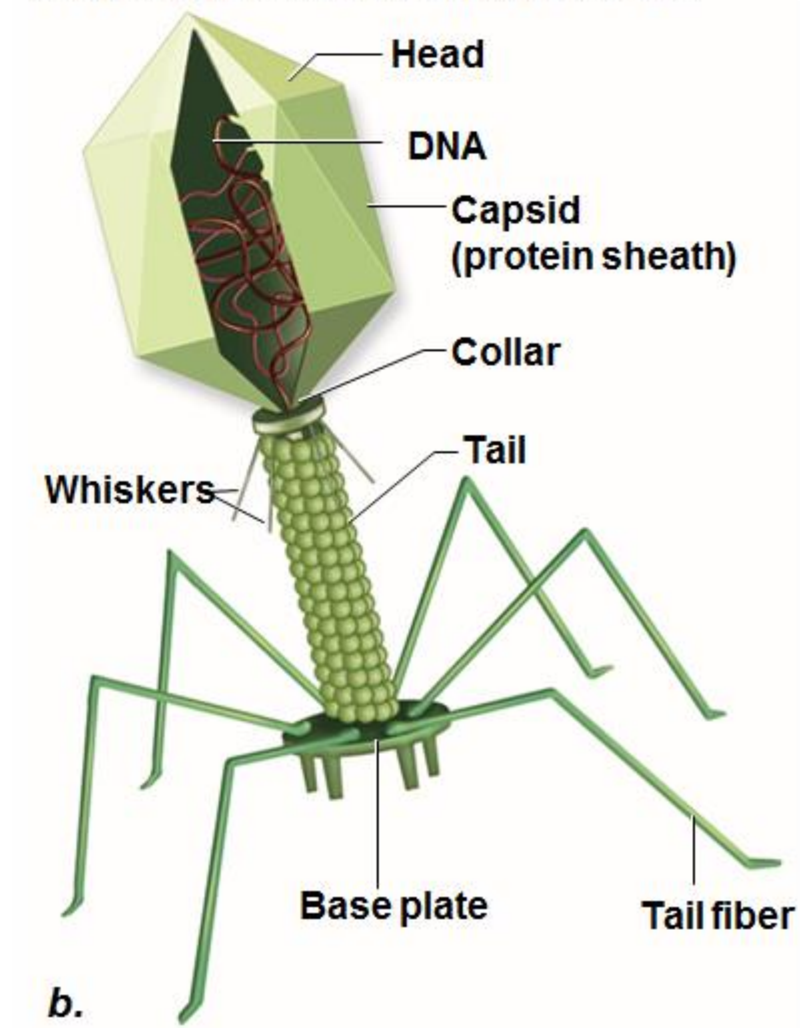
http://www.microbiologybytes.com/virology/Polyomaviruses.html

• Complex binary shape of bacteriophage



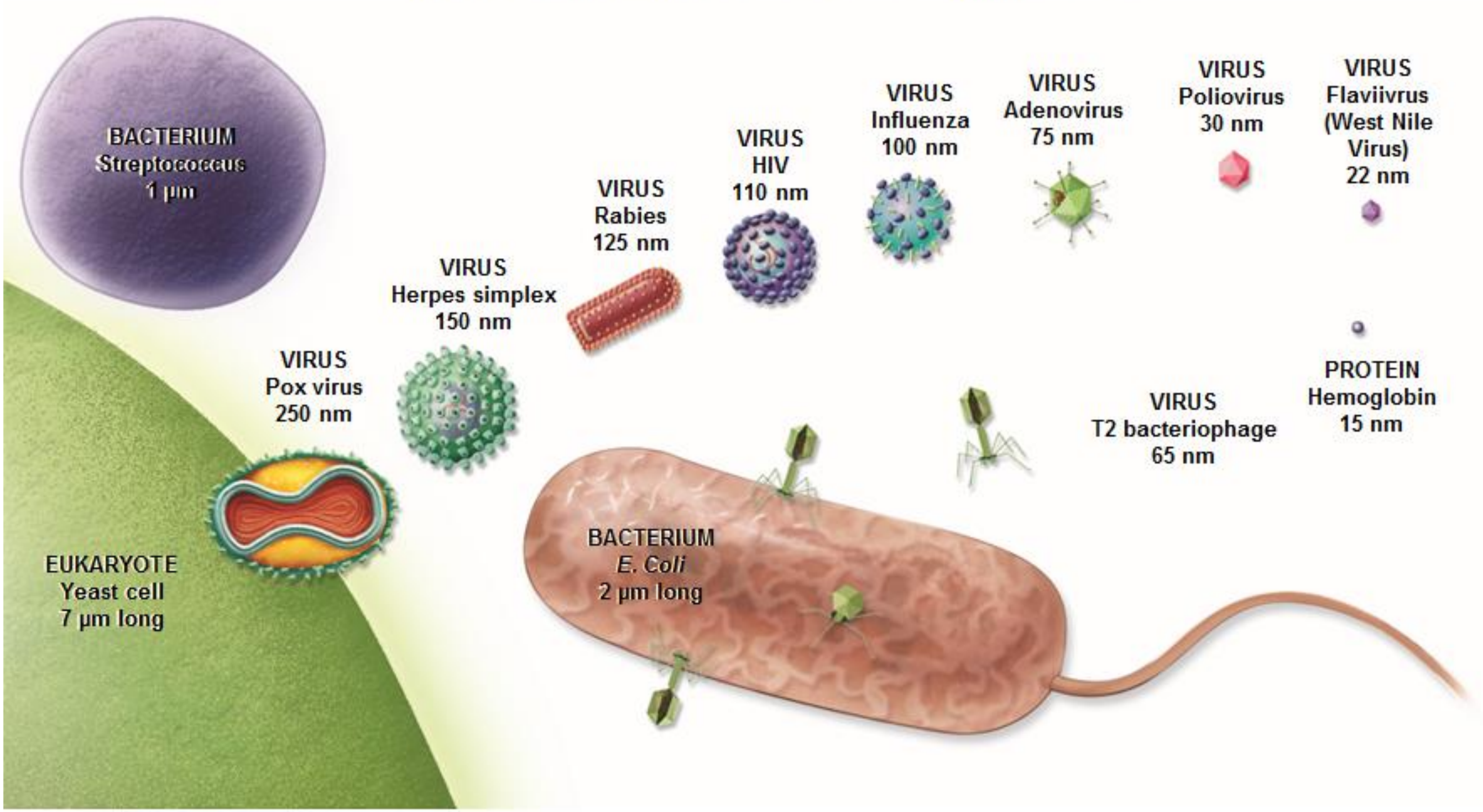
a.

a: © Dept. of Biology, Biozentrum/SPL/Photo Researchers, Inc.



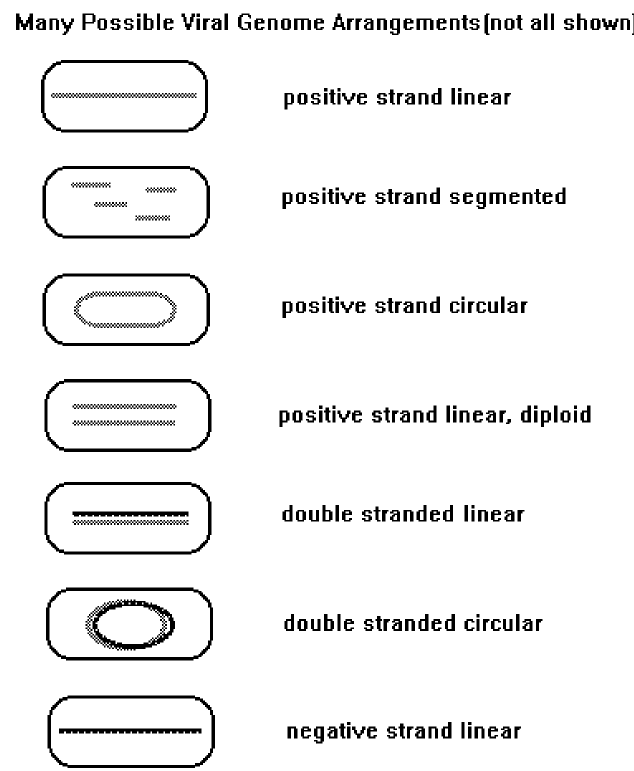
b.

Viruses vary in size, as well as in shape



Viral Genomes

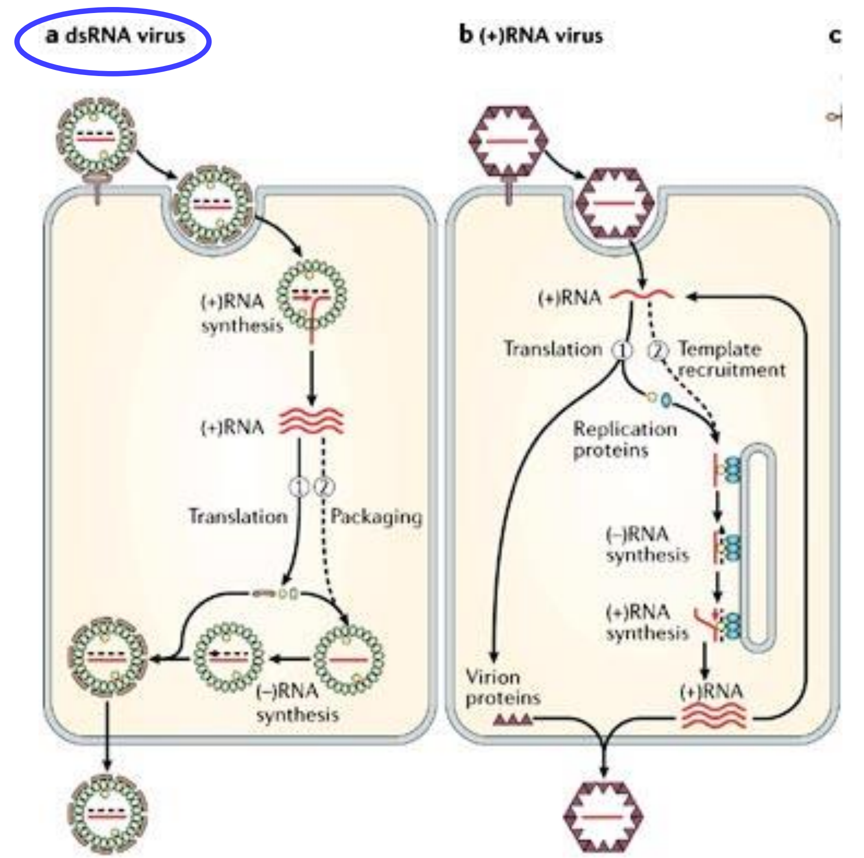
- Vary greatly in both type of nucleic acid and number of strands
  - DNA or RNA
  - Single or double stranded



http://www.mansfield.ohio-state.edu/~sabedon/biol3025.htm

Viral Genomes

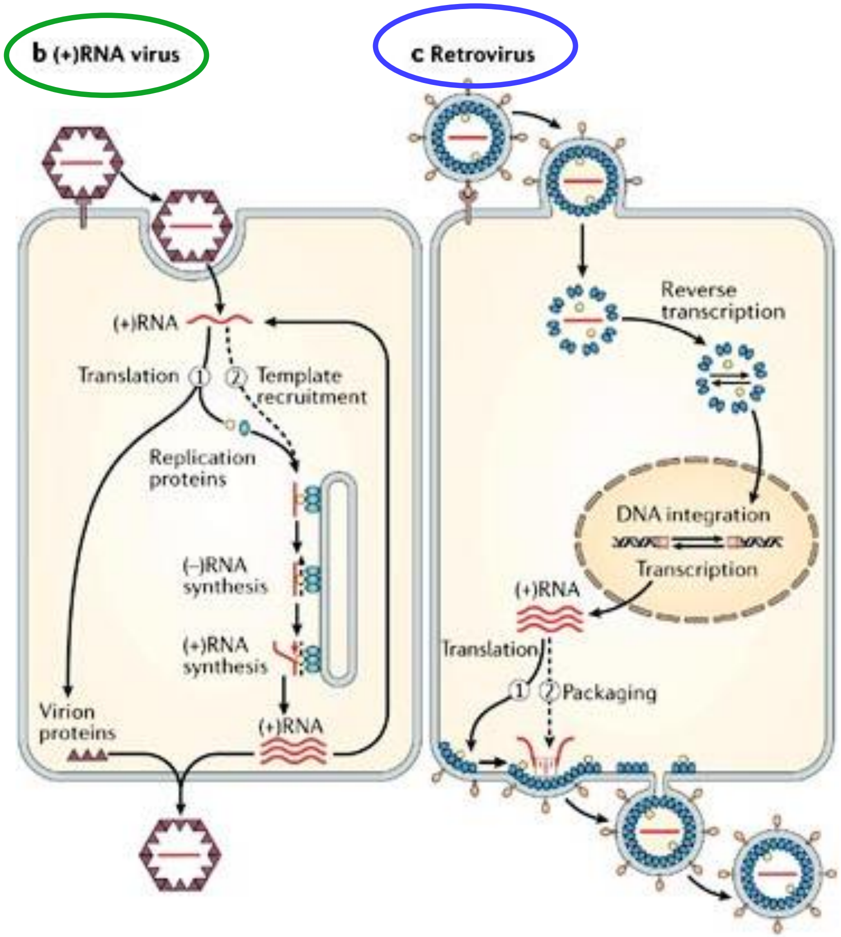
- Most DNA viruses are double-stranded (dsDNA)
  - Replicated in nucleus of eukaryotic host cell
- Most RNA viruses are single-stranded (ssRNA)
  - Replicated in the host cell's cytoplasm
  - Replication in cytosol is error-prone
    - high rates of mutation
    - difficult targets for immune system and vaccines/drugs



http://www.nature.com/nrmicro/journal/v4/n5/box/nrmicro1389_BX1.html

Viral Genomes

- RNA viruses
  - **Positive-strand virus** – viral RNA serves as mRNA
  - Negative-strand virus – genome is complementary to the viral mRNA
  - **Retroviruses** (HIV) employ reverse transcriptase to reverse transcribe viral RNA into DNA



http://www.nature.com/nrmicro/journal/v4/n5/box/nrmicro1389_BX1.html

TABLE 27.1 Important Human Viral Diseases

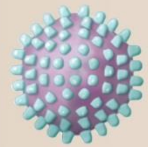
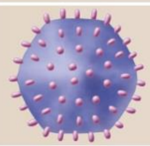
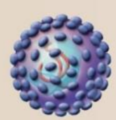
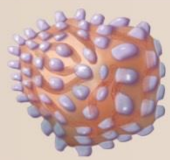
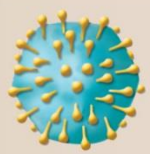
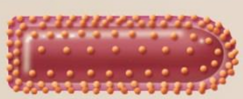
Disease	Pathogen	Genome	Vector/Epidemiology
Chicken pox	Varicella-zoster virus 	Double-stranded DNA	Spread through contact with infected individuals. No cure. Rarely fatal. Vaccine approved in U.S. in early 1995. May exhibit latency leading to shingles. A vaccine for shingles that consists of a higher dose of the '95 vaccine was approved in 2006.
Hepatitis B (viral)	Hepadnavirus 	Double-stranded DNA	Highly infectious through contact with infected body fluids. Approximately 1% of U.S. population infected. Vaccine available. No cure. Can be fatal.
Herpes	Herpes simplex virus 	Double-stranded DNA	Blisters; spread primarily through skin-to-skin contact with cold sores/blisters. Very prevalent worldwide. No cure. Exhibits latency—the disease can be dormant for several years.
Mononucleosis	Epstein–Barr virus 	Double-stranded DNA	Spread through contact with infected saliva. May last several weeks; common in young adults. No cure. Rarely fatal.
Smallpox	Variola virus 	Double-stranded DNA	Historically a major killer; the last recorded case of smallpox was in 1977. A worldwide vaccination campaign wiped out the disease completely.
AIDS	HIV 	(+) Single-stranded RNA (two copies)	Destroys immune defenses, resulting in death by opportunistic infection or cancer. For the year 2010, WHO estimated that 34 million people are living with AIDS, with an estimated 2.7 million new HIV infections and an estimated 1.8 million deaths.
Polio	Enterovirus 	(+) Single-stranded RNA	Acute viral infection of the CNS that can lead to paralysis and is often fatal. Prior to the development of Salk's vaccine in 1954, 60,000 people a year contracted the disease in the U.S. alone.

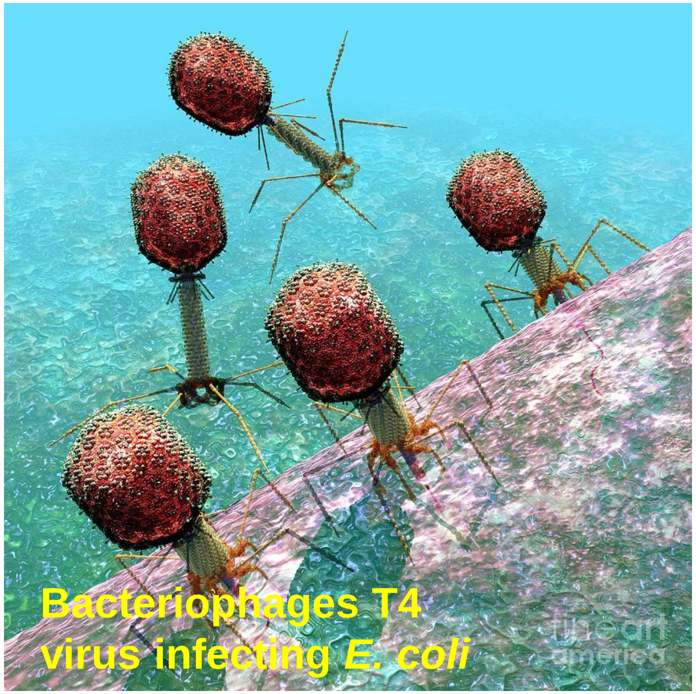
TABLE 27.1 Important Human Viral Diseases

West Nile fever	Flavivirus 	(+) Single-stranded RNA	Spread by mosquitoes and can be amplified in bird hosts. Can lead to neurological problems. Present in U.S. since 1999.
Ebola	Filoviruses 	(–) Single-stranded RNA	Acute hemorrhagic fever; virus attacks connective tissue, leading to massive hemorrhaging and death. Peak mortality is 50–90% if untreated. Outbreaks confined to local regions of central Africa.
Influenza	Influenza viruses 	(–) Single-stranded RNA (eight segments)	Historically a major killer (20–50 million died during 18 months in 1918–1919); wild Asian ducks, chickens, and pigs are major reservoirs. The ducks are not affected by the flu virus, which shuffles its antigen genes while multiplying within them, leading to new flu strains. Vaccines are available.
Measles	Paramyxoviruses 	(–) Single-stranded RNA	Extremely contagious through contact with infected individuals. Vaccine available. Usually contracted in childhood, when it is not serious; more dangerous to adults.
SARS	Coronavirus 	(–) Single-stranded RNA	Acute respiratory infection; an emerging disease, can be fatal, especially in the elderly. Commonly infected animals include bats, foxes, skunks, and raccoons. Domestic animals can be infected.
Rabies	Rhabdovirus 	(–) Single-stranded RNA	An acute viral encephalomyelitis transmitted by the bite of an infected animal. Fatal if untreated. Commonly infected animals include bats, foxes, skunks, and raccoons. Domestic animals can be infected.

Bacteriophage

- Viruses that infect bacteria
- Diverse and united only by bacterial hosts
- Called “phage” for short
- *E. coli*-infecting viruses are the best studied
  - Include the “T” series (T1, T2, etc.)

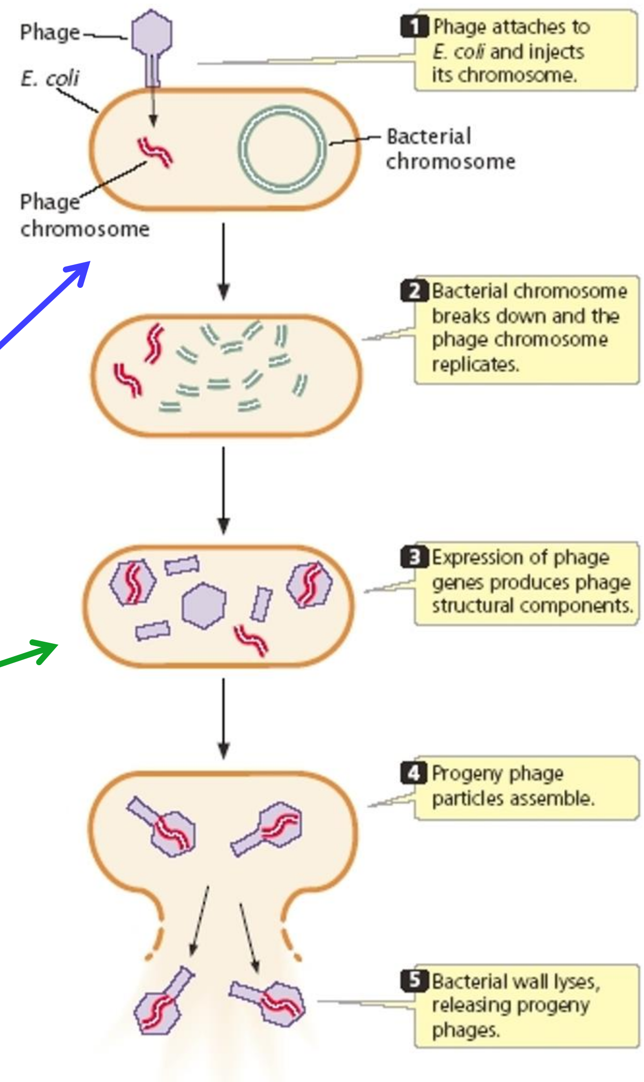
- Viruses have also been found in archaea
  - Different from bacterial viruses
  - Characterization in early stages



http://fineartamerica.com/featured/bacteriophage-t4-virus-group-1-russell-kightley.html

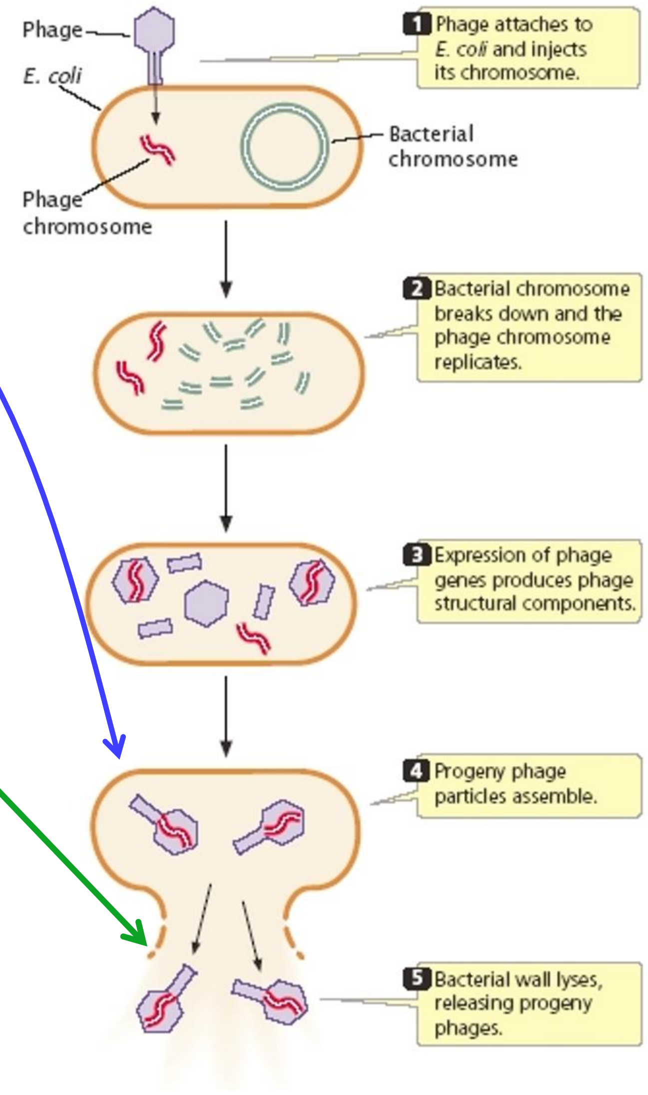
Reproductive cycles Bacteriophages

- **Attachment** or adsorption
  - Target part of bacterial outer surface
  - Recognition of appropriate host
- **Penetration** or injection
  - T4 pierces cell wall to inject viral genome
- **Synthesis**
  - Phage may immediately take over the cell's replication and protein synthesis enzymes to synthesize viral components



http://www.nature.com/scitable/content/a-schematic-of-the-lifecycle-of-a-35875

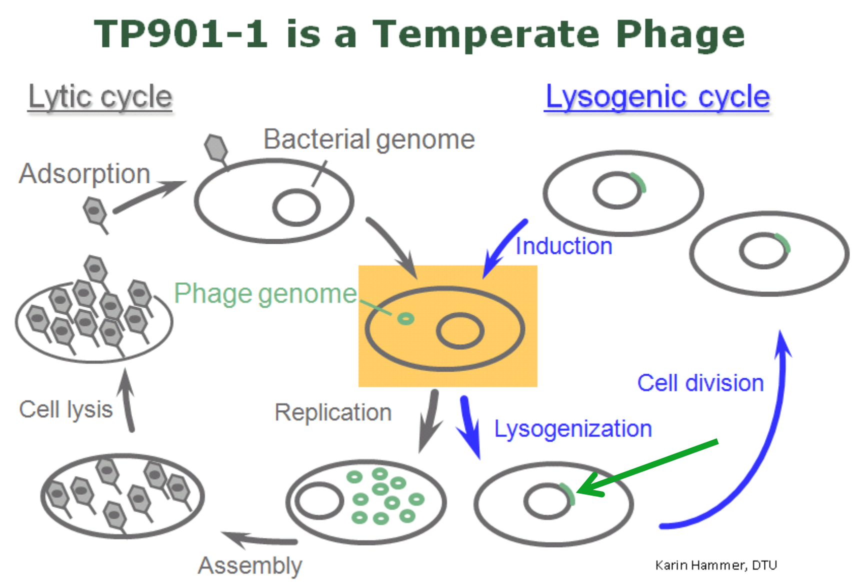
- **Assembly**
  - Assembly of components
- **Release**
  - Mature virus particles are released through enzyme that lyses host or budding through host cell wall
- **Eclipse period**
  - Time between adsorption (first entering cell) and the formation of new viral particles
  - If a cell is lysed at this point, few if any active virions can be released



http://www.nature.com/scitable/content/a-schematic-of-the-lifecycle-of-a-35875

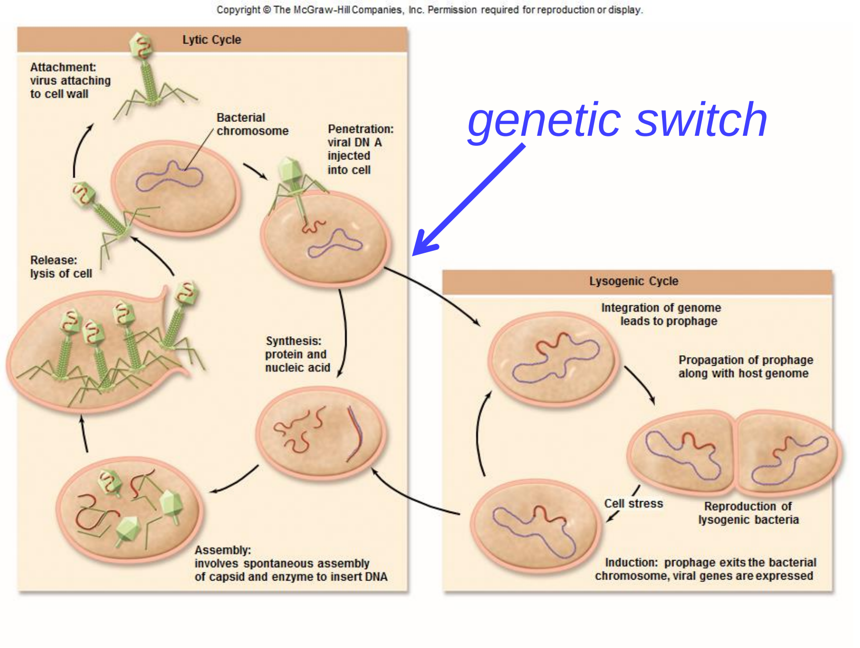
- **Lytic cycle**
    - Virus lyses infected host cell
    - **Virulent** or lytic phages

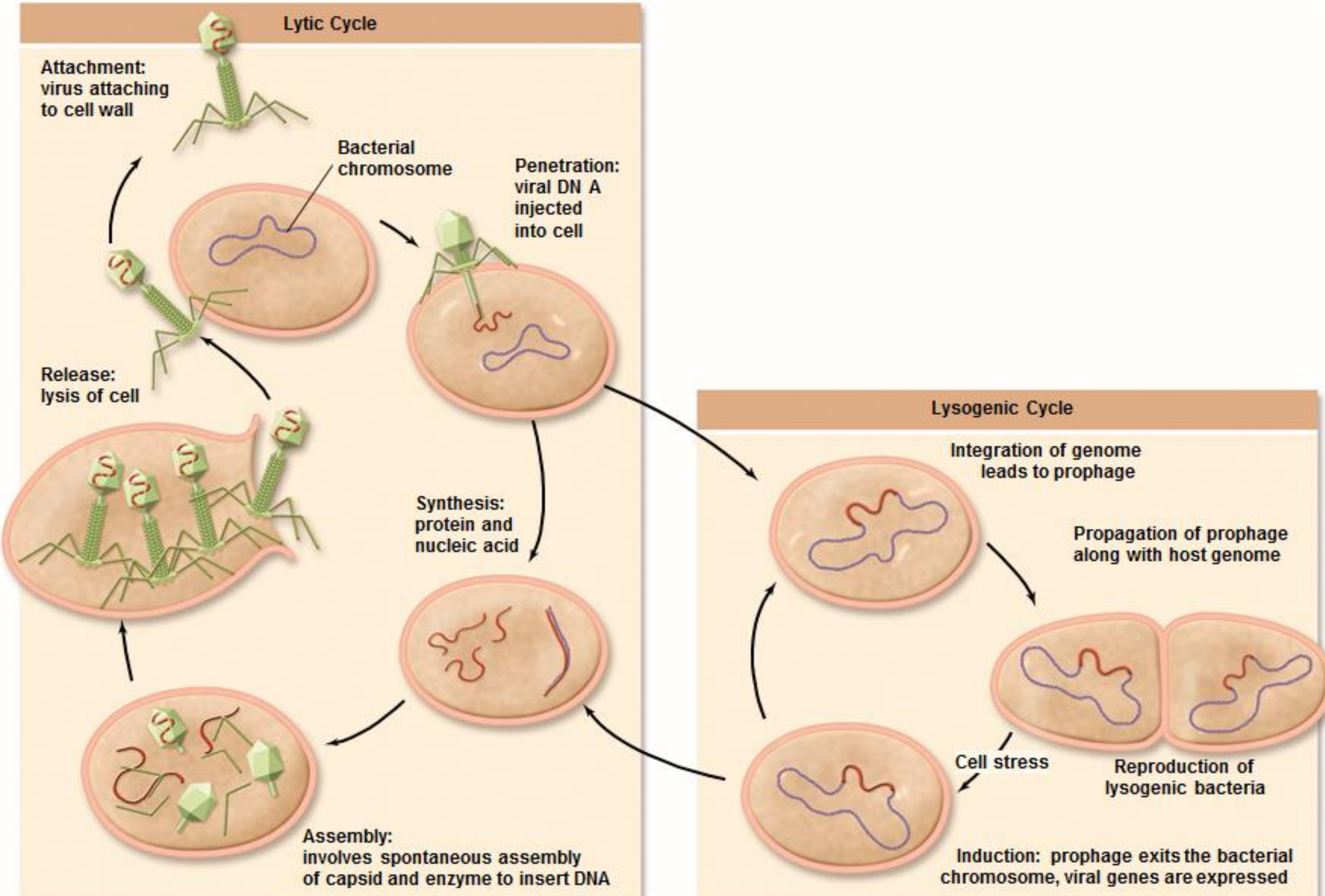
- **Lysogenic cycle**
    - Virus does not immediately kill infected cell
    - Integrates viral nucleic acid into host cell genome – **prophage**
    - Integration allows a virus to be replicated along with the host cell's DNA as the host divides
    - **Temperate** or lysogenic phage



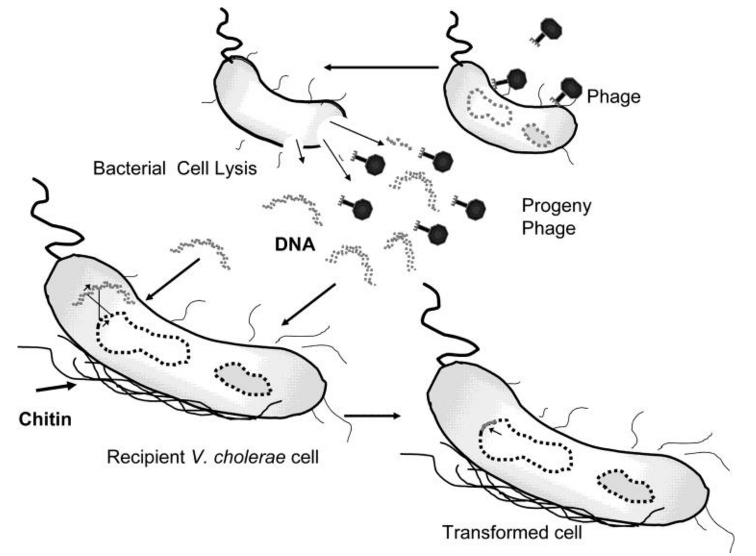
http://www.nature.com/nrmicro/journal/v4/n5/box/nrmicro1393_BX1.html

- Binal phage lambda (λ) of *E. coli*
  - Best studied biological particle
  - When phage λ infects a cell, the early events constitute a <u>*genetic switch*</u> that will determine whether the virus is lytic or lysogenic
  - Induction during stress
    - Prophage can be excised and begins lytic cycle
    - Requires turning on the gene expression necessary for the lytic cycle




Lytic Cycle
Attachment: virus attaching to cell wall
Bacterial chromosome
Penetration: viral DN A injected into cell
Synthesis: protein and nucleic acid
Assembly: involves spontaneous assembly of capsid and enzyme to insert DNA
Release: lysis of cell
Lysogenic Cycle
Integration of genome leads to prophage
Propagation of prophage along with host genome
Reproduction of lysogenic bacteria
Cell stress
Induction: prophage exits the bacterial chromosome, viral genes are expressed

- **Phage conversion**
  - Phenotype or characteristics of the lysogenic bacterium is altered by the prophage
    - Due to viral DNA inserted into host genome
  - *Vibrio cholerae* phage conversion
    - Lysogenic phage introduced a gene coding for cholera toxin
    - Gene became incorporated into host genome
    - Converts harmless bacteria into disease-causing form



http://www.pnas.org/content/105/33/11951/F3.expansion.html

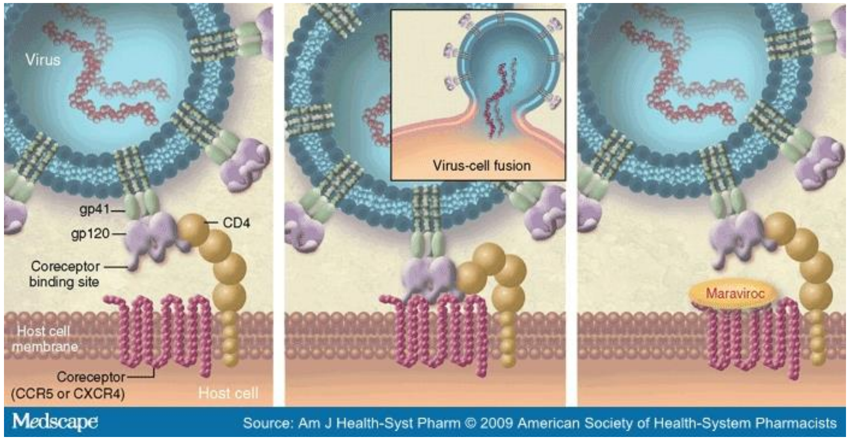
Human Immunodeficiency Virus

- **HIV** causes **acquired immune deficiency syndrome** (AIDS)
- AIDS was first reported in the U.S. in 1981
  - Origin in Africa in 1950s
- Some people are resistant to HIV infection
  - Exposed repeatedly never become positive
  - Others become HIV-positive without developing AIDS
  - Others have little resistance and progress rapidly from infection to death

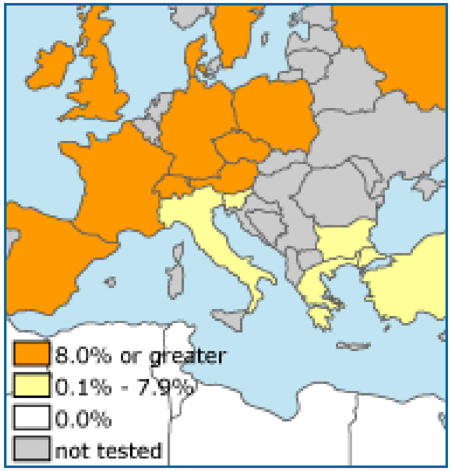
HIV (green) budding from a lymphocyte, SEM

http://en.wikipedia.org/wiki/HIV/AIDS

- Variability in resistance may be due to selective pressure by smallpox virus
  - Before its eradication, smallpox killed billions
    - Individuals without smallpox receptor were resistant to smallpox
    - CCR5 receptor used by HIV may have been used by smallpox
    - Therefore those resistant to smallpox also resistant to HIV
    - Historical appearance and distribution of CCR5 mutation correlates with historic distribution of smallpox

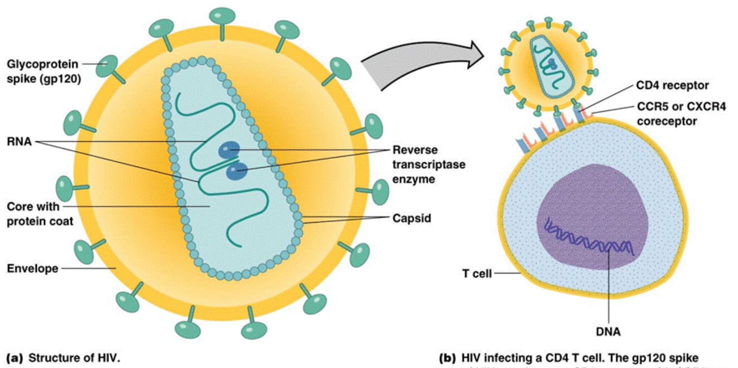


Left: Role of CCR5 protein in recognition/entry of HIV into host cell.
Right: Frequencies of mutant CCR5 allele are higher in European populations, which tend to be more resistant to HIV.



http://www.medscape.com/viewarticle/705842_3 http://evolution.berkeley.edu/evolibrary/news/081001_hivmalaria http://classes.midlandstech.edu/carterp/Courses/bio225/chap19/lecture8.htm

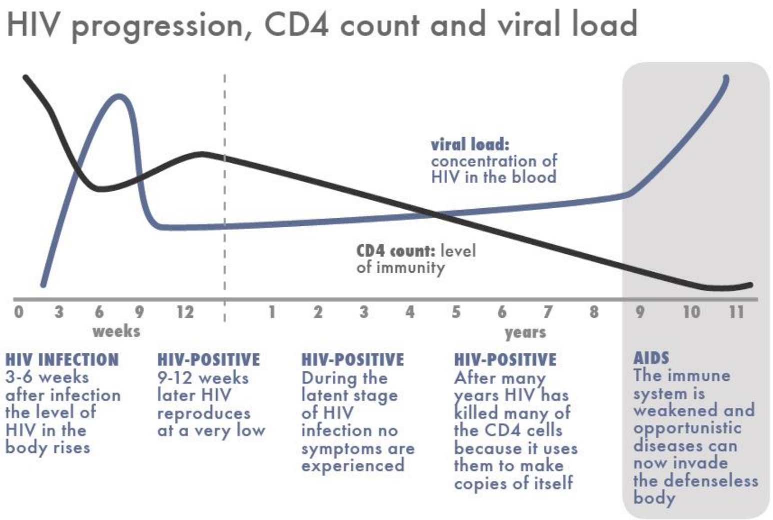
- HIV targets $CD4^+$ cells, mainly helper T cells
  - Without these cells, the body cannot mount an effective immune response
  - Host may ultimately die from a variety of opportunistic infections that do not normally cause disease



(a) Structure of HIV.

(b) HIV infecting a CD4 T cell. The gp120 spike of HIV attaches to a CD4 receptor with CCR5 or CXCR4 coreceptors. The HIV capsid then enters the cell by fusion, leaving its envelope behind.

- Clinical symptoms of AIDS usually appear after 8–10 year latent period
  - Provirus integrates in genome of macrophages and $CD4^+$ cells

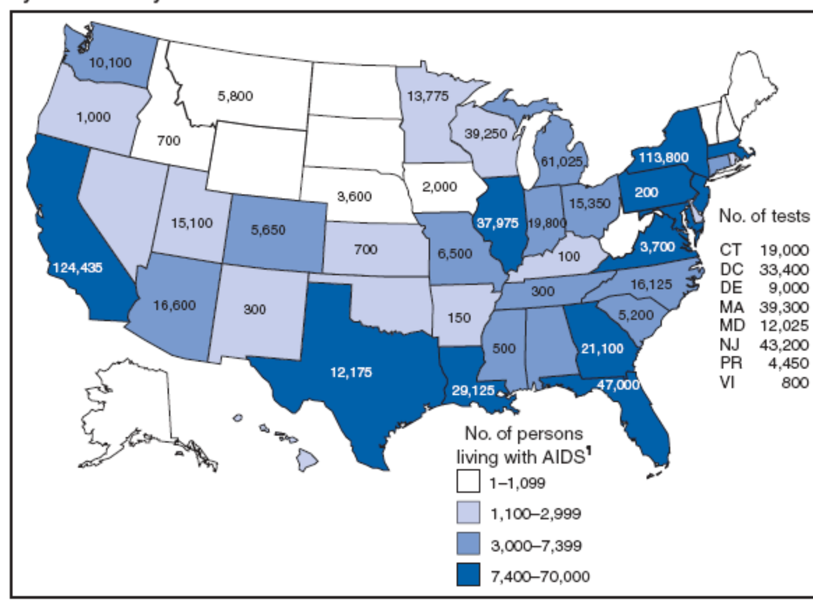


http://www.journaids.org/index.php/essential_information/hivaids_overview/

- HIV testing
  - Not a test for circulating virus
  - Test for presence of antibody against HIV
  - Further testing confirms HIV-positive status

- Spread of AIDS
  - Carriers have no clinical symptoms but are infectious
  - Infection continues throughout latent period
  - Mutation allows the virus to overcome immune system and AIDS begins

FIGURE. Number of rapid HIV* tests distributed by CDC during September 2003–December 2005 and estimated number of persons† living with AIDS§ at the end of 2004, by state/territory — United States

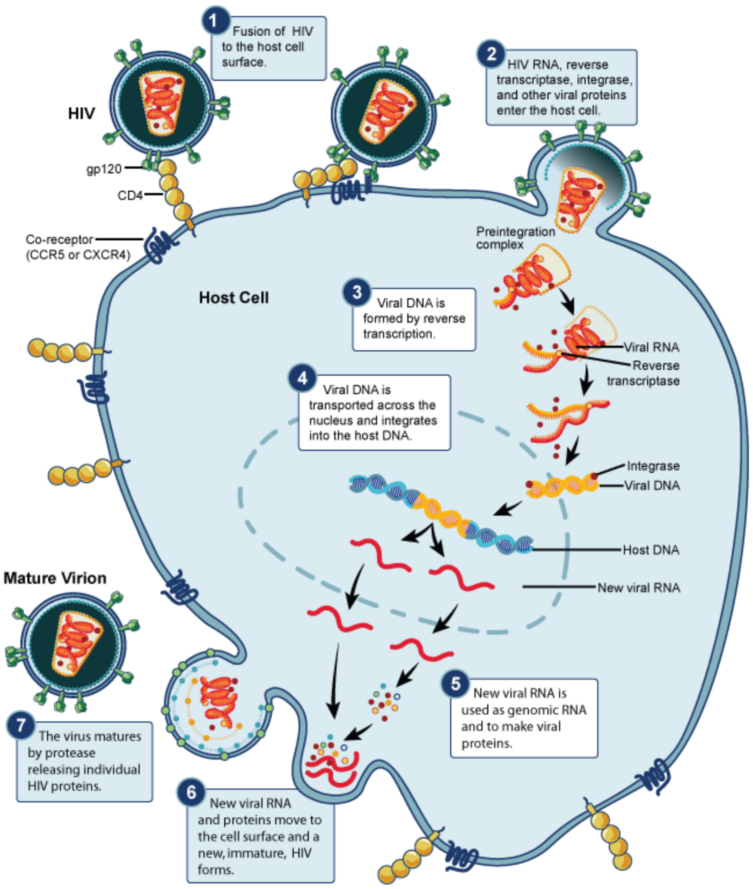


* Human immunodeficiency virus.
† Aged ≥13 years.
§ Acquired immunodeficiency syndrome.
¶ CDC. HIV/AIDS surveillance report, 2004. Vol. 16. Atlanta, GA: US Department of Health and Human Services, CDC; 2005:22. Available at http://www.cdc.gov/hiv/stats/2004surveillancereport.pdf.

http://www.thebody.com/content/art17197.html

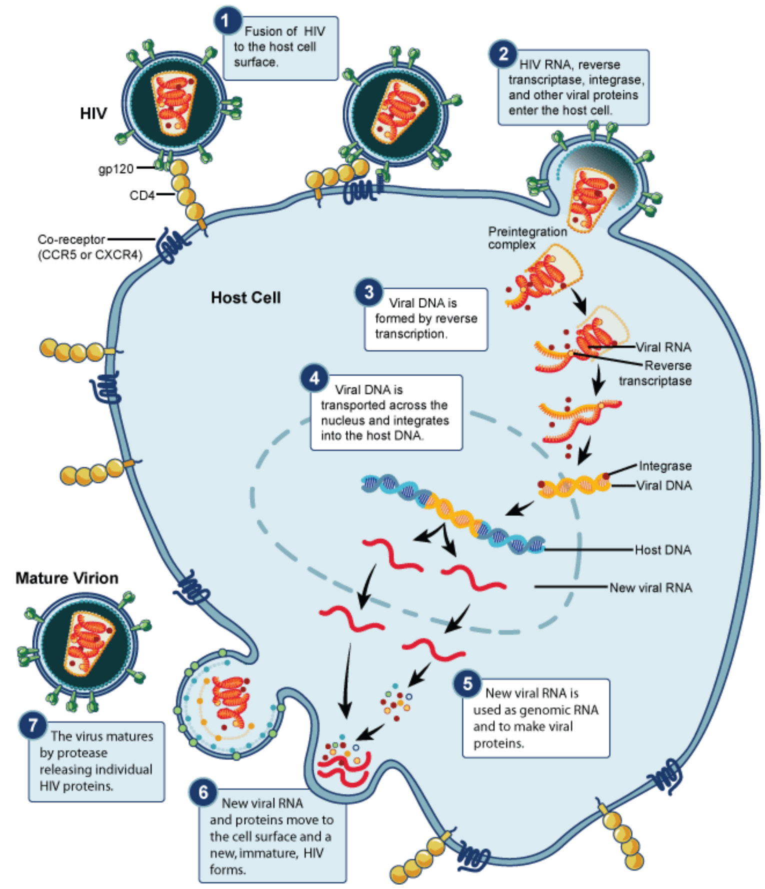
HIV Infection Cycle

- Model for animal viruses
    - Details may vary for other viruses
- Attachment (1)
    - Virus only attacks $CD4^+$ cells
    - Viral gp120 attaches to CD4 protein on macrophages and $CD4^+$ cells
    - Coreceptors like CCR5 affect likelihood of entry
- Entry through fusion pore (2)

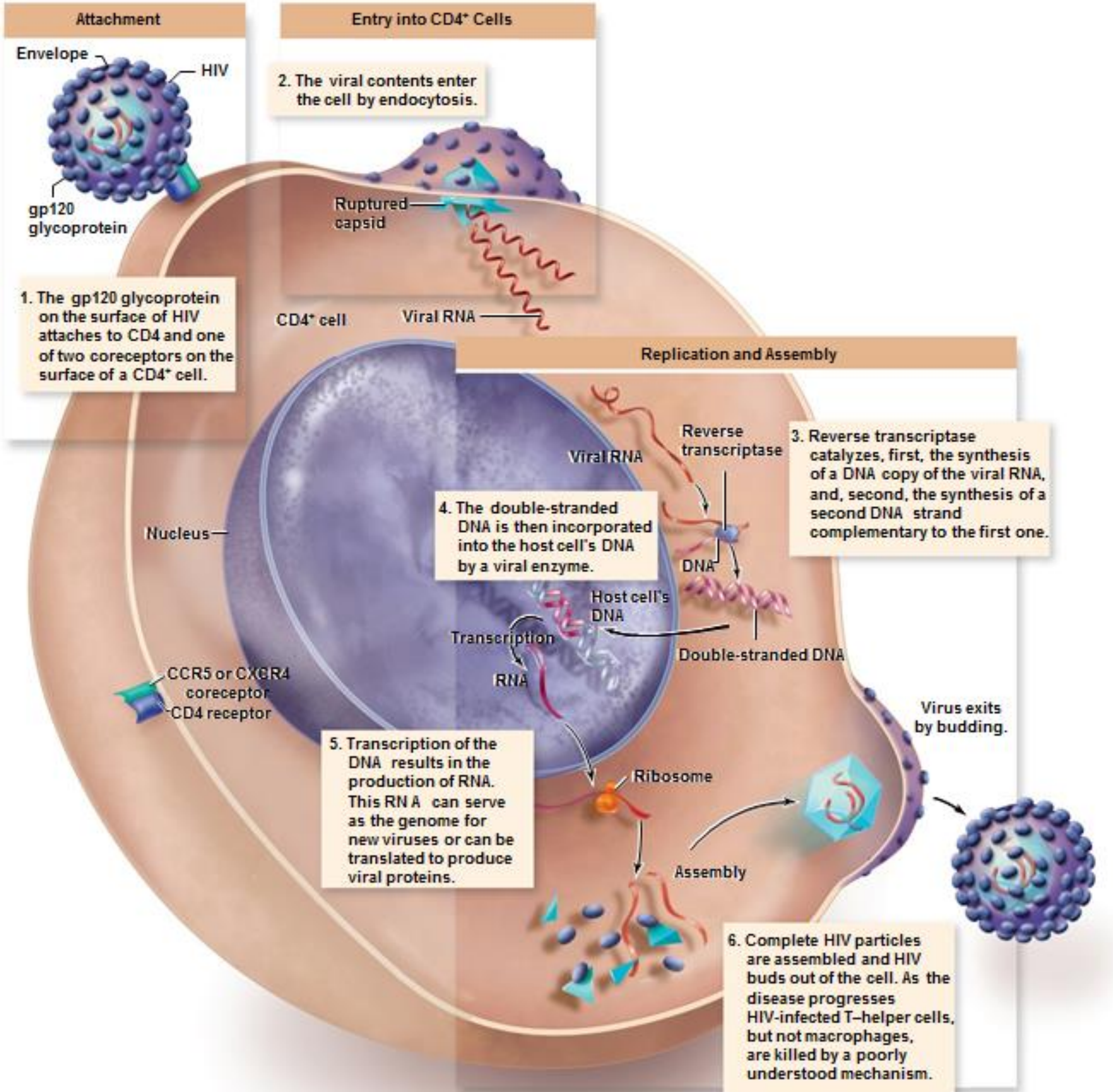


http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/pages/hivreplicationcycle.aspx

- Replication
  - Reverse transcriptase converts virus RNA to double-stranded DNA (3)
    - Mutations common in process
  - DNA is incorporated into host genome (4)
  - Variable period of dormancy
- Assembly (5)
    - Making many copies of virus
- Release (6)
    - New viruses exit by budding

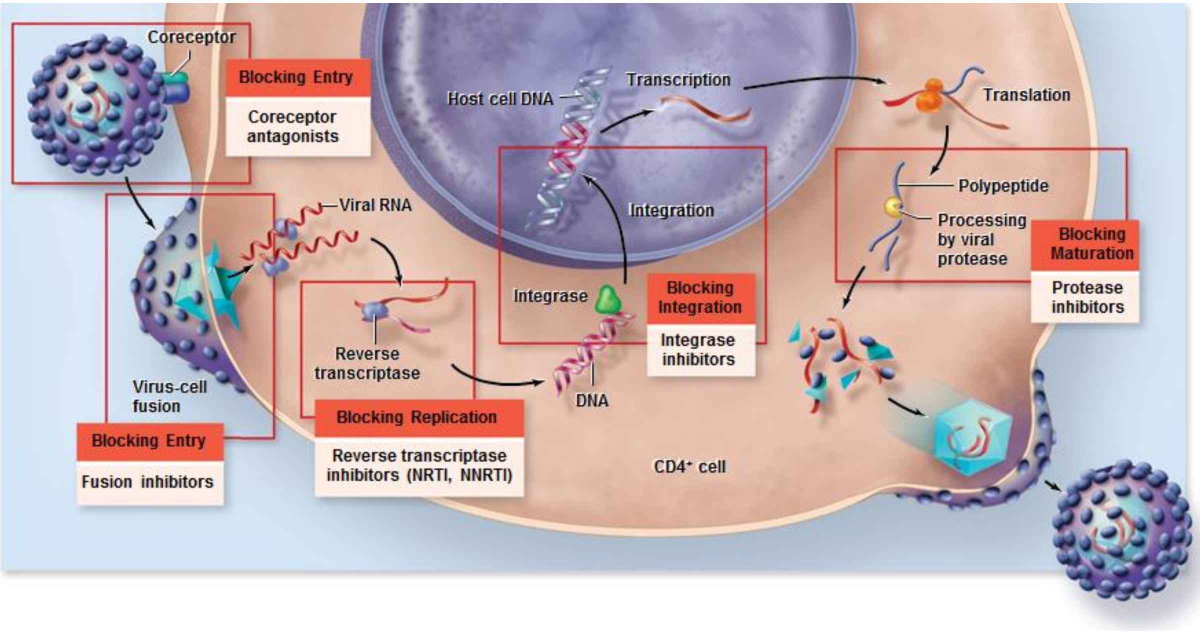


http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/pages/hivreplicationcycle.aspx

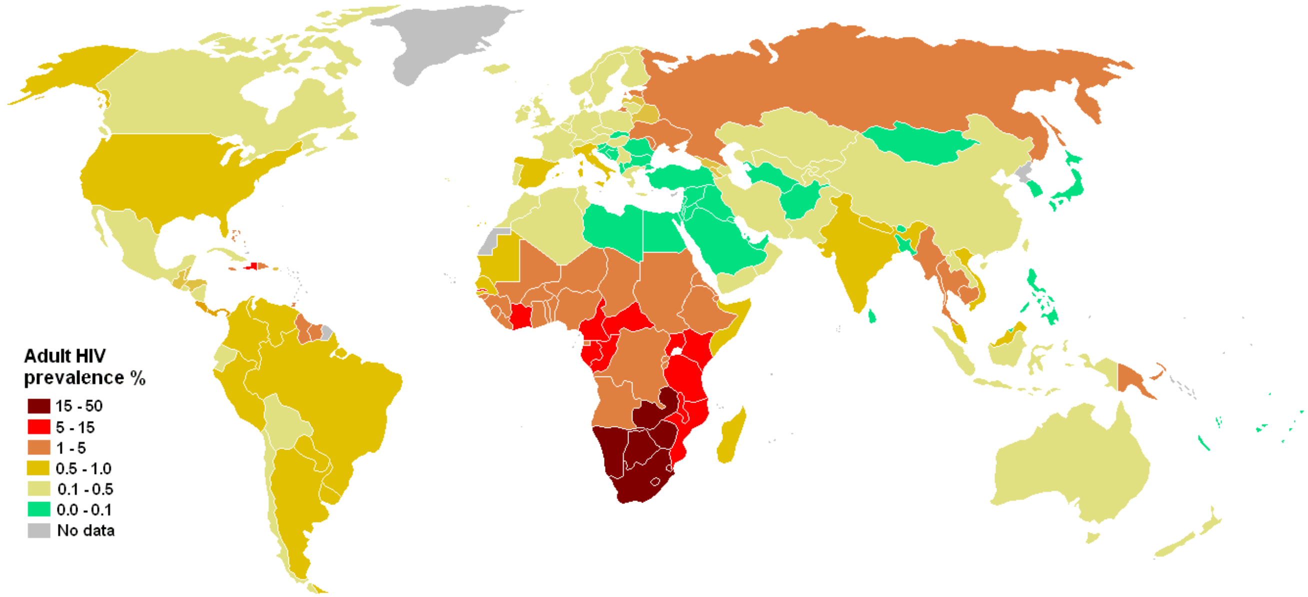

Attachment
Envelope
HIV
gp120 glycoprotein
1. The gp120 glycoprotein on the surface of HIV attaches to CD4 and one of two coreceptors on the surface of a CD4+ cell.
Entry into CD4+ Cells
2. The viral contents enter the cell by endocytosis.
Ruptured capsid
CD4+ cell
Viral RNA
Replication and Assembly
Reverse transcriptase
3. Reverse transcriptase catalyzes, first, the synthesis of a DNA copy of the viral RNA, and, second, the synthesis of a second DNA strand complementary to the first one.
Viral RNA
4. The double-stranded DNA is then incorporated into the host cell's DNA by a viral enzyme.
Nucleus
DNA
Host cell's DNA
Transcription
Double-stranded DNA
RNA
CCR5 or CXCR4 coreceptor
CD4 receptor
Virus exits by budding.
5. Transcription of the DNA results in the production of RNA. This RN A can serve as the genome for new viruses or can be translated to produce viral proteins.
Ribosome
Assembly
6. Complete HIV particles are assembled and HIV buds out of the cell. As the disease progresses HIV-infected T–helper cells, but not macrophages, are killed by a poorly understood mechanism.

AIDS treatments

- FDA lists 32 antiretroviral drugs used in AIDS therapy
- Targets four aspects of HIV life cycle
  - Blocking viral entry (CCR5)
  - Interfering with genome replication (AZT blocks reverse transcription)
  - Block integration of viral DNA (integrase inhibitor)
  - Maturation of HIV proteins (protease inhibitors)



- Vaccine development has been unsuccessful
  - Problem had been seen as high mutation rate
  - Real problem is no vaccine yet has produced strong cellular immune response
  - Attenuated SIV vaccine
    - Mutated back into infective virus
    - Experimental animals developed simian AIDS

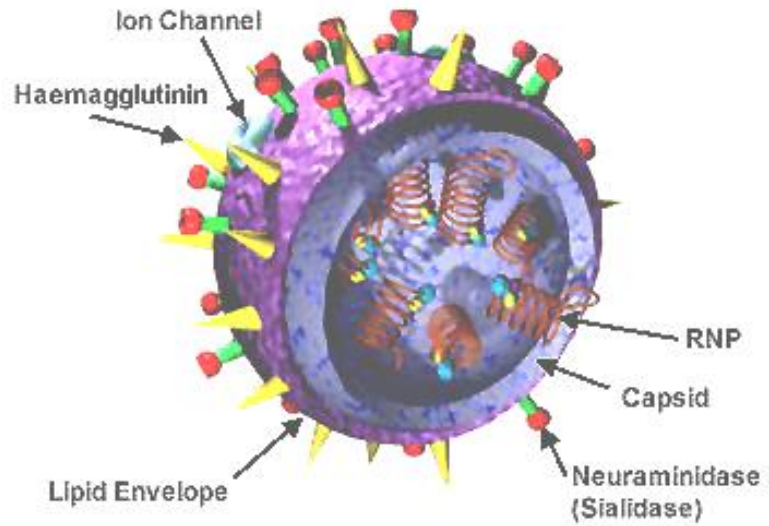


http://2007.igem.org/Ljubljana/AIDSplague

Influenza

- One of the most lethal viruses in human history
  - 20–50 million people died worldwide between 1918 and 1919

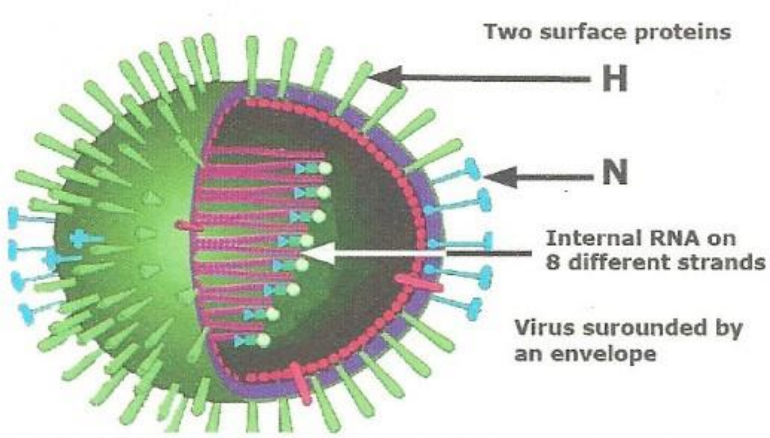
- Flu viruses are enveloped animal viruses
  - 3 "types" based on capsid protein
    - Type A - Serious epidemics in humans and other animals
    - Types B and C – Mild human infections
  - Subtypes differ in protein spikes
    - Hemagglutinin (H) – Aids in viral entry
    - Neuraminidase (N) – Aids in viral exit



http://en.wikipedia.org/wiki/Influenza

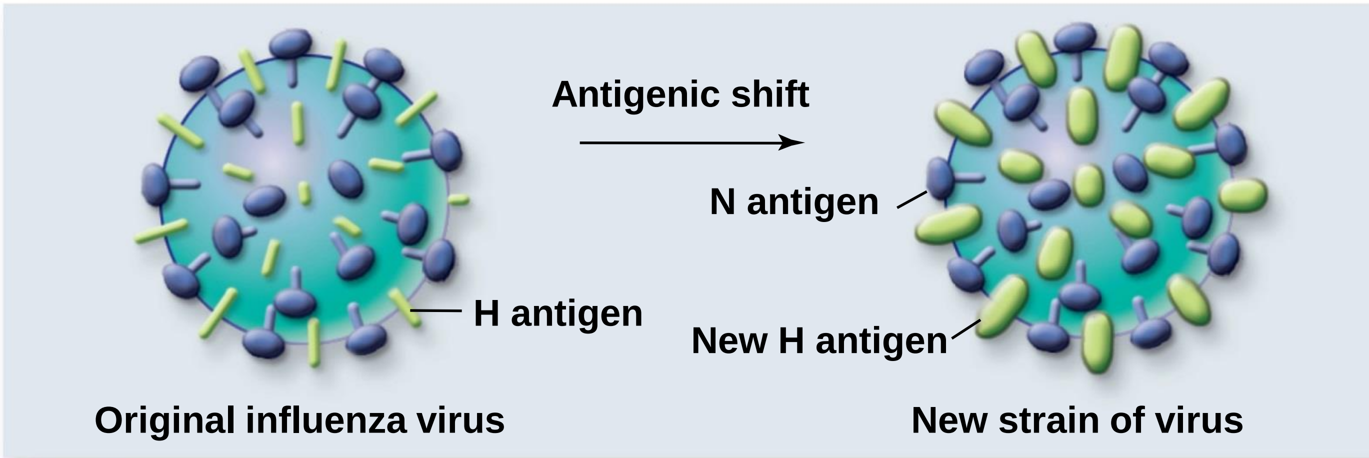
- H and N molecules accumulate mutations (**drift**)
  - Thus we have yearly flu shots, and not a single vaccine
  - Type A viruses are classified into 13 distinct H subtypes and 9 distinct N subtypes

- Flu viruses can also undergo genetic recombination when 2 subtypes infect the same cell (**shift**)
  - Creates novel combinations of spikes unrecognizable by human antibodies

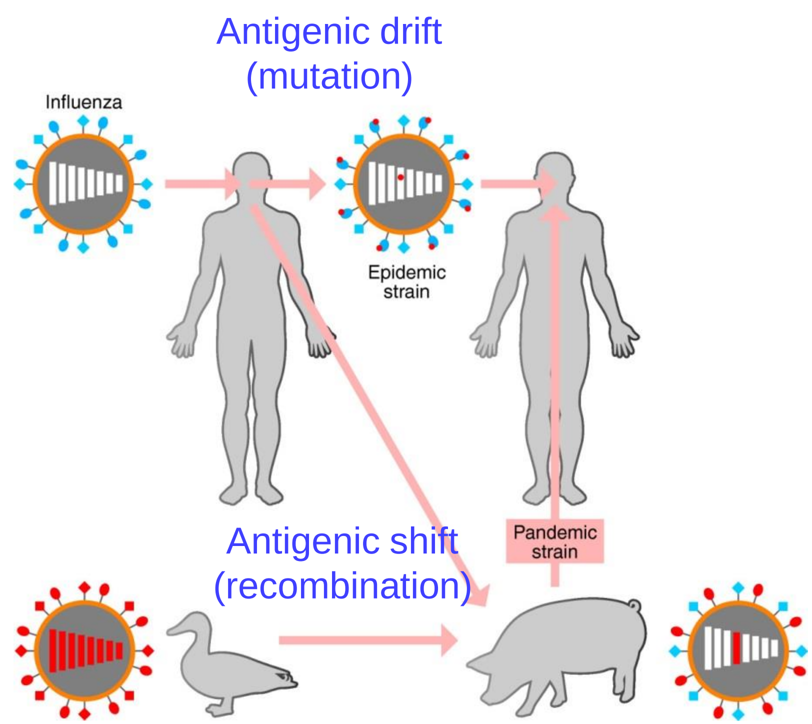


Cartoon of the influenza virus showing major components

http://www.petpigs.com/resources/2009-h1n1-influenza-pandemic/novel-influenza-a-h1n1

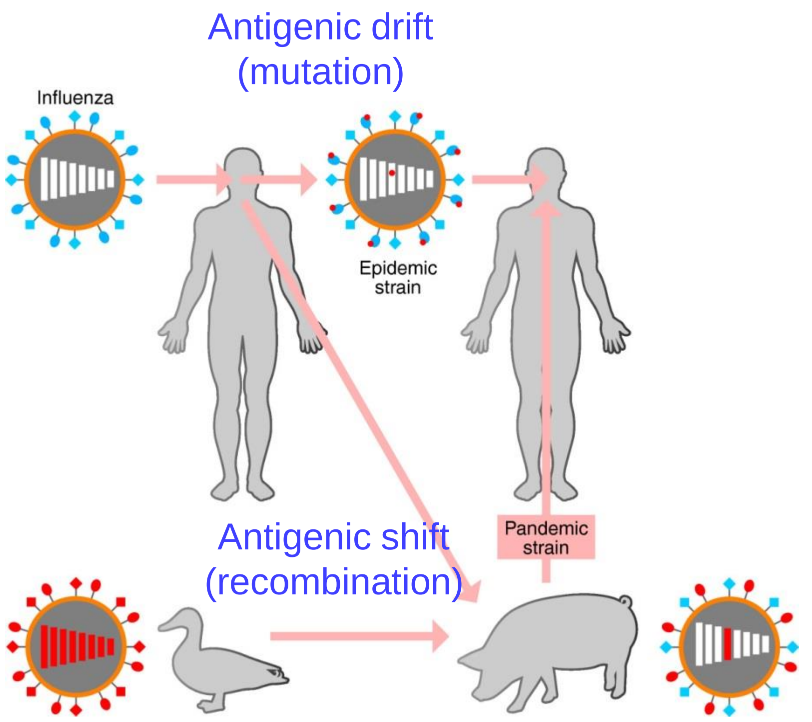


- **Antigenic shifts** (exchange between types) have caused pandemics
  - Spanish flu of 1918, A(H1N1)
    - Killed 20–50 million worldwide
  - Asian flu of 1957, A(H2N2)
    - Killed over 100,000 Americans
  - Hong Kong flu of 1968, A(H3N2)
    - Infected 50 million in U.S., killing 70,000



http://jbiol.com/content/8/5/46/figure/F1?highres=y

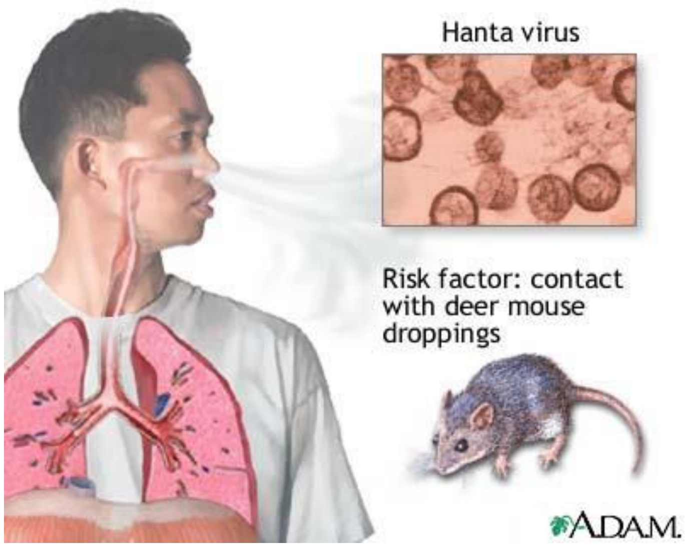
- New strains of flu often originate in the Far East
  - Virus hosts are ducks, chickens, and pigs
    - In Asia, livestock often live in close proximity to each other and humans
  - Simultaneous infection with different strains favors genetic recombination (**antigenic shift**)
    - Hong Kong flu arose from recombination between a duck and human version

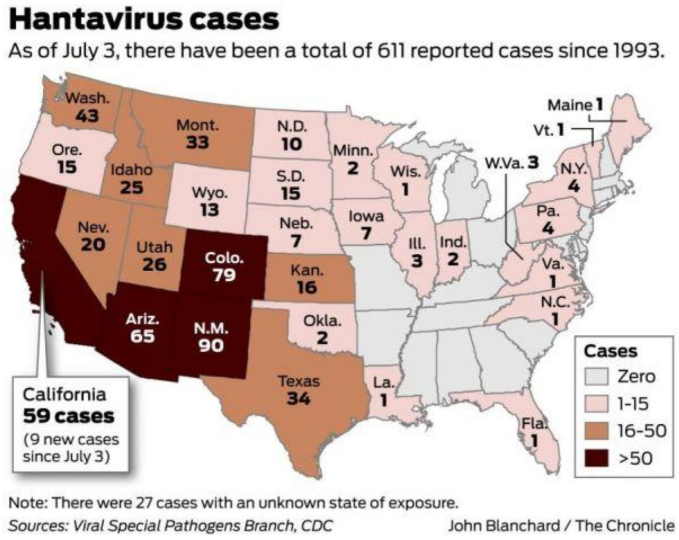


http://jbiol.com/content/8/5/46/figure/F1?highres=y https://ufhealth.org/hantavirus

Emerging Viruses

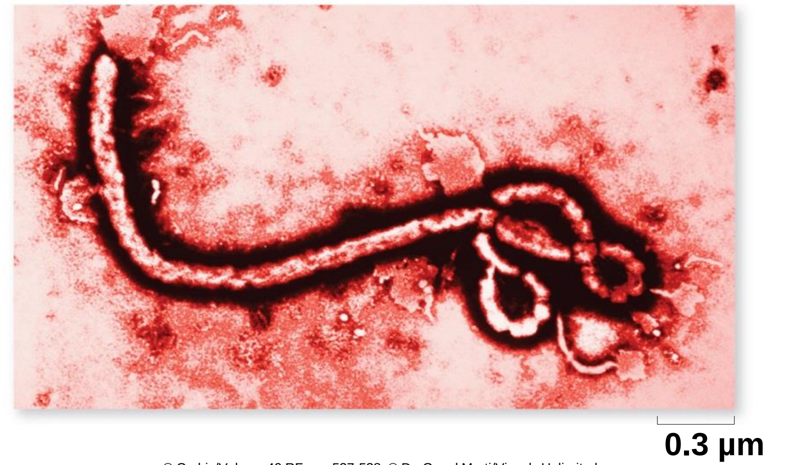
- Viruses that extend their host range
- Often deadly to new host
- Considerable threat in the aviation age
  - You can “jump” continents on an airplane before knowing you are ill
- **Hantavirus**
  - Causes deadly pneumonia
  - Natural host is deer mice
  - Controlling deer mice has limited disease



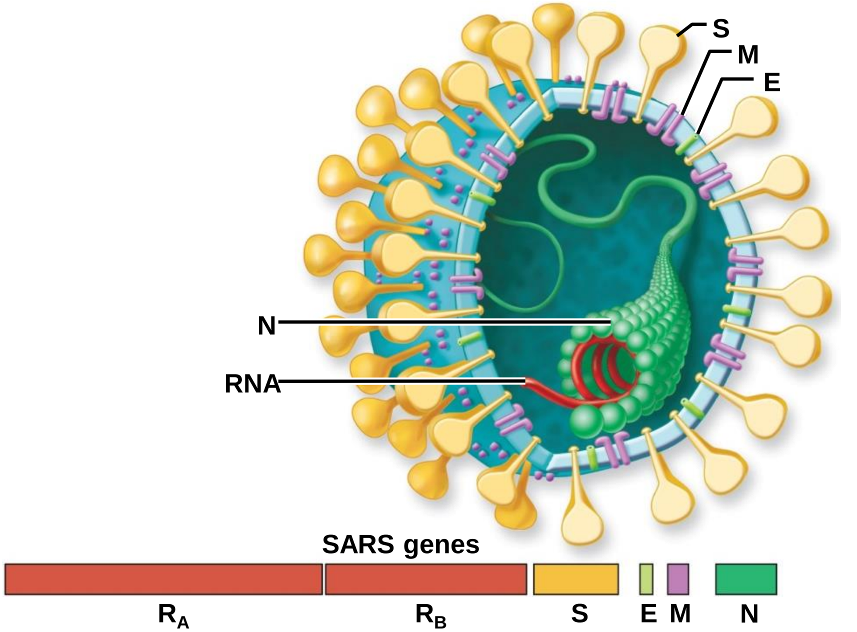


http://www.sfgate.com/health/article/Hantavirus-outbreak-puzzles-experts-3888327.php

- **Ebola virus**
  - Causes severe hemorrhagic fever
  - Among most lethal infectious diseases
  - Host is unknown

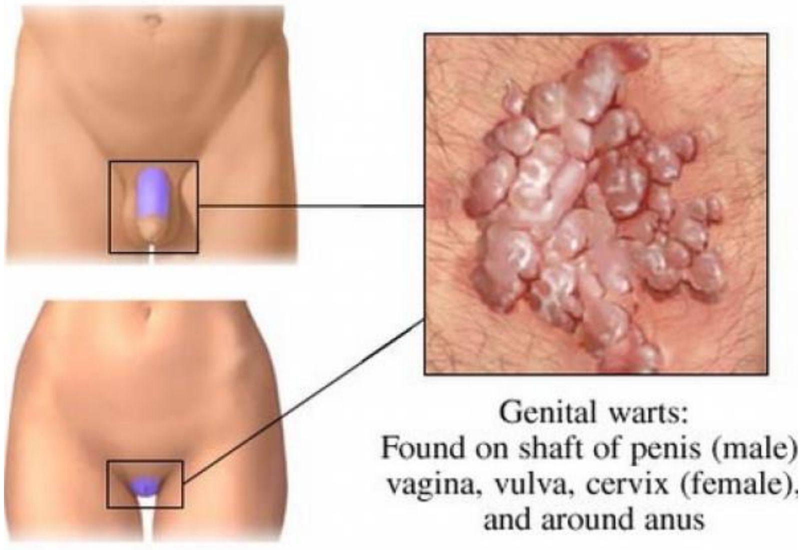


- **SARS**
  - Severe acute respiratory syndrome
  - Caused by a coronavirus
  - Host is civet (weasel-like)
  - Mutation rate low compared to HIV
  - SARS vaccines currently being developed



Viruses and Cancer

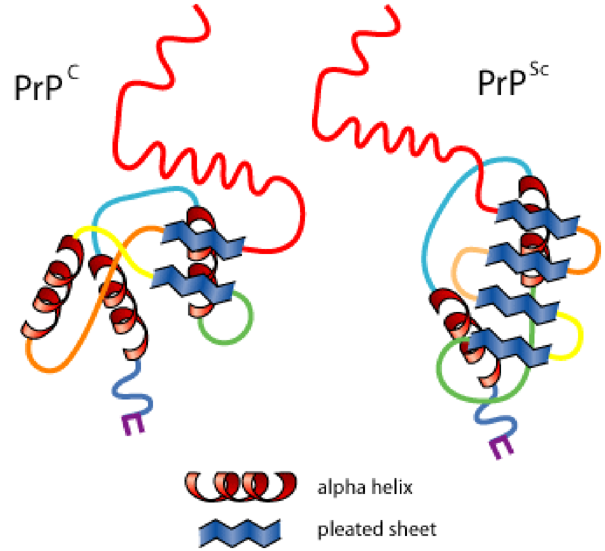
- Viruses may contribute to about 15% of all human cancers
- Viruses can cause cancer by altering the growth properties of human cells
  - Triggering expression of oncogenes
  - Disrupt cell cycle control genes
- In June 2006, FDA approved use of a new HPV vaccine to prevent cervical cancer
  - Administered to women and young girls over the age of 11 to prevent cervical cancer

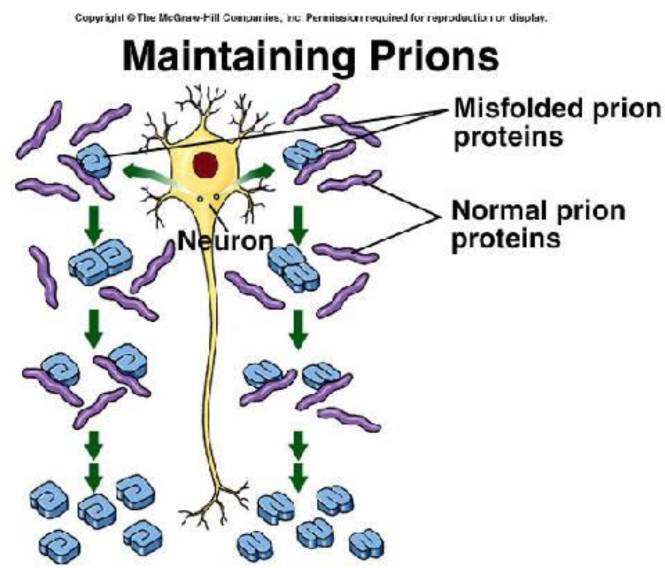


http://www.mediahex.com/Council_for_Mutual_Economic_Assistance http://wonderfulpants.wordpress.com/diseases/prion-disease/

Prions

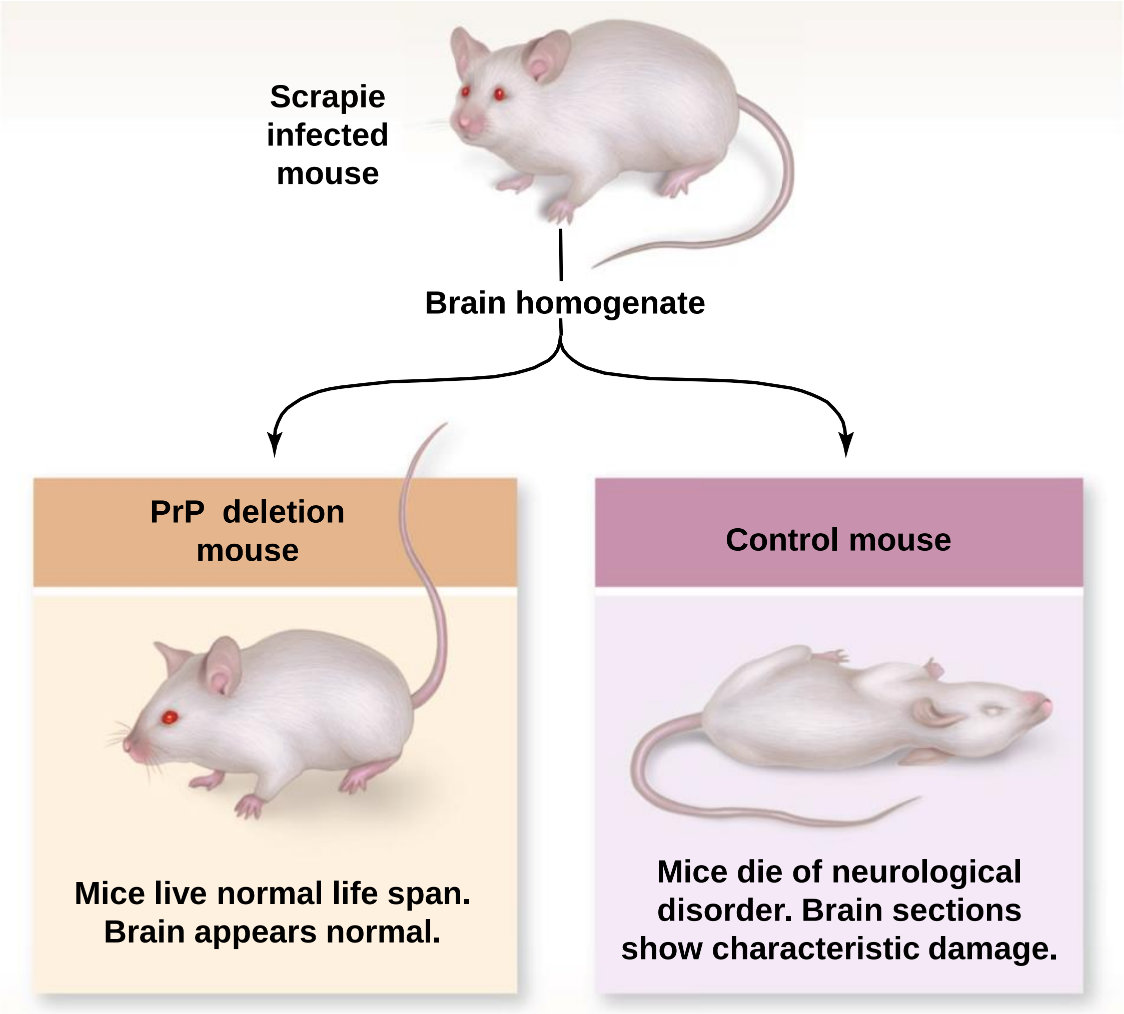
- “Proteinaceous infectious particles”
- Cause transmissible spongiform encephalopathies (TSEs) – as neurons die, spaces are left causing spongy appearance
  - “Mad cow” disease – BSE
  - Scrapie in sheep
  - Creutzfeldt–Jacob disease in humans (CJD)
- Host has normal prion proteins (PrP^c)
  - Misfolded proteins (PrP^{sc}) cause disease
  - Misfolded prions may cause normal proteins to misfold



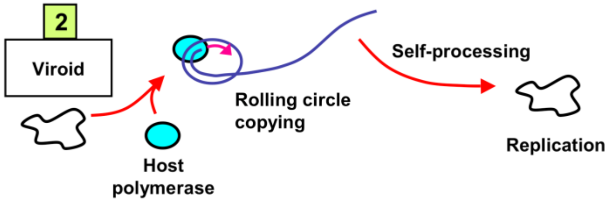


http://faculty.southwest.tn.edu/rburkett/viruses_and_prions.htm

Normal PrP protein is necessary for productive infection by scrapie infectious particle.

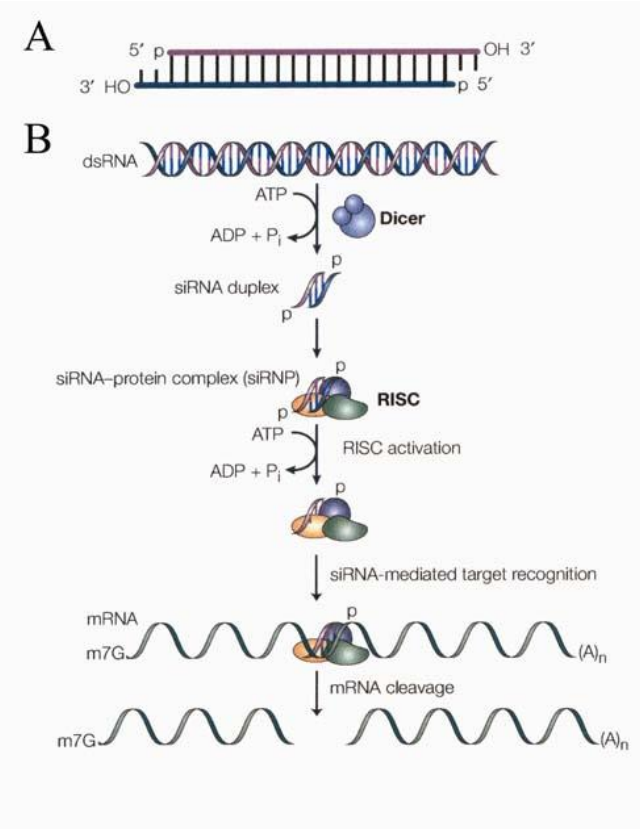


http://biopolyverse.com/2011/05/03/does-%E2%80%98dark%E2%80%99-biology-have-its-charms/



Viroids

- Tiny naked molecules of circular RNA that infect plants
- Cause diseases in plants
  - Recent outbreak killed over 10 million coconut palms in the Philippines
- Autonomously replicate
  - Info appears to be in 3-D structure and not RNA
  - Might use plant siRNA (small interfering RNA) machinery to affect gene expression (e.g. post-transcriptional gene silencing)



http://theses.ulaval.ca/archimede/fichiers/21404/ch03.html