Viruses
So What Is A Virus?

- Tiny packet of **nucleic acid** (DNA or RNA) contained in a protein **capsid**.
So What Is A Virus?

- Sometimes, special enzymes needed by the virus to replicate are contained within the capsid as well.

Adenovirus: DNA virus with a polyhedral capsid and a fiber at each corner.

T-even bacteriophage: DNA virus with a polyhedral head and a helical tail.
So What Is A Virus?

- Viruses come in many different shapes and sizes.
How Viruses Are Classified.

• 1\textsuperscript{st} – Structure of the nucleic acid.
  – DNA (single or double stranded) or RNA, + sense or – sense.
• 2\textsuperscript{nd} – Size and Shape.
  – Most are helical or icosahedral (i-cosa-hedral), - like a soccer ball.
How Viruses Are Classified.

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- **3rd** – Presence of outer envelope.
  - Envelope is part of host cell membrane.
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• 4\textsuperscript{th} – Mode of replication.
Are Viruses Living Organisms?

• What characteristics make something alive?
  – (1) organization, (2) acquisition of materials and energy, (3) maintain homeostasis, (4) respond to stimuli, (5) reproduce and develop, (6) adaptation

• Viruses can’t reproduce without a host cell.
• Viruses don’t maintain any kind of homeostasis.
• Viruses don’t have a metabolism.
• So, no they are not alive.
So If Viruses Can’t Reproduce, How Do They Replicate Themselves?

• Viruses are **obligate intracellular parasites**. They lack ribosomes and enzymes necessary for reproduction.
  – Hijack a cell’s protein and nucleic acid synthesizing machinery.

• Protein capsid (or spikes if envelope) is specific to protein receptors on host cell, and attach or enter host cell. Also, viral genome specific to certain hosts.
  – This makes viruses VERY host specific...even tissue specific (**tissue tropism**).
Viral variability

• It is estimated that there are trillions of different types of viruses.
• Because viruses evolve quickly, they are always changing.
• We have only described a few thousand different viruses (~2700 ‘species’).
So If Viruses Can’t Reproduce, How Do They Replicate Themselves?

• Once inside, the host cell reads the viral genome.

• Host cell machinery (ribosomes, enzymes, ATP, tRNA, amino acids) is used to produce new viruses.
Reproduction of Bacteriophages

• **Bacteriophages** are type of bacterial virus.

• They take 2 paths during infection:
  – Lytic Cycle
  – Lysogenic Cycle
Reproduction of Bacteriophages

- **Lytic Cycle**
  - **Attachment**
    - Virus attaches.
  - **Penetration**
    - Injects genetic material.
  - **Biosynthesis**
    - Hijacks the metabolic machinery.
  - **Maturation**
    - Builds new viruses.
  - **Release**
    - Ruptures host cell wall to release new viruses.

- Causes **very rapid death** of bacterial cell.

1. **Attachment** - Capsid combines with receptor.
2. **Penetration** - Viral DNA enters host.
3. **Biosynthesis** - Viral components are synthesized.
4. **Maturation** - Assembly of viral components.
5. **Release** - New viruses leave host cell.
Reproduction of Bacteriophages

- **Lysogenic Cycle**
  - Attachment
  - Penetration
  - **Integration**: Viral DNA combines with host DNA.
  - Can stay latent for years before entering Lytic cycle.
  - Environmental stressors can trigger entry into lytic cycle.

- **Lytic Cycle**
  - Attachment
  - Penetration
  - Biosynthesis
  - Maturation
  - Release
Phage Conversion

• Sometimes, incorporation of the bacteriophage genes during lysogenic cycle can cause phenotypic changes to bacteria.

• Cholera
  – Only bacteria infected by a specific bacteriophage, and in the lysogenic cycle, produce the toxin that causes cholera.
Herpesviruses

- Characteristics
  - Double-stranded, linear DNA genomes.
  - Enveloped icosahedral capsid.
  - Nuclear-replicating
    - DNA enters nucleus of host cell.
    - Transcribed to mRNA.
    - mRNA enters cytosol and uses host cell machinery to produce viral components.
  - Maintain **episomal latency** in neurons – DNA doesn’t integrate into host genome, but floats in nucleus (or as mRNA in cytosol) for lifetime.
Herpesviruses

• Not limited to “herpes.”
• Includes (among many others)
  – Varicella-zoster virus (chickenpox)
  – Herpes simplex virus
  – Epstein-Barr virus
Herpesviruses

• Virus can exit episomal latency sporadically.
• Herpes simplex virus
  – Cold sore is result of body fighting virus.
  – Immune system can fight it during lytic cycle, but it can’t get to it during episomal latency.
Viral Heirlooms

• Human Herpesvirus 6 (HHV-6)
  – Instead of floating in cytosol or nucleus as independent DNA, HHV-6 inserts itself into telomeres of DNA.
  – Can be passed down to children (90% of you have it).

• Symptom
  – Roseola (aka 3 day fever)- blotchy rash, raised or flat
Retroviruses

- A type of **RNA virus**.
  - Virus enters by **receptor-mediated endocytosis**.
- Animal cells are designed to read DNA to start process of protein synthesis.
- Retroviruses contain **reverse transcriptase (RT)**: an enzyme that turns viral RNA into viral cDNA.
Reproduction of Animal Viruses: Retroviruses

- Viral cDNA then integrates with host cell DNA within the nucleus, leading to **proviral latency**.
- When exiting latency, host cell reads the **provirus** (integrated cDNA).
  - Viral protein production
  - Virus assembly
  - Release
- Uses in gene therapy??
Positive-sense vs Negative-sense viruses

• Only applies to single-stranded RNA viruses

• **Positive-sense viruses**
  – Viral genome has same base sequence as mRNA used to produce viral proteins, allowing genome to be used directly.

• **Negative-sense viruses**
  – Viral genome is complementary to mRNA. Negative-sense RNA must first be used to produce positive-sense RNA before proteins can be made.
Human Immunodeficiency Virus

- **Retrovirus** with 2 copies of single-stranded, positive-sense RNA.
- Attacks helper T-cells.
- Non-symptomatic for 8-10 yrs, but are infectious (making control very difficult).
  - Latency period due to functioning immune response. Mutations in virus, along with periodic immune suppressions allow virus to outpace immune response leading to AIDS (acquired immune deficiency syndrome).
HIV Infection

- Protein receptor for HIV is **CD4**.
- CD4 is exclusive to helper T-cells
  - (it’s the receptor that binds MHC II on dendritic cells).

- However, a **co-receptor** called **CCR5** must also be bound for the virus to enter.
HIV Resistance

• A mutation on one receptor (CCR5) may be preventing HIV from entering host cells.
HIV Infection

- Once RNA enters cell, **reverse transcriptase (RT)** synthesizes double stranded DNA, which incorporates itself into genome.
HIV Infection

• Enters proviral latency period ...then begins transcription, translation, assembly, and budding.
HIV Infection

- Budding is important because it doesn’t kill the host cell...increases viral production per cell.
  - Naked viruses lyse the host cell, killing it.
HIV Evolution

• During viral replication, many mutations occur
  – RT is not as accurate as DNA polymerase.
  – This is a common problem with many retroviruses.

• Mutations may allow viral spikes to bind co-receptors other than CCR5, accelerating AIDS.
Hard To Cure Some Viral Infections

• Retroviruses show high mutation rates.
  – Most RNA viruses are replicated and assembled in the cytosol (cytosol is an uncontrolled environment.

• Replication rate is also very high.
  – One HIV patient can have many variations of the HIV virus, brought about through mutations.

• So if you design an anti-viral medication, chances are good that at least 1 strain will be resistant...
  (think about bottlenecks and adaptive radiation).
Treatments for HIV

• Blocking viral entry
  – Certain drugs can bind the CCR5 co-receptor, preventing viral entry.
Treatments for HIV

• Reverse transcriptase inhibitors
  – Because RT is not a cellular enzyme, these are specific to retroviruses.
  – FDA has cleared ~20 of these drugs.
Treatments for HIV

• Integrase inhibitors
  – Prevent viral DNA from entering nucleus or preventing integration into host genome.
Treatments for HIV

• Protease inhibitors
  – Drugs that bind to viral enzymes called protease, preventing them from cleaving viral polypeptides into functional viral proteins preventing viral assembly.
Combination Therapy

• A combination of these drugs is the standard treatment (typically combinations of reverse transcriptase inhibitors)
• Can eliminate HIV from blood stream, but not from lymph tissue.
• If drug regime is discontinued, virus levels return.
Influenza virus

- Single-stranded, negative-sense RNA (multiple segments), enveloped helical capsid.
Influenza virus

- **H-antigen** and **N-antigen** - proteins spikes in envelope responsible for viral entry (H) and viral release (N).
  - Combination of H & N important immune system recognition.
Influenza virus

• Factors that lead to novel Influenza viruses
  1. Particularly high mutation rate of H & N antigens.
  2. Infection by two subtypes of influenza can lead to genetic recombination of flu RNA, further changing the H:N fingerprint.
• Exacerbated by fact that pigs vulnerable to both human strains and bird strains, where recombination can lead to very novel, and very deadly strains.
Filoviruses

- Single stranded RNA, negative-sense, enveloped helical capsid.
- Cause severe **hemorrhagic fever** (multisystem, damages vascular system, hemorrhaging, impaired body regulation).
  - Ebola is one of only 2 types of filovirus.
  - Replication not completely understood.
Flaviviruses

• Single stranded, positive-sense, enveloped RNA virus, icosahedral shaped capsid.
• Replication thought isolated to cytoplasm.
• Diseases are almost all vector borne (mosquitoes mostly!)
• Zika is an example of a Flavivirus.
History of ZIKA

• Named after the Zika Forest in Uganda, where it was discovered in 1947.
  – Circulated around isolated parts of Africa & Asia.
  – Until recently, thought to be harmless.

• 2007 – Zika outbreak in Yap Islands where ~70% of population was infected.

• May 2015, Zika spotted in Brazil
Microcephaly

• Nov. 2015
  • Doctors noticed 27x increase in incidence of microcephaly.

• Microcephaly can be caused by several factors
  – Nutrition
  – Genetics
  – Alcohol or other teratogens

• However, the only major change in Brazil that lined up with microcephaly was Zika.
Linking Microcephaly to Zika

• Blood tests of pregnant women with babies affected with microcephaly revealed Zika RNA.

• Currently, scientists are studying all aspects of Zika.
  – Immunizations
  – Ecology and physiology of mosquito vectors

• A major concern is that Zika will mutate and
  – Find another vector, or become airborne.
  – Become more dangerous (like West Nile did).
Zika

• Virus transmitted by several mosquitos (*Aedes aegypti* mosquito biggest threat in Americas for now...daytime feeder)

• Big in C. America, Caribbean, parts of Africa and Asia
  – >1,000,000 people infected since 2015.

![A. aegypti and A. albopictus distributions](image)
Zika

• Virus can be found in
  – Blood, urine, semen, saliva, cerebrospinal fluid, breast milk, amniotic fluid.
Replication of Zika

- Entry via receptor-mediated endocytosis.
- Positive-sense RNA translated into a polypeptide, which is cleaved into viral proteins.
  - Viral replication and assembly occurs at the endoplasmic reticulum surface.
  - In addition to producing polypeptides, positive-sense RNA is used to produce negative-sense RNA, which is used to make more positive-sense RNA.
Why Is It Such A Concern?

- Rate of transfer is increasing rapidly
- Olympics coming to Brazil in 2016
- Sexually transferred
- Birth defects
  - Microcephaly – thought that virus attacks nervous system stem cells & glial cells, the loss of which keeps brain from forming correct architecture.
  - Infection earlier in gestation likely to cause more widespread damage.
Zika symptoms

• ~20% infected people show symptoms.
  – Low grade fever
  – Maculopapular rash
  – Arthralgia's (pain in joints...small joints mainly)
  – Conjunctivitis
  – Guillain-Barré Syndrome
Differential Diagnosis

- Dengue Fever
  - High Fever
  - Muscle pain (not althralgias)
  - No conjunctivitis

- Chikungunya virus
  - High Fever
  - Large joint pain (knees, hips, shoulders)
  - Also associated with microcephaly
How To Diagnose ZIKA

• Early phase (0-7 days)
  – Best time! Virus is still spreading in blood. Body hasn’t yet made antibodies.
  – Base diagnosis on viral detection
  – Use reverse transcriptase PCR

• Late phase (7+ days)
  – Serology (Looking for antibodies)
  – ZIKA IgM (IgM is first antibody to be expressed in acute infection... IgE antibodies take over later).
    • Lots of crossover between ZIKA and Dengue IgM. ZIKA IgM should be 4x higher than Dengue IgM. If not, it is a questionable diagnosis.
Treatment for ZIKA

• Support.

• Use Tylenol, not Aspirin
  – Aspirin can increase risk for bleeding... risk due to hemorrhagic fever.

• There is no cure, or vaccination.

• If you are pregnant, seek professional help
CDC Recommendations

• If pregnant or may become pregnant
  – Avoid areas with active transmission.
  – Avoid mosquito bites by
    • Wearing long sleeves and pants.
    • Applying DEET when outside
    • NO standing water