Chapter 13:
Viruses

Introduction to Viruses
- “Virus” originates from Latin word “poison”.
- Term was originally used by Pasteur to describe infectious agent for rabies.
- First virus discovered was tobacco mosaic disease virus (TMV) in 1890s.
- Distinguished from bacteria by being “filterable agents” in early 1900s.
- In 1930s: TMV was isolated and purified. Electron microscope was used to observe viruses.
- By 1950s science of virology was well established.

Characteristics of all viruses
- Acellular infectious agents
- Obligate intracellular parasites
- Possess either DNA or RNA, never both
- Replication is directed by viral nucleic acid within a cell
- Do not divide by binary fission or mitosis
- Lack genes and enzymes necessary for energy production
- Depend on host cell ribosomes, enzymes, and nutrients for protein production
- Smaller than most cells

Components of mature viruses (virions):
- **Capsid**: Protein coat made up of many protein subunits (capsomeres). Capsomere proteins may be identical or different.
- **Genetic Material**: Either RNA or DNA, not both

Nucleocapsid = Capsid + Genetic Material

Additionally some viruses have an:
- **Envelope**: Consists of proteins, glycoproteins, and host lipids. Derived from host membranes.
- **Naked**: Viruses lack envelope.
Viruses Have Either DNA or RNA Inside a Protein Capsid (Nucleocapsid)

Viruses are classified by the following characteristics:
- Type of genetic material
- Capsid shape
- Number of capsomeres
- Size of capsid
- Presence or absence of envelope
- Host infected
- Type of disease produced
- Target cell
- Immunological properties

Types of viral genetic material:
Genetic material may be single stranded or double stranded:
- Single stranded DNA (ssDNA):
  - Paroviruses
- Double stranded DNA (dsDNA):
  - Herpesviruses
  - Adenoviruses
  - Poxviruses
  - Hepadnaviruses* (Partially double stranded)
- Single stranded RNA (ssRNA): May be plus (+) or minus (−) sense:
  - Picornaviruses (+)
  - Retroviruses (+)
  - Rhabdoviruses (−)
- Double stranded RNA (dsRNA):
  - Reoviruses

Capsid morphology:
- Helical: Ribbon-like protein forms a spiral around the nucleic acid. May be rigid or flexible.
  - Tobacco mosaic virus
  - Ebola virus
- Polyhedral: Many-sided. Most common shape is icosahedron, with 20 triangular faces and 12 corners.
  - Poliovirus
  - Herpesvirus
- Complex viruses: Unusual shapes
  - Bacteriophages have tail fibers, sheath, and a plate attached to capsid.
  - Poxviruses have several coats around the nucleic acid.

Host Range: Spectrum of hosts a virus can infect.
- Bacteria (Bacteriophages)
- Animals
- Plants
- Fungi
- Protists

Viral Specificity: Types of cells that virus can infect.
- Dermotropic
- Neurotropic
- Pneumotropic
- Lymphotropic
- Viscerotrophic Liver, heart, spleen, etc.

Life Cycle of Animal Viruses
1. Attachment or adsorption: Virus binds to specific receptors (proteins or glycoproteins) on the cell surface.
2. Penetration: Virus enters cell through one of the following processes:
   - Direct fusion with cell membrane
   - Endocytosis through a clathrin coated pit
3. Uncoating: Separation of viral nucleic acid from protein capsid. Lysoosomal, cytoplasmic or viral enzymes may be involved.
Life Cycle of a DNA Virus

4. Synthetic Phase: Involves several processes:
   - Synthesis of viral proteins in cytoplasm
   - Replication of viral genome:
     - DNA viruses typically replicate in nucleus
     - RNA viruses replicate in cytoplasm
   - Assembly of progeny virus particles

The synthetic stage can be divided into two periods:
   - **Early period**: Synthesis of proteins required for replication of viral genetic material.
   - **Late period**: Nucleic acid replication and synthesis of capsid and envelope proteins

Life Cycle - Animal Viruses (Continued)

5. Release of progeny virions:

   A. Lysis of cells: Naked viruses and pox viruses leave cell by rupturing the cell membrane.
      Usually results in death of the host cell.
      Example: Poliovirus

   B. Budding: Enveloped viruses incorporate viral proteins in specific areas of a membrane and bud through the membrane. Envelope contains host lipids and carbohydrates. Host cell does not necessarily die.
      Example: Human Immunodeficiency Virus

Life Cycle of Bacteriophages

T-Even Bacteriophages: Lytic Cycle

1. Attachment or adsorption: Virus tail binds to specific receptors on the cell surface.

2. Penetration: Virus injects genetic material (DNA) into cell. Tail releases lysozyme, capsid remains outside.

3. Biosynthesis: Viral proteins and nucleic acids are made.
   Eclipse phase: No virions can be recovered from infected cells.

4. Maturation: Bacteriophage capsids and DNA are assembled into complete virions.

5. Release: Bacteriophage virions are released from the cell. Plasma membrane breaks open and cell lysed.
   Burst time: Time from attachment to release of new virions (20-40 minutes).
   Burst size: Number of new phage particles that emerge from a single cell (50-200).
**Lytic Cycle of Bacteriophage**

- **Attachment and Penetration**: Virus tail binds to specific receptors on the cell surface and injects genetic material (DNA) into cell.
- **Circularization**: Phage DNA circularizes and enters either lytic or lysogenic cycle.

**Lysogenic Cycle**

- **Integration**: Phage DNA integrates with bacterial chromosome and becomes a prophage. Prophage remains latent.
- **Excision**: Prophage DNA is removed due to a stimulus (e.g., chemicals, UV radiation) and initiates a lytic cycle.

**Important Human Viruses**

**DNA Virus Families**

1. **Adenoviruses**: Cause respiratory infections, such as the common cold. First isolated from adenoids.
2. **Poxviruses**: Produce skin lesions. Pox is a pus filled vesicle. Cause the following diseases:
   - Smallpox
   - Cowpox
   - Molluscum contagiosum
3. **Herpesviruses**: Herpetic means to cause spreading cold sores. Over 100 species. Eight infect humans:
   - Herpes simplex 1 (oral herpes)
   - Herpes simplex 2 (genital herpes)
   - Varicella-zoster virus (chickenpox and shingles)
   - Epstein-Barr virus
   - Kaposi’s sarcoma virus

**Smallpox: Poxviruses Cause Pus Filled Vesicles**

Disease was eradicated worldwide by immunization in 1977. Source: Microbiology Perspectives, 1999.
**Important Human Viruses (Continued)**

**DNA Virus Families**

4. **Papovaviruses**: Cause warts (papillomas), tumors (polyomas), and cytoplasmic vacuoles. Human papilloma virus is sexually transmitted and causes most cases of cervical cancer in women. Cervical cancers typically take over 20 to 30 years to develop, most women develop them in their 40s and 50s or older. Pap smears are used to detect them.

5. **Hepadnaviruses**: Cause hepatitis and liver cancer. Hepatitis B virus.

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**RNA Virus Families**

1. **Picornaviruses**: Naked viruses with a single strand of RNA. Include the following:
   - Poliovirus
   - Hepatitis A virus
   - Rhinoviruses: Over 100 viruses that cause the common cold.

2. **Togaviruses**: Enveloped ssRNA viruses. Cause rubella and horse encephalitis.


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**Important Human Viruses (Continued)**

**RNA Virus Families**

4. **Retroviruses**: Unique family of enveloped viruses. Have the ability to convert their RNA genetic material into DNA through an enzyme called reverse transcriptase. Viral DNA is integrated into host chromosome (provirus) where it can remain dormant for a long time. Include HIV-1 and HIV-2 which cause AIDS and Human T Lymphocyte viruses which cause cancer.

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**Biological Properties of Hepadnaviruses**

- Enveloped virus. Envelope contains middle, large, and major surface proteins.
- Many incomplete viral particles found in infected individuals.
- Small circular DNA molecules that are partially double stranded.
  - Long Strand: Constant length. 3200 nucleotides
  - Short strand: 1700 to 2800 nucleotides.
- Genome encodes for a handful of proteins:
  - Surface antigens
  - Envelope proteins
  - Polymerase
  - Protein X: Stimulates gene expression

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**Rabies is Caused by a Rhabdovirus**

*Hydrophobia in rabies patient.*

Source: *Diagnostic Pictures in Infectious Diseases, 1995*

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**Retroviruses Convert RNA into DNA via Reverse Transcriptase**

![Diagram of retroviruses converting RNA into DNA via reverse transcriptase.](image)
Viruses and Cancer

- **Oncogenic viruses**: Approximately 10% of all cancers are virus induced.
- **Oncogenes**: Viral genes that cause cancer in infected cells.
- **Provirus**: Viral genetic material integrates into host cell DNA and replicates with cell chromosome. Some viruses may incorporate host genes which can cause cancer under certain conditions.
  
  Example: Retroviruses

DNA Oncogenic Viruses:
- Adenoviridae (Rodents)
- Herpesviridae (Epstein-Barr Virus and Kaposi’s Sarcoma Herpes Virus)
- Papovaviridae (Papillomaviruses)
- Hepadnaviridae (Hepatitis B)

RNA Oncogenic Viruses:
- Retroviridae (Human T cell leukemia 1 & 2)

Detection of Viruses

- **Electron microscopy**
- **Immunologic Assays**: Detect specific viral proteins or antibodies to them.
  - Western blotting
  - ELISA
- **Biological Assays**: Detect cytopathic effects (CPE) caused by viral infection of cells.
  - Tissue culture for lytic viruses
  - Focus formation for transforming oncogenic viruses
- **Hemagglutination Assay**: Many viruses clump red blood cells.
- **Molecular Assays**: Assay for viral nucleic acids.
  - PCR (Polymerase chain reaction)
  - Southern (DNA) or Northern (RNA)

Antiviral Therapeutic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Virus</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Influenza</td>
<td>Inhibits uncoating</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Herpes simplex</td>
<td>Inhibits DNA polymerase</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster</td>
<td></td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>Cytomegalovirus</td>
<td>Inhibits DNA polymerase</td>
</tr>
<tr>
<td>Ribivarin</td>
<td>Respiratory syncitial</td>
<td>Inhibits viral enzymes for guanine biosynthesis</td>
</tr>
<tr>
<td></td>
<td>virus/ Lassa virus</td>
<td></td>
</tr>
<tr>
<td>Azidothymidine</td>
<td>HIV</td>
<td>Inhibits reverse transcriptase</td>
</tr>
<tr>
<td>Interferon</td>
<td>Cytomegalovirus</td>
<td>Inhibits protein synthesis</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>Degrades ssRNA</td>
</tr>
</tbody>
</table>

Viral Vaccines

First vaccine was used by Jenner (1798) against smallpox and contained live vaccinia (cowpox) virus.

I. Live attenuated vaccines: Mutant viral strains produce an asymptomatic infection in host.
   
   Examples: Polio (oral, Sabin vaccine), measles, yellow fever, mumps, rubella, and chickenpox.
   
   - Advantages: Better immune response
   - Disadvantages: May cause disease due to contamination, genetic instability, or residual virulence.
   
   Oral polio vaccine recently discontinued in U.S.

II. Killed or inactivated vaccines: Virus is typically grown in eggs or cell culture and inactivated with formalin.
   
   Examples: Polio (shots, Salk vaccine), rabies, and influenza A & B.
   
   Advantages: Immunization with little or no risk of infection.
   
   Disadvantages: Less effective immune response, inactivation may alter viral antigens.

III. Recombinant vaccines: Viral subunits are produced by genetically engineered cells.
   
   Example: Hepatitis B
   
   Advantages: Little or no risk of infection.
   
   Disadvantages: Less effective immune response.
**Hepatitis B is a Major Health Threat**

- Fifth leading cause of deaths due to infectious disease in the world.
  - 2 million deaths per year.
- Over 300 million infected individuals worldwide.
  - In Southeast Asia and Africa 10% population is infected.
  - In North America and Europe 1% population is infected.
- Highly contagious. Virus particles found in saliva, blood, and semen.
- Mechanisms of transmission:
  - Mother to infant: Primarily at birth.
  - Intimate or sexual contact.
  - Blood transfusions or blood products.
  - Direct contact with infected individuals: Health care workers.

**Characteristics of Hepatitis B Infection**

- Incubation period: 2 to 6 months.
- Several possible outcomes:
  - Asymptomatic infection: Most individuals.
  - Acute Hepatitis: Liver damage, abdominal pain, jaundice, etc. Strong immune response usually leads to a complete recovery.
  - Fulminant Hepatitis: Usually fatal. Rare.
  - Chronic Hepatitis: Poor immune response to virus, which remains active for years. May be healthy, experience fatigue, or have persistent hepatitis. Associated with development of liver cancer and cirrhosis.

**Herpesviruses**

- Family of over 100 viruses which infect a broad range of animals.
- Polyhedral capsid: Icosahedral capsid, 100-110 nm in diameter.
- Envelope: Contains viral glycoproteins on its surface. Virion is about 200 nm in diameter.
- Tegument: Unique to herpesviruses. Amorphous material surrounding capsid. Contains several viral proteins.
- Large genome: 140-225 kb of linear dsDNA which circularizes after infection.

**Infectious Diseases Causing Most Deaths Worldwide in 1998**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause</th>
<th>Deaths/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Respiratory*</td>
<td>Bacterial or viral</td>
<td>4,400,000</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>Bacterial or viral</td>
<td>3,200,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bacterial</td>
<td>3,100,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan</td>
<td>3,100,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Viral</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Measles</td>
<td>Viral</td>
<td>1,500,000</td>
</tr>
<tr>
<td>AIDS</td>
<td>Viral</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Neonatal Tetanus</td>
<td>Bacterial</td>
<td>600,000</td>
</tr>
</tbody>
</table>

*: Pneumonia, bronchitis, influenza, etc.

**Characteristics of Hepatitis B Infection**

- Several possible outcomes:
  - Cirrhosis of the Liver: Severe organ damage, leading to liver failure.
  - Hepatocellular Carcinoma: Usually takes 30 to 50 years to develop. May develop in children.

**Morphology of Herpesviruses**

A. Schematic Representation  
B. Electron micrograph

Source: Virology 3rd edition, 1996
Biological Properties of Herpesviruses

- Encode large array of enzymes involved in nucleic acid metabolism.
- Synthesis of viral DNA and assembly of capsid occurs in the nucleus.
- Production of infectious progeny causes destruction of infected cell.
- Latency: Can remain latent in their natural hosts. Viral DNA remains as closed circular molecule and only a few viral genes are expressed.

Human Herpesviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Common Name/Disease</th>
<th>Class</th>
<th>Size</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV-1</td>
<td>Herpes simplex 1 (HSV-1)</td>
<td>α</td>
<td>150 kb</td>
<td>Sensory ganglia</td>
</tr>
<tr>
<td>HHV-2</td>
<td>Herpes simplex 2 (HSV-2)</td>
<td>α</td>
<td>150 kb</td>
<td>Sensory ganglia</td>
</tr>
<tr>
<td>HHV-3</td>
<td>Varicella zoster virus</td>
<td>α</td>
<td>130 kb</td>
<td>Sensory ganglia</td>
</tr>
<tr>
<td>HHV-4</td>
<td>Epstein-Barr virus</td>
<td>γ</td>
<td>170 kb</td>
<td>B cells</td>
</tr>
<tr>
<td>HHV-5</td>
<td>Human Cytomegalovirus</td>
<td>β</td>
<td>230 kb</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>HHV-6/7</td>
<td>Human Herpesvirus 6/7</td>
<td>β</td>
<td>160 kb</td>
<td>CD4 T cells</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Human Herpesvirus 8</td>
<td>γ</td>
<td>140 kb</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

Clinical Manifestations of HSV-1

Epidemiology: 70-90% of adults are infected. Most are asymptomatic.

- Gingivostomatitis: Most common manifestation of primary HSV-1 infection. Initial infection typically occurs in early childhood.
- Recurrent herpetic labialis: Cold sores, fever blisters. After primary disease, virus remains latent in trigeminal ganglion. During reactivation, virus travels down nerve to peripheral location to cause recurrence.
- Whitlow: Infection of finger.
- **Keratoconjunctivitis**: Most common cause of corneal blindness in US.
- **Eczema herpeticum**: Severe herpetic outbreaks in areas with eczema.
- **Herpes gladiatorum**: Inoculation of abraded skin by contact with infected secretions.
- **HSV encephalitis**: Most common cause of acute sporadic encephalitis in US.
- **Chronic herpes simplex infection**: Lesions in atypical oral locations. Immunocompromised patients.

**Clinical Manifestations of HSV-2**

**Epidemiology**: Acquisition follows typical pattern of STD. Seroprevalence ranges from 10% to 80%. Most individuals are asymptomatic.
- **Genital Herpes**: Most common manifestation HSV-2 infection. Most common cause of genital ulcers in U.S. Lesions on cervix, perineum, or penis shaft. Recurrence rates vary widely.
- **Perirectal Herpes**: Can be severe in AIDS patients.
- **Orofacial herpes**: Less than 5% of cases.
- **Neonatal Herpes**: Due to contact with infected genital secretions during delivery. Severe disease with encephalitis, pneumonitis, hepatitis, and retinitis.

**Genital Herpes**

Herpes simplex 2 infection with fluid filled vesicles on penis.
Source: Mike Remington, University of Washington Viral Disease Clinic

**Clinical Manifestations of Varicella Zoster (HHV-3)**

- **Chickenpox (Varicella)**: Most common manifestation of primary herpes zoster infection.
  **Epidemiology**: 3 million cases/year in US, highest incidence in the spring. Highly communicable. Airborne or skin transmission.
  Incubation period 14 days.
  **Symptoms**: Malaise, sore throat, rhinitis, and generalized rash that progresses from macules to vesicles. Intraseoral lesions may precede rash.
  **Complications**: Reye’s syndrome, bacterial superinfection of lesions, varicella pneumonia and neonatal varicella (30% mortality).
  **Vaccine**: Prevents chickenpox in 70-90% of recipients.

Acyclovir resistant peri-rectal HSV2 infection in HIV infected male.
Source: AIDS, 1997
Clinical Manifestations of Varicella Zoster (HHV-3)
- **Shingles (Herpes Zoster):** Recurrence of latent herpes zoster infection.
  - **Epidemiology:** Occurs in 10-20% of individuals at some stage of life. Incidence increases with old age, impaired immunity, alcohol abuse, and presence of malignancy.
  - **Symptoms:** Vesicular eruption on skin or mucosa, that follows pathway of nerves. Typically unilateral, stopping at midline.
  - **Complications:** Post-herpetic neuralgia can last months to years.

EBV Associated Diseases (HHV-4)
- **Epidemiology:** 90% of adults are infected.
  - Initial infection typically occurs in early childhood or adolescence.
  - Most individuals are asymptomatic, but shed virus in saliva throughout life.
  - **Infectious mononucleosis:** A minority of infected individuals. Fever, pharyngitis, and lymphadenopathy. Splenomegaly is common.
  - **Endemic Burkitt’s Lymphoma (Africa)**
  - **Nasopharyngeal carcinoma (Asia)**
  - **Oral Hairy Leukoplakia:** In HIV + individuals.

Shingles in an AIDS Patient

Oral Hairy Leukoplakia with bilateral thickening of the tongue.

Burkitt’s Lymphoma with right facial swelling. Associated with EBV.
Source: Handbook of pediatric oral pathology, 1981.
Non-Hodgkin’s Lymphoma: In HIV + individuals
Hodgkin’s Lymphoma: 50% of cases.
Smooth muscle tumor (children)
Thymic lymphoepithelioma
Salivary gland carcinoma
Urogenital carcinoma

Clinical Manifestations of Cytomegalovirus (HHV-5)

Epidemiology: 50% of US population is seropositive.
Transmission: Perinatal, early childhood, sexual, transfusions, and organ transplants.
Symptoms: Most cases are asymptomatic.
  - Congenital CMV: May cause intellectual or hearing deficits.
  - Pneumonitis in bone marrow transplants.
  - Retinitis, esophagitis, and colitis are common in AIDS patients

HHV-8 Associated Diseases
First identified in 1995.
Kaposi’s Sarcoma: Accounts for 80% of all cancers in AIDS patients.
Lesions are flat or raised areas of red to purple to brown discoloration. May be confused with hemangioma or hematoma.
  - Strong male predominance.
  - 2/3 of affected patients present oral lesions
  - Oral lesions are initial presentation in 20% of patients.
  - Progressive malignancy that may disseminate widely.
  - Oral lesions are a major source of morbidity and frequently require local therapy.

Kaposi’s Sarcoma hemorrhagic mass on anterior maxillary gingiva.

Endemic Kaposi’s Sarcoma, nodular form.
**Introduction to Influenza Viruses**

- Enveloped ssRNA virus (negative strand).
  - Genome is divided into 8 segments, each containing 1 or 2 genes.
  - RNA is replicated in cell's nucleus.
- Helical nucleocapsid contains transcriptase.
- Envelope forms as virus buds from cell membrane.
- Two surface glycoproteins:
  - **Hemagglutinin**: Binds to sialic acid on host cell surfaces.
  - **Neuraminidase**: Enzyme that cleaves sialic acid.
- Fusion of envelope with cell surface membrane requires cleavage of hemagglutinin by host cell enzymes.
  - Serine proteases found in respiratory tract of mammals and digestive tract of birds.
  - Mutant hemagglutinin can be cleaved by other enzymes in body, causing infections throughout body.

**Structure of Influenza Virus**

- Nucleocapsid
- Envelope
- Hemagglutinin
- Neuraminidase

**Influenza Virus Strains**

**I. Influenza A:**
- Promiscuous: Infects humans, pigs, chickens, seals, horses, whales, and birds.
- Diverse group of substrains:
  - 15 different hemagglutinin molecules
  - 9 different neuraminidase molecules
- Also contains M2 protein: Ion channel, blocked by antiviral drugs amantidine and rimantidine
- Can mutate through antigenic shift in cells that are infected with two or more substrains.
- Responsible for all pandemics.

**II. Influenza B:**
- Only infects humans.
- Little diversity: Only one form of HA and NA.
- Lacks M2 protein and not inhibited by antiviral drugs amantidine and rimantidine.
- Can mutate through antigenic drift only.

**III. Influenza C:**
- Not important human pathogen

**Influenza Pandemics**

- All caused by influenza type A.
- The deadliest major pandemic occurred in 1918, during World War I (Spanish flu).
  - Over 30 million deaths worldwide in less than 10 months.
  - 600,000 deaths in the U.S.
  - Caused by H1N1 subtype of influenza A
- Asian flu in 1957:
  - Caused by H2N2 subtype of influenza A
- 1968 Hong Kong flu:
  - Caused by H3N2 subtype of influenza A
- In 1997 a new strain appeared in Hong Kong (H5N1) that appeared to have jumped directly from birds to humans.

**Influenza Epidemics**

- Smaller than pandemics, occur regularly.
- In 1994 flu epidemic:
  - Infected 90 million Americans (35% of population)
  - Over 69 million lost days of work.
- Typical epidemics in the U.S.
  - Infects 10-20% of population.
  - Causes 20,000 deaths per year from complications.