Title: Vaccines and Antiviral Drugs
Instructor: Consetta Helmick
Lecture 2  Vaccines and Antiviral Drugs

• History
• Polio
• Childhood Immunization
• Vaccinations
• How to give a vaccination
• Types of Vaccines
• Antiviral Drugs
A Glimpse of History

- **Variolation** described in old Chinese writings
  - Sung dynasty (960–1280 A.D.)
  - Powdered scabs from smallpox lesions inhaled or placed in skin; produced mild disease, gave immunity
    - Occasionally fatal; person also contagious
    - Practiced in China, Mideast a thousand years ago, long before people understood that microbes cause disease
    - Lady Mary Wortley Montagu, wife of British ambassador to Turkey, had her children immunized
      - Became popular in Europe
      - Because of dangers and cost, many people remained unprotected
A Glimpse of History

- **Variolation** (continued...)
  - Edward Jenner noticed milkmaids who recovered from cowpox rarely got smallpox
    - In 1796, exposed boy (James Phipps) to material from cowpox lesion; 6 weeks later exposed to smallpox
      - Phipps did not catch, was immune
      - Jenner and others worked to spread variolation using less dangerous cowpox material
    - Pasteur later used word *vaccination* to describe protective inoculation
  - In 1967, WHO started intensive smallpox vaccination program; with no animal hosts or non-immune humans, last case occurred in Somalia, Africa, in 1977
Campaign to Eliminate Poliomyelitis

- Three types of poliovirus; entry is via the mouth
  - Virus infects throat and intestinal tract, invades blood
  - From bloodstream, can invade nerve cells, cause disease
  - Salk vaccine (mid-1950s) contains inactivated viruses of all three types
    - Dramatically lowered rate of disease but required series of injections for maximum protection
- Sabin attenuated vaccine available in 1961
  - Cheaper oral vaccination, although still three doses
  - Induced better mucosal immunity (secretory IgA response), so better herd immunity
  - Attenuated viruses can mutate; ~1 out of 2.4 million doses results in poliomyelitis
Childhood Immunizations

- The Importance of Childhood Immunizations
  - Prior to vaccinations, numerous deaths, disabilities
    - Many still become ill or die from preventable diseases
    - Some parents refuse to vaccinate children, fear harm
    - Vaccines victims of their own success, have lulled people into false sense of security: risk of vaccine seems greater than risk of diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases per Year Before Immunization</th>
<th>Decrease After Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164 (1900–1904)</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885 (1920–1922)</td>
<td>Nearly 100%</td>
</tr>
<tr>
<td>Pertussis (whooping cough)</td>
<td>147,271 (1922–1925)</td>
<td>93.4%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314 (1922–1926)</td>
<td>98.1%</td>
</tr>
<tr>
<td>Paralytic poliomyelitis</td>
<td>16,316 (1951–1954)</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282 (1958–1962)</td>
<td>Nearly 100%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209 (1968)</td>
<td>99.8%</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>50,230 (1966–1969)</td>
<td>98%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b invasive disease in children</td>
<td>20,000 (estimated)</td>
<td>99.8%</td>
</tr>
</tbody>
</table>
Childhood Immunizations

• The Importance of Childhood Immunizations
  – Benefits greatly outweigh very slight risk
    • Child with measles has 1:2,000 chance of serious brain inflammation vs. 1:1,000,000 chance from vaccine
    • Between 1989–1991, immunization rates dropped 10%; outbreak of 55,000 cases resulted in 120 deaths
    • Routine pertussis immunization yielded significant decrease in incidence, saved many lives
      – But because of some adverse reactions to killed whole cell vaccine, many parents refused to vaccinate
      – By 1990, highest incidence of pertussis in 20 years, deaths of some children
      – Safer acellular subunit vaccine is now used
    • No evidence of link between vaccines and autism
Childhood Immunizations

• Current Progress in Immunization
  – Recent advances yielding safer, more effective vaccines
    • E.g., conjugate vaccines that enlist T-cell help
    • New adjuvants being developed
    • Administering of cytokines with vaccine
  – Novel types being actively studied
    • Peptide vaccines (key antigen)
    • Edible vaccines (transfer genes for key antigens into plants; could eliminate global difficulties of transport, storage)
    • DNA-based vaccines (inject into muscle tissue, which expresses for a short time)
Immunization

- **Immunization** is process of inducing immunity
  - Has probably had greatest impact on human health of any medical procedures
  - Example of how knowledge is power with respect to fighting disease
  - Useful applications of immunological reactions in diagnostic tests
Principles of Immunization

• Immunity acquired naturally or artificially
  – Via normal events (e.g., exposure to infectious agent) or by inducing via immunization
  – Also passive or active

### Active Immunity

- **Natural Active Immunity**: Immunity that results from an immune response in an individual after exposure to an infectious agent.
- **Artificial Active Immunity**: Immunity that results from an immune response in an individual after vaccination.

### Passive Immunity

- **Natural Passive Immunity**: Immunity that results when antibodies from a woman are transferred to her developing fetus during pregnancy or to an infant during breast feeding.
- **Artificial Passive Immunity**: Immunity that results when antibodies contained in the serum of other people or animals are injected into an individual.
Principles of Immunization

• Active Immunity: follows antigen exposure
  • Natural (infection) or artificial (immunization)

• Passive Immunity: antibodies from another
  – Natural: during pregnancy, mother’s IgG antibodies cross placenta; breast milk contains secretory IgA
    • No memory; protection is lost once antibodies degrade
  – Artificial: injection of antiserum (contains antibodies)
    • Can prevent disease before or after likely exposure
    • Limit duration of certain diseases
    • Block action of microbial toxins
      – Antitoxin is antiserum that protects against a toxin
  • Hyperimmune globulin (antibodies to specific disease)
  • Immune globulin (IgG fraction from many donors; variety)
Vaccines and Immunization

• **Vaccine** is preparation of pathogen or its products
  – Used to induce active immunity
  – Protect individual; prevent spread in population

  • **Herd immunity** develops when critical portion of population is immune to disease; infectious agent unable to spread due to insufficient susceptible hosts

  • Responsible for dramatic declines in childhood diseases
    – Diseases sometimes reappear and spread as result of failure to vaccinate children

  • **Effective vaccines** should be safe, have few side effects
    – Give long lasting protection
    – Ideally low in cost, stable, easy to administer
How Vaccines are Given

• Some vaccines routinely given
• Others only under certain circumstances

• Two general categories:
  – Attenuated
  – Inactivated
Types of Vaccines

- **Comparison of Attenuated and Inactivated Vaccines**
  - **Attenuated**: elicits stronger immune response, but can sometimes cause disease
  - **Inactivated**: elicits weaker immune response, but cannot cause infections

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Attenuated Vaccines</th>
<th>Inactivated Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody response (memory)</td>
<td>IgG; secretory IgA if administered orally or nasally</td>
<td>IgG</td>
</tr>
<tr>
<td>Cell-mediated immune response</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>Long-term</td>
<td>Short-term</td>
</tr>
<tr>
<td>Need for adjuvant</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of doses</td>
<td>Usually single</td>
<td>Multiple</td>
</tr>
<tr>
<td>Risk of mutation to virulence</td>
<td>Very low</td>
<td>Absent</td>
</tr>
<tr>
<td>Risk to immunocompromised recipient</td>
<td>Can be significant</td>
<td>Absent</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Injection, oral, or nasal</td>
<td>Injection</td>
</tr>
<tr>
<td>Stability in warm temperatures</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Types</td>
<td>Attenuated viruses, attenuated bacteria</td>
<td>Inactivated whole agents, toxoids, subunit vaccines, VLPs, polysaccharide vaccines</td>
</tr>
</tbody>
</table>
Types of Vaccines

• Attenuated Vaccines: weakened form of pathogen
  – Replicates in recipient; disease undetectable or mild
    • Grown under conditions resulting in mutations, or genetically manipulated to replace genes
  – Advantages: single dose usually induces long-lasting immunity due to microbe multiplying in body
    • Can also inadvertently immunize others by spreading
  – Disadvantages: can sometimes cause disease in immunosuppressed individuals
    • Can occasionally revert or mutate, become pathogenic
    • Generally not recommended for pregnant women
    • Usually require refrigeration to keep active
  – Measles, mumps, rubella, chickenpox, yellow fever, Sabin vaccine against polio are examples
Types of Vaccines

• Inactivated Vaccines: unable to replicate
  – **Advantage**: cannot cause infections or revert to pathogenic forms
  – **Disadvantage**: no replication, so no amplification *in vivo*; immune response is limited
    • Several booster doses usually needed
    • Often contain *adjuvant* to enhance immune response
  – Multiple different types:
    • **Inactivated whole agent vaccines**: contain killed microorganisms or inactivated viruses
      – Treated with formalin or other chemical that does not significantly change surface epitopes
      – Includes influenza, rabies, Salk polio vaccine
Types of Vaccines

• Inactivated Vaccines (continued...)
  – Multiple different types:
    • **Toxoids**: toxins treated to destroy toxic part, retain antigenic epitopes
      – Includes diphtheria, tetanus
    • **Subunit vaccines**: consist of key protein antigens or antigenic fragments from pathogen
      – Avoids cell parts that may cause side effects
      – E.g., acellular pertussis (aP) vaccine
    • **Recombinant vaccines**: subunit vaccines produced by genetically engineered microorganisms
      – E.g., hepatitis B virus; yeast cells produce part of viral protein coat
Types of Vaccines

• Inactivated Vaccines (continued…)
  – Multiple different types:
    • VLP (virus-like particle) vaccines: empty capsids produced by genetically engineered organisms
      – E.g., human papillomavirus (HPV)
    • Polysaccharide vaccines: made from capsules
      – Not effective in young children; polysaccharides are T-independent antigens, which elicit poor response
      – E.g., pneumocococcus vaccines for adults
    • Conjugate vaccines: polysaccharides linked to proteins
      – Converts polysaccharides into T-dependent antigens
      – E.g., *Haemophilus influenzae* type b (Hib) has nearly eliminated Hib meningitis in children; *Streptococcus pneumoniae* vaccine promises to do the same
Antiviral Drugs

- Viruses difficult to target selectively
  - Rely on host cell’s metabolic machinery; lack cell walls, ribosomes, other structures targeted by antibiotics
  - Many encode polymerases; represent potential targets
  - Scientists trying to develop antiviral drugs that interfere with viral replication
  - Current options effective only against specific type of virus; none eliminate latent infections
# Antiviral Drugs  Mode of Action

## TABLE 20.2 Characteristics of Antiviral Drugs

<table>
<thead>
<tr>
<th>Target/Drug Examples</th>
<th>Comments/Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral Entry</strong></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide, Maraviroc</td>
<td>Used to treat HIV infections.</td>
</tr>
<tr>
<td><strong>Viral Uncoating</strong></td>
<td></td>
</tr>
<tr>
<td>Amantadine and rimantadine</td>
<td>Reduce severity and duration of influenza A infections, but resistance limits their use.</td>
</tr>
<tr>
<td><strong>Nucleic Acid Synthesis</strong></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogs</td>
<td>Primarily used to treat infections caused by herpesviruses and HIV; they do not cure latent infections. The drugs are converted within eukaryotic cells to a nucleotide analog; virally encoded enzymes are prone to incorporate these, resulting in premature termination of synthesis or improper base-pairing of the viral nucleic acid. Acyclovir is used to treat herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. Ganciclovir is used to treat cytomegalovirus infections in immunocompromised patients. Ribavirin is used to treat respiratory syncytial virus (RSV) infections in newborns. Combinations of nucleoside analogs such as zidovudine (AZT), didanosine (ddI), and lamivudine (3TC) are used to treat HIV infections.</td>
</tr>
<tr>
<td>Acyclovir, ganciclovir, ribavirin, zidovudine (AZT), didanosine (ddI), lamivudine (3TC)</td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside polymerase inhibitors</td>
<td>Primarily used to treat infections caused by herpesviruses. They inhibit the activity of viral polymerases by binding to a site other than the nucleotide-binding site. Foscarnet is used to treat ganciclovir-resistant cytomegalovirus (CMV) and acyclovir-resistant herpes simplex virus (HSV).</td>
</tr>
<tr>
<td>Foscarnet</td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td>Used to treat HIV infections. They inhibit the activity of reverse transcriptase by binding to a site other than the nucleotide-binding site and are often used in combination with nucleoside analogs.</td>
</tr>
<tr>
<td>Nevirapine, delavirdine, efavirenz</td>
<td></td>
</tr>
<tr>
<td><strong>Genome Integration</strong></td>
<td>Used to treat HIV infections.</td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
</tr>
<tr>
<td><strong>Assembly and Release of Viral Particles</strong></td>
<td>Used to treat HIV infections. They inhibit protease, an essential enzyme of HIV, by binding to its active site.</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Indinavir, ritonavir, saquinavir, nelfinavir</td>
<td></td>
</tr>
<tr>
<td>Neuraminidase inhibitors</td>
<td>Used to treat influenza virus infections.</td>
</tr>
<tr>
<td>Zanamivir, oseltamivir</td>
<td></td>
</tr>
</tbody>
</table>
Antiviral Drugs  Mode of Action

• Entry Inhibitors
  – New group of drugs prevent viral entry into host cell
    • Enfuvirtide binds to an HIV protein that promotes fusion of viral envelope with cell membrane
    • Maraviroc blocks HIV co-receptor CCR5

• Viral Uncoating
  – Nucleic acid must separate from protein coat
  – Two drugs target this step—amantadine, rimantadine
    • Block influenza A viruses, prevent or reduce severity
    • Viral strains easily develop resistance; usefulness limited
Antiviral Drugs  Mode of Action

- **Nucleic Acid Synthesis**
  - Nucleoside Analogs: structure similar to nucleosides
    - Phosphorylated *in vivo* by virally encoded or normal cellular enzyme to form nucleotide analog
    - Incorporation into nucleotide chain can stop nucleotides from being added or alter base-pairing properties
    - Selective toxicity since virally encoded enzymes more likely than host cell polymerases to incorporate
      - More damage done to rapidly replicating viral genome
      - But only effective against replicating viruses
  - Most reserved for severe infections; significant side effects
    - Acyclovir is exception; treats herpesvirus with little harm to uninfected cells since only converted by virally encoded enzymes present only in infected cells
Antiviral Drugs  Mode of Action

• Nucleic Acid Synthesis
  – Nucleoside Analogs (continued...)
    • Ganciclovir used to treat life- or sight-threatening cytomegalovirus (CMV) infections in immunocompromised
    • Ribavirin used to treat respiratory syncytial virus infections (RSV) in newborns
    • Nucleoside reverse transcriptase inhibitors (NRTIs) used to treat HIV; virus rapidly develops mutational resistance
      – Often used in combination with other anti-HIV drugs
      – NRTIs include zidovudine (AZT), didanosine (ddI), and lamivudine (3TC); two often used in combination
Antiviral Drugs Mode of Action

• Nucleic Acid Synthesis
  – Non-Nucleoside Polymerase Inhibitors
    • Inhibit viral polymerases by binding to site other than nucleotide-binding site
    • Foscarnet used to treat ganciclovir-resistant CMV and acyclovir-resistant HSV
  – Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) inhibit reverse transcriptase by binding to site other than nucleotide-binding site
    • Often used with nucleoside analogs to treat HIV infections
    • Include nevirapine, delavirdine, efavirenz
Antiviral Drugs  Mode of Action

• Integrase Inhibitors
  – Offer new option for treating HIV infections
    • Inhibit HIV-encoded enzyme integrase; prevent virus from inserting DNA copy of genome into host cell
    • Raltegravir is first approved drug of this class

• Assembly and Release of Viral Particles
  – Virally encoded enzymes required for assembly, release
  – Protease Inhibitors
    • During replication of HIV, several proteins translated as a polyprotein that must be cleaved
    • Includes indinavir, ritonavir, saquinavir, nelfinavir
  – Neuraminidase Inhibitors
    • Enzyme encoded by influenza viruses, needed for release