Vaccines and Immunization

• A **vaccine** is a suspension of pathogens or portions of pathogens that is used to induce artificially acquired active immunity.

• Jenner was the first physician to use cowpox to immunize people against smallpox.

• Today, smallpox has been eradicated by vaccination!

• The major idea is to stimulate the normal immune response without causing the disease! This depends on the formation of memory cells.
Types of Vaccinations

• Inactivated whole-agent vaccines consist of killed bacteria or inactivated viruses.

• Attenuated whole-agent vaccines - contain weakened pathogens. Pathogens are often exposed to formalin, which in general does not destroy antigenicity but does limit pathogenicity.

• Toxoids are inactive toxins, and can be the basis for a vaccine when the disease is caused by a toxin.
Why vaccinate?

- The obvious answer might be to protect oneself from disease, which is certainly true.
- Another extremely important aspect of vaccination programs has to do with protecting the public’s health!
- The more people that get vaccinated, the population begins to build up a so-called herd immunity - there will be less carriers, less of a reservoir for the pathogen. Therefore, even individuals who have not been immunized will have a lesser chance of contracting disease.
- It is possible to completely eradicate a pathogen from a population through vaccination programs. Smallpox has been eradicated from the entire world, and other viruses are currently targeted.
Common vaccines and Current Immunization schedule

- **HepB** - given at birth to prevent hepatitis B disease
- **DTP** - diphtheria, tetanus, pertussis - uses diphtheria and tetanus toxoids, and attenuated *Bordetella pertussis*. (common bacterial diseases) - given at 2 months
- **Hib** - (*Haemophilus influenzae*) given at 2 months to prevent this common cause of meningitis
- **IPV** - (Inactivated poliovirus) - given at 2 months
- **MMR** - Measles, mumps, rubella [german measles] - attenuated virus (common viral diseases) - given at 1 year
- **Chickenpox** (Varicella) - attenuated virus, given at 1 yr.
- **PCV** (*Pneumococcal* conjugate) - given at 2 months to prevent this common cause of meningitis and pneumonia
Principles of chemotherapy

• Antimicrobial drugs are substances (unlike disinfectants and antiseptics) meant to be taken internally to kill or retard the growth of pathogens in individuals with infections.

• As with vaccines, the most effective drugs have high toxicity to the pathogen, but low toxicity and low occurrence of adverse side effects in the human host.

• Microbial drug resistance is a major challenge to modern medicine.
### Terminology

- **Antibiotics** are ALL naturally occurring chemicals produced by ascomycete fungi or bacteria.

- **Synthetic** drugs are produced in the laboratory.

- **Semisynthetics** are laboratory-modified versions of antibiotics. (Their synthesis begins with the natural antibiotic.)
Principles of chemotherapy - functional classes of drugs

• Antimicrobial drugs are placed into the following categories depending on their mode of action. The drugs usually act in one of the following ways:
  – Inhibition of cell wall synthesis/destruction of cell walls
  – Inhibition of nucleic acid function or nucleic acid synthesis
  – Protein synthesis inhibition
  – Interference with the function of the plasma membrane
Drugs that affect the bacterial cell wall
“Penicillin”

• "Penicillin" actually refers to a group of over 50 chemically related antibiotics, all of which share a functional group called a beta-lactam ring in a core region called the nucleus of the molecule.

• Many different species of the mold *Penicillium* produce slightly different versions of penicillin, differentiated by the side chain attached to the nucleus.

• They have a narrow spectrum (generally are effective against gram-positive cocci and spirochetes) and work by inhibiting peptidoglycan cross-linking.
Penicillin G

Penicillin V

Natural (antibiotic) penicillins
• They are also susceptible to penicillinases, enzymes that many bacteria have evolved that make them resistant to penicillin (especially *Staphylococcus*).

• Many semi-synthetic penicillins are made in the laboratory by simply adding different side chains to the nucleus made by the fungus. They are in general resistant to penicillinases (until new versions evolve) and can be made to have a broader spectrum. Examples include ampicillin, amoxycillin, methicillin, carbenicillin, and oxacillin.
Semisynthetic penicillins
Other antibiotics that interfere with cell wall synthesis

- **Cephalosporins** are produced by a fungal genus related to *Penicillium* (*Cephalosporium*), and are similar in structure, but sufficiently different to be effective against penicillin-resistant organisms.

- **Monobactams** - related chemically to penicillin, but contain only one ring. An example is Aztreonam. Strangely, it affects only gram-negative cells.

- **Bacitracin** is a polypeptide produced by *Bacillus subtilis*, and damages cell walls by interfering with NAG/NAM polymerization. It is mainly effective against gram-positive bacteria and is limited to topical use.

- **Vancomycin** - produced by an exotic species of *Streptomyces*, it is usually used to treat infections by staphylococci resistant to penicillin and other drugs.
Antibiotics that interfere with Protein synthesis

• Aminoglycosides - amino sugars linked by glycosidic bonds, these are made by various *Streptomyces* species, and include Streptomycin and Neomycin, which is often used topically. They are broad spectrum, as are pretty much all of the antibiotics that inhibit protein synthesis.

• Tetracyclines - complex ring structures produced by various species of *Streptomyces*. Often adversely affect the normal microbiota, and can cause upset stomach and yeast infection. Tetracycline itself is the most famous of this group.
Protein synthesis inhibitors

- Chloramphenicol - organic compound containing an alcohol group, it is inexpensive but often has severe side effects, so is rarely used. It is used in research to inhibit protein synthesis in bacteria.

- Macrolides - contain a complex structure called a macrocyclic lactone ring, and are produced by (you guessed it) various *Streptomyces* species. The most famous is erythromycin, which is similar in its spectrum of activity to penicillin, and is often used as an alternative.
Antibiotics that damage the plasma membrane

• Polymyxin B is produced by *Bacillus polymyxa*; it is effective mostly against gram-negative bacteria and is often used topically.

• (A very popular over the counter antibiotic cream contains bacitracin, neomycin, and polymyxin B).
Antibiotics that inhibit nucleic acid synthesis

- Rifamycins - also produced by *Streptomyces* species, the most commonly used is the semi-synthetic **rifampin**. Rifampin inhibits mRNA synthesis (transcription), and is often used against *Mycobacterium* species that cause tuberculosis and leprosy. It is also often used in research laboratories to inhibit transcription.
Bacterial drug resistance

• Bacteria generally become resistant by one of three methods:

  – Destruction or inactivation of the antibiotic (e.g., penicillinases)

  – Prevention of penetration of the drug into the microbe (MAR mutation - multiple antibiotic resistance in gram-negative cells)

  – alteration of target sites (mainly for those that inhibit protein synthesis). Changing the rRNA or ribosomal protein sequence may render the drug ineffective.
Antiviral drugs

- Amantidine was the first discovered drug that works against a virus: it blocks the uncoating step of the influenza A virus. It is still sometimes used, but is limited in its overall usefulness.
- Most antiviral drugs in use today are nucleoside analogs, that is, they resemble a normal DNA or RNA nucleoside, but are different enough that they cause chain termination during replication.
  - Acyclovir (Zovirax, Valtrex) is commonly prescribed for herpes infections of various types.
  - AZT, ddI, and ddC are used in the treatment of AIDS.
- Protease inhibitors are also currently used for HIV.
Antifungal drugs

• Since fungi are eukaryotes, it stands to reason that in general, drugs toxic to them will also be toxic to us.

• One big difference, however, has to do with the abundant steroids in their cell membranes: fungi contain ergosterol, while human plasma membranes contain cholesterol. Therefore, many anti-fungal drugs target ergosterol biosynthesis.

• Also, as you know, fungi contain cell walls made of chitin that can be the targets of various drugs.