PREVENTION OF INFECTIOUS DISEASES
Factors Associated with Potential for Eradication of a Communicable Disease (1)

Factors Associated with Disease
- Ease of diagnosis and treatment
- Low prevalence of subclinical disease
- High disease burden and economic impact
- Immunity is long term or lifelong
- Disease cannot be reactivated
- Disease has predictable seasonality

Factors Associated with the Etiologic Agent
- Lack of an animal reservoir or vector
- Only one causative agent or serotype
- Short incubation period

Factors Associated with Potential for Eradication of a Communicable Disease (2)

Factors Associated with the Host or Target Population
- Correlates or protection can be demonstrated
- Host cannot be re-infected with the agent
- Host cannot shed the organism once infection is resolved
- Public acceptance of the vaccine and other control measures is high

Factors Associated with the Vaccine
- Can confer long-lasting protection in a few injections
- Minimal handling and storage requirements (e.g., cold chain)
- Simple administration
- Can be administered simultaneously with other vaccines or adapted to schedules and timing of the national childhood immunization programs
- Few short- or long-term adverse effects
- Low cost to produce and purchase vaccine

Source: adapted from Evans AS. Am J Epidemiol 185; 122(2):199-207.
Control Measures Applied to the Host: Active Immunization

- **vaccination** is:
  - the process of administration of an antigen.

- **immunization** is:
  - the development of a specific immune response.
Principles of Vaccination (1)

- Self vs. nonself
- Protection from infectious disease
- Response indicated by the presence of antibody
- Very specific to a single organism
Principles of Vaccination (2)

Active immunity:
• Protection produced by the person’s own immune system
• Usually permanent

Passive immunity:
• Protection transferred from another human or animal
• Temporary protection that wanes with time
Principles of Vaccination (3)

Antigen

- A live or inactivated substance (e.g., protein, polysaccharide) capable of producing an immune response

Antibody:

- Protein molecules (immunoglobulin) produced by B lymphocytes to help eliminate an antigen
<table>
<thead>
<tr>
<th>Type</th>
<th>Acquired through</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive immunity</td>
<td>Natural maternal antibody</td>
</tr>
<tr>
<td></td>
<td>Immune globulin(^*)</td>
</tr>
<tr>
<td></td>
<td>Humanized monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>Antitoxin(^\d)</td>
</tr>
<tr>
<td>Active immunity</td>
<td>Natural infection</td>
</tr>
<tr>
<td></td>
<td>Vaccines(^\dd)</td>
</tr>
<tr>
<td></td>
<td>Attenuated organisms</td>
</tr>
<tr>
<td></td>
<td>Inactivated organisms</td>
</tr>
<tr>
<td></td>
<td>Purified microbial macromolecules</td>
</tr>
<tr>
<td></td>
<td>Cloned microbial antigens</td>
</tr>
<tr>
<td></td>
<td>Expressed as recombinant protein</td>
</tr>
<tr>
<td></td>
<td>As cloned DNA alone or in virus vectors</td>
</tr>
<tr>
<td></td>
<td>Multivalent complexes</td>
</tr>
<tr>
<td></td>
<td>Toxoid(^$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black widow spider bite</td>
<td>Horse antivenin</td>
</tr>
<tr>
<td>Botulism</td>
<td>Horse antitoxin</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Horse antitoxin</td>
</tr>
<tr>
<td>Hepatitis A and B</td>
<td>Pooled human immune gamma globulin</td>
</tr>
<tr>
<td>Measles</td>
<td>Pooled human immune gamma globulin</td>
</tr>
<tr>
<td>Rabies</td>
<td>Pooled human immune gamma globulin</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>Monoclonal anti-RSV*</td>
</tr>
<tr>
<td>Snake bite</td>
<td>Horse antivenin</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Pooled human immune gamma globulin or horse antitoxin</td>
</tr>
</tbody>
</table>

*Respiratory syncytial virus

Types of Vaccines

- Passive – injection of immunoglobulins, short immunity
- Inactivated (killed) – limited immune response
- DNA – Plasmid containing DNA that codes for desired antigen
- Attenuated – large response and reversion to virulence
- Recombinant – live or inactivated
  - Transvected – insertion of antigen into carrier (e.g., yeast)
  - Conjugate
  - Vector – insertion of gene into a carrier/vector agent
- Toxoids – block toxin but not infection
- Subunit – components of agent
Active Immunization:
Types of Antigens

• Inactivated toxins
  – Diphtheria toxoid
  – Tetanus toxoid
  – *Clostridium perfringens* toxoid (pig bel vaccine)
Active Immunization: Types of Antigens (continued)

- **Inactivated complex antigens.**
  - Whole cell pertussis vaccine
  - Inactivated polio vaccine
  - Influenza vaccine
Active Immunization:
Types of Antigens (continued)

• Purified antigens
  – Acellular pertussis vaccine
  – Polyvalent capsular polysaccharide pneumococcal
  – Polysaccharide meningococcal; protein-polysaccharide conjugate *Haemophilus influenzae* type b
  – Plasma-derived hepatitis B vaccines
Active Immunization:
Types of Antigens (continued)

• Recombinant antigens

Hepatitis B recombinant vaccine is an example of a vaccine composed of hepatitis B surface antigen (HBsAg) sub-units made through recombinant DNA technology.
Active Immunization:
Types of Antigens (continued)

• Live, attenuated vaccines
  – Measles vaccine
  – Oral polio vaccine
  – Mumps vaccine
  – Rubella vaccine
  – Yellow fever
  – Smallpox vaccine
  – BCG (bacille Calmette-Guérin) vaccines
  – Passage in cell lines
  – Reversion to virulence
Active Immunization: Types of Antigens (continued)

How Are Vaccines Made?

- Attenuate (live) Serial passage → Attenuated
- Inactivated
  - Disrupt → Purify → Subunit
  - Extract DNA
    - Insert in yeast or bacteria → Express antigen → Purify → Recombinant vaccine
    - Insert DNA into vector → Vectored
  - Cold adapted “parent” → Naked DNA
  - Reassortant
### TABLE 18-4  
Classification of common vaccines for humans

<table>
<thead>
<tr>
<th>Disease or pathogen</th>
<th>Type of vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHOLE ORGANISMS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial cells</strong></td>
<td></td>
</tr>
<tr>
<td>Anthrax</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Cholera</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Pertussis*</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Plague</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Live attenuated BCG†</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Live attenuated</td>
</tr>
<tr>
<td><strong>Viral particles</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Measles</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Mumps</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Polio (Sabin)</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Polio (Salk)</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Rubella</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Varicella zoster (chickenpox)</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated</td>
</tr>
</tbody>
</table>

Part 2 of Table 18.4

<table>
<thead>
<tr>
<th>PURIFIED MACROMOLECULES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxoids</strong></td>
</tr>
<tr>
<td>Diphtheria</td>
</tr>
<tr>
<td>Tetanus</td>
</tr>
<tr>
<td><strong>Capsular polysaccharides</strong></td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
</tr>
<tr>
<td>type b</td>
</tr>
<tr>
<td><em>Neissera meningitidis</em></td>
</tr>
<tr>
<td>Polysaccharide</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>23 distinct capsular polysaccharides</td>
</tr>
<tr>
<td><strong>Surface antigen</strong></td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
</tbody>
</table>

*There is also an acellular pertussis vaccine consisting of toxoids and inactivated bacteria components.*

*Bacillus Calmette-Guerin (BCG) is an avirulent strain of Mycobacterium bovis.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Attenuated vaccine</th>
<th>Inactivated vaccine</th>
<th>DNA vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Selection for avirulent organisms: virulent pathogen is grown under adverse culture conditions or prolonged passage of a virulent human pathogen through different hosts</td>
<td>Virulent pathogen is inactivated by chemicals or irradiation with $\gamma$-rays</td>
<td>Easily manufactured and purified</td>
</tr>
<tr>
<td>Booster requirement</td>
<td>Generally requires only a single booster</td>
<td>Requires multiple boosters</td>
<td>Single injection may suffice</td>
</tr>
<tr>
<td>Relative stability</td>
<td>Less stable</td>
<td>More stable</td>
<td>Highly stable</td>
</tr>
<tr>
<td>Type of immunity induced</td>
<td>Humoral and cell-mediated</td>
<td>Mainly humoral</td>
<td>Humoral and cell-mediated</td>
</tr>
<tr>
<td>Reversion tendency</td>
<td>May revert to virulent form</td>
<td>Cannot revert to virulent form</td>
<td>Cannot revert</td>
</tr>
</tbody>
</table>

Substrate to support virus production; e.g., egg, HeLa cells, etc.
Vaccine Additives

Antibiotics – prevent growth of contaminating bacteria

Aluminum gels/salts – adjuvant that stimulates a greater immune response

Egg protein – vaccines prepared in eggs; not suitable for allergic persons; e.g., most influenza vaccines

MSG – stabilizes vaccines against heat, light, acidity, humidity

Thiomerosal – mercury-containing preservative
Vaccine Characteristics

- Inactivated vaccines
  - Limited immune response
  - Immunity may wane over time
  - No secondary spread

- Live vaccines
  - Replicate *in vivo*
  - Induce larger immune response
  - Induce immune memory/recall
  - Can revert to virulence
  - Can be secondarily transmitted to others
Routes of Administration

- Intramuscular
  - Stimulates systemic immunity
  - May induce injection reactions

- Subcutaneous

- Oral
  - Easily administered
  - Induces gastric mucosal and systemic immunity

- Nasal
  - Easily administered
  - Induces nasal mucosal and systemic immunity
FIGURE 18-3 Immunization with a single dose of the Salk polio vaccine induces a rapid increase in serum antibody levels, which peak by 2 weeks and then decline. Induction of immunologic memory follows a slower time course, reaching maximal levels 6 months after vaccination. The persistence of the memory response for years after primary vaccination is responsible for immunity to poliomyelitis. [From M. Zanetti et al., 1987, Immunol. Today 8:18.]
Active Immunization: Calculation of Vaccine Efficacy

• Formula for calculation of vaccine efficacy (VE):

\[
VE = \frac{\text{Attack rate in Unvaccinated} - \text{Attack rate in Vaccinated}}{\text{Attack rate in Unvaccinated}}
\]
Active Immunization: Herd Immunity

- Besides protection of the individual, vaccination may also provide a degree of community protection called herd immunity.

- **Herd immunity:**
  
The relative protection of a population group achieved by reducing or breaking the chains of transmission of an infectious agent because most of the population is resistant to infection through immunization.
Active Immunization:  
Herd Immunity (continued)  

The mechanisms of herd immunity include:

- Direct protection of vaccinees against disease or transmissible infection
- Indirect protection of nonrecipients by virtue of surreptitious vaccination (e.g., spread of attenuated vaccines), passive antibody, or just reduced sources of transmission
- Level to achieve herd immunity depends on infectiousness of agent
Evaluation of Vaccines (1)

- Pre-clinical evaluation (animals)
  - Safety/toxicity
  - Biologic activity
  - Dose/route of administration

- Phase I (small numbers of human volunteers)
  - Dose
  - Safety/toxicity
  - Biologic/immune response
Evaluation of Vaccines (2)

- Phase 2 (50-100 human volunteers)
  - Safety/toxicity
  - Immune response (humoral and cell-mediated)
  - Demonstration of protection

- Phase 3 (greater numbers of susceptible volunteers)
  - Requires study sites with adequate disease incidence
  - Requires vaccinated and control groups of susceptible volunteers
  - Further evaluation of safety/toxicity
  - Provides estimate of level of efficacy
Evaluation of Vaccines (3)

- Field trials (large populations of susceptible volunteers)
  - Large-scale double-blind efficacy trials
  - In different geographic areas
  - In different racial/ethnic/cultural groups
  - Observation of rare adverse/unusual reactions

- Post licensing monitoring/surveillance (Vaccine Adverse Event Reporting System (VAERS))
  - Case definition must recognize modified disease
  - Surveillance for rare adverse reactions and vaccine failures
  - Population effectiveness (e.g., control/elimination/eradication)
  - Problems in scaling up coverage
Basic laboratory research

Preclinical – growth in tissue culture systems and animal testing for immunogenicity and safety; challenge testing in animals

Investigational New Drug (IND) application sponsor submits proposal for testing in humans

Phase I – vaccine trials – test vaccine in 20-80 volunteers for safety and immune response

Phase II – vaccine trials – test in several hundred volunteers for safety, immunogenicity, dose, immunization schedule, and method of delivery
Required Steps for Vaccine Approval (2 of 2)

**Phase III** – vaccine trial – test in thousands of volunteers; randomized double-blinded using placebo and nature challenge; look for unusual/rare adverse events

**Biologics license application** – approval by Food & Drug Administration for labeling and public use

**Phase IV** – post-licensure monitoring for rare and unexpected adverse outcomes

**Vaccine Adverse Event Reporting System (VAERS); CDC** – voluntary reporting system for adverse events
Characteristics of an Ideal Vaccine

1. Produces a good humoral, cell-mediated, and local immune response, similar to natural infection, in a single dose
2. Elicits protections against clinical disease and re-infection
3. Provides protection for several years, preferably a lifetime
4. Results in minimal immediate adverse effects or mild disease with no delayed effects that predispose to other diseases
5. Induced immunity confers protections to multiple strains of organisms
6. Can be administered simply in a form that is practically, culturally, and ethically acceptable to the target population
7. Vaccine preparations do not require special handling (e.g., a cold chain)
8. Does not interfere significantly with the immune response to other vaccines given simultaneously
9. Costs and benefits associated with receiving the vaccine clearly outweigh the costs and risks associated with natural infection

Loughlin AM & Strathdee SA. Vaccines: past, present and future. In Infectious Disease Epidemiology, 2nd ed, Jones & Bartlett, 2007; p 347.
Human Microbial Communities (microbiota)
Human Microbial Communities (microbiota) and Their Genes (1)

Number of cells in average human = $10^{14}$

Number of bacteria in average human = $10^{17}$

Ratio of bacteria: cells = >10:1

Percent of total body mass = 1-3%

+ viruses and fungi
Human Microbial Communities (microbiota) and Their Genes (2)

**Diversity:**

- The microbial community of each individual is unique and constant (relative to between-individual diversity)
- Components of microbial community within an individual undergo constant changes
- A few signature taxa dominate (= 17-84% of total)
- By ethnicity
### Human Microbial Communities (microbiota) and Their Genes (3)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Number of Different Bacterial Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut</td>
<td>500-1000</td>
</tr>
<tr>
<td>Skin</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Eyes</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>750+</td>
</tr>
<tr>
<td>Vagina</td>
<td>Varies with menstrual cycle and race; primarily lactobacillus (20+ types)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Few</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Mean non-zero abundance (size) and population prevalence (intensity) of microbial clades

Abundant taxa in the human microbiome that have been metagenomically and taxonomically well defined in the HMP population.

a–c. Prevalence (intensity, colour denoting phylum/class) and abundance when present (size) of clades in the healthy microbiome. The most abundant metagenomically-identified species (a), 16S-identified genera (b) and PATRIC^{12} pathogens (metagenomic)

Factors that Disturb the Human Microbial Community

Disturbants:
- Oral antibiotics – gut, oral cavity
- Oral antivirals – gut, oral cavity
- Microbicides – contraceptives, condoms
- Soap – skin
- Invasive procedures – gut, respiratory system, vagina
- Bacterial and viral infections – all systems
- Diet
- Epigenetics*

Restoration:
- Fecal milkshakes (not sold by Baskin-Robbins), pills

*chemical changes to the genome that affect how DNA is packaged and expressed without altering amino acid sequence
Human Microbiota Influences

- Susceptibility to infectious diseases
- Host response to infectious agents
- Efficacy of antibiotics and antivirals
- Susceptibility to chronic diseases
- Manifestations and course of chronic diseases
- Host response to treatment of chronic diseases
Twelve Tips to Prevent Infections

1. Wash hands frequently and sing “Happy Birthday”
2. Don’t share personal items (toothbrushes, towels, handkerchiefs, etc.)
3. Cover your mouth when you cough or sneeze
4. Get vaccinated
5. Use safe cooking practices (e.g., refrigeration to avoid food-borne illnesses)
6. Be a smart traveler (e.g., safe drinking water, cooked food)
7. Practice safe sex (condoms)
8. Don’t pick your nose
9. Exercise caution with animals (zoonotic diseases) – sleep with people not dogs
10. Watch the news (current outbreaks, Salmonella spread, etc.)
11. Practice healthy lifestyle (diet, exercise, habits)
12. Maintain beneficial microbiome