Vaccines and Vaccination

- Chapter 21
- Components of a vaccine
- Selection of antigens to be used in a vaccine
- Immune effector mechanisms activated by vaccines
- Practical consideration for vaccine development and use
- Examples of successful vaccines
- Factors that prevent development of vaccines against certain microorganisms

What is a Vaccine?

- A preparation that stimulates an immune response to protect against foreign substances
- A successful vaccine will induce a memory response

Vaccination

- US Centers for Disease Control declarations
- #1 public health achievement of the 20th century
- Elimination of smallpox in 1977
- Impending elimination of paralytic polio

Goal of Vaccination
Vaccines can control viral epidemics

Vaccination

Table 21.1 Decrease in cases of vaccine-preventable diseases in the United States through 1998 as reported by the U.S. Centers for Disease Control and Prevention

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of cases</th>
<th>Baseline</th>
<th>1998</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>7,405</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>41</td>
<td>97.9</td>
<td></td>
</tr>
<tr>
<td>Paralytic polio</td>
<td>16,316</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>666</td>
<td>99.6</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>364</td>
<td>99.3</td>
<td></td>
</tr>
<tr>
<td>H. influenzae type b</td>
<td>20,000</td>
<td>63</td>
<td>99.7</td>
<td></td>
</tr>
</tbody>
</table>

Baseline = 20th-century annual prevaccine infection rate.

Vaccine Development

- Edward Jenner first vaccine in 1796
- Infected an 8-year-old boy with cowpox
- Then challenged with infection with smallpox
-Boy did not get smallpox

- 1774 Benjamin Jesty inoculated wife and daughters with cowpox hoping to protect from smallpox
  - Did not challenge with smallpox
  - But family did not get smallpox
  - Jenner got his idea from Jesty

Vaccine Development

- Louis Pasteur found that he could prevent disease by using a weakened microorganism infection
  - Used anthrax in cattle and rabbits in humans

- Emil Adolf von Behring and Shibasaburo Kitasato
  - Developed a serum therapy for diphtheria
  - Antibodies in immune serum

- Maxwell Finland used specific antiserum against strep pneumoniae to treat patients at Boston City Hospital
  - Before antibiotics were developed
What are the phases for vaccine development?

• The Phases of Clinical Trials
  
• Preclinical
  • Phase 1
  • Phase 2
  • Phase 3

What are the phases for vaccine development?

Preclinical
  • Design and production of the vaccine product
  • In vitro assays
  • Small animal models
  • Non-human primate models

What are the phases for vaccine development?

Phase I
  • Under 50 participants per dose or approach
  • Low-risk population
  • Measures safety and how the drug/vaccine is tolerated
  • (Measures immune response)
  • 8-12 months to complete

Phase II
  • Hundreds of participants
  • Low and higher risk
  • Expanded safety
  • Measures immune response
  • 18-24 months
What are the phases for vaccine development?

Phase III
- Thousands of participants
- Moderate to high risk
- Expanded safety
- Determines efficacy and immune response
- Approximately 3 years

Vaccination
- Types of protection
- Active Immunization
  - Develop an immune response after immunization or infection
  - T and B cell responses elicited
  - Cell mediated and antibody mediated immune responses
- Passive Immunization
  - Given antibodies from another individual or organism or from the lab
- Serum sickness
  - Recipient makes antibodies against antigens in Horse serum
  - Human serum better, but expensive and not widely available
- Purified IgG from human serum
  - Bloodborne pathogen scare (HIV, hepatitis)
- Monoclonal antibodies produced in the lab
  - Testing and marketing currently

Active Immunization

<table>
<thead>
<tr>
<th>Disease</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>Corynebacterium diphtheriae</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Clostridium tetani</td>
</tr>
<tr>
<td>Meningitis and sepsis</td>
<td>Hemophilus influenza type b</td>
</tr>
<tr>
<td>Pneumonia and sepsis</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Salmonella enterica serovar Typhi</td>
</tr>
<tr>
<td>Plague</td>
<td>Yersinia pestis</td>
</tr>
<tr>
<td>Anthrax</td>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>M. tuberculosis</td>
</tr>
<tr>
<td>Cholera</td>
<td>Vibrio cholera</td>
</tr>
</tbody>
</table>

Viral vaccines developed to

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of virus</th>
<th>Vaccine constituents</th>
<th>Vaccine constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>Variola virus</td>
<td>Vaccinia virus</td>
<td>Vaccinia virus</td>
</tr>
<tr>
<td>Polio</td>
<td>Picornavirus</td>
<td>Oral: live, attenuated virus</td>
<td>Oral: live, attenuated virus</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Picornavirus</td>
<td>Inactivated virus particles</td>
<td>Inactivated virus particles</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepadnavirus</td>
<td>Recombinant antigen</td>
<td>Recombinant antigen</td>
</tr>
<tr>
<td>Influenza</td>
<td>Orthomyxovirus</td>
<td>Inactivated virus</td>
<td>Inactivated virus</td>
</tr>
<tr>
<td>Measles (rubeola)</td>
<td>Parainfluenza</td>
<td>Live, attenuated virus</td>
<td>Live, attenuated virus</td>
</tr>
<tr>
<td>Mumps</td>
<td>Parainfluenza</td>
<td>Live, attenuated virus</td>
<td>Live, attenuated virus</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>togavirus</td>
<td>Live, attenuated virus</td>
<td>Live, attenuated virus</td>
</tr>
<tr>
<td>Chicken pox (varicella)</td>
<td>Varicella-zoster</td>
<td>Live, attenuated virus</td>
<td>Live, attenuated virus</td>
</tr>
<tr>
<td>Rabies</td>
<td>Lyssavirus</td>
<td>Inactivated virus</td>
<td>Inactivated virus</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Flavivirus</td>
<td>Live, attenuated virus</td>
<td>Live, attenuated virus</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Flavivirus</td>
<td>Inactivated virus</td>
<td>Inactivated virus</td>
</tr>
</tbody>
</table>

Active Immunization
Active Immunization

Passive Immunization

Table 21.1. Passive immunotherapeutic reagents available for postexposure prophylaxis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prophylactic agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td>Equine botulism antitoxin</td>
</tr>
<tr>
<td>Measles</td>
<td>Human or equine (only human choice)</td>
</tr>
<tr>
<td>Rubella</td>
<td>Human rubella immunoglobulin</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Human tetanus immune globulin</td>
</tr>
<tr>
<td>Rabies</td>
<td>Human rabies immune globulin</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Normal human immune globulin</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Human hepatitis B immune globulin, usually for neonates born to infected mothers to prevent neonatal transmission</td>
</tr>
<tr>
<td>Spider toxins</td>
<td>Horse antivenin</td>
</tr>
<tr>
<td>Snake toxins</td>
<td>Antivenins developed to be specific to the particular snake toxin</td>
</tr>
</tbody>
</table>

Vaccination

- Usually killed bacterial or fungal cells do not generate protective immunity

- Only some killed viral particles generate protective immunity
  - Inactivated polio vaccine

- Only a small minority of antigenic targets actually provide protective immunity
  - Certain classes of antigens are associated with protective immunity

Certain classes of antigens are associated with protective immunity

- Antibody mediated immunity protective antigens
  - Toxins
  - Microbial surface antigens
  - Prominent viral surface capsid proteins
  - Surface capsular polysaccharides of some bacteria and fungus

- Cell mediated immunity protective antigens
  - Harder to define
  - Can be anywhere in microbe
  - Only effective if they can be presented by APCs to T cells
Certain classes of antigens are associated with protective immunity

Table 21.3 Microbial antigens that can be targeted for vaccine development

<table>
<thead>
<tr>
<th>Type of organisms</th>
<th>Antigenic target</th>
<th>Mechanisms of immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Toxins</td>
<td>Neutralization of toxin</td>
</tr>
<tr>
<td></td>
<td>Capsular polysaccharides</td>
<td>Orophagocytic killing</td>
</tr>
<tr>
<td></td>
<td>Surface proteins</td>
<td>Orophagocytic killing</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Capsid coat protein</td>
<td>Neutralization of infectivity</td>
</tr>
<tr>
<td></td>
<td>Internal core antigens</td>
<td>CMI</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>Capsular polysaccharide</td>
<td>Orophagocytic killing</td>
</tr>
<tr>
<td></td>
<td>Surface proteins</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Protozoan parasites</strong></td>
<td>Surface proteins</td>
<td>Antibody-mediated neutralization CMI</td>
</tr>
</tbody>
</table>

Requirements for a Safe vaccine

- Safe, minimal side effects
- Effective duration - depends on use
- Immunogenic - needs adjuvant or protein carrier
- Nonimmunosupressive - measles vaccine FcR binding
- Host responds with proper type of immunity - CMI vs Ab
- Cost vs benefits
  - Monetary to produce and deliver and any health risk associated with its use
  - Benefit to individual and population
- Relative risk of vaccine vs infection

Certain antigens are associated with protective immunity

Table 21.4 A selection of 17 deleterious antigens as targets for parasite-neutralizing immune response

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Type of pathogen targeted</th>
<th>Effectors of immunity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 21.5 Types of effector mechanisms known to be involved in immunity to microbial pathogens that would need to be elicited by a vaccine

<table>
<thead>
<tr>
<th>Effector mechanisms</th>
<th>Type of pathogen targeted</th>
<th>Mediators of immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Need to know what effector mechanisms need to be provoked by vaccine for protective immunity
Vaccine Duration

- Antigenic variation is the most common microbial mechanism for evading the host defenses
  - Microbe may produce up to hundreds or thousands of distinct surface antigens
  - Effective immunity is needed against many if not all these

- Antigenic drift
  - Influenza virus
  - Mutations in HA and NA

- Antigenic shift
  - Influenza virus
  - Reassortment of genes for HA and NA between 2 different viruses

Smallpox Eradication

What was it about smallpox?

- No secondary hosts
- Long incubation
- Low communicability
- No persistent infection
- Easily diagnosed
- Infection confers long term immunity
- One stable serotype
- Vaccine existed
- Vaccine is stable and inexpensive
What was it about smallpox?

- Severe disease with high morbidity and mortality
- Much cheaper to eradicate than treat
- Eradication from developed countries demonstrated feasibility
- Few cultural or social barriers to case-tracing

What if we stopped vaccinations?

- Before immunization nearly everyone in US got measles
- ≈ 450 deaths/yr 1953-1963
- 3/1000 deaths in US
- 1/100 deaths in developing world
- >90% not immune will get measles if exposed to the virus
- If measles vaccination were stopped we would see:
  - 2.7 million measles deaths worldwide