Passive vs Active Immunity

- Passive immunization: transfer of antibodies
- Vaccines are active immunizations (mimic natural infections)

Passive Immunization

- Lasts as long as antibodies are present.
- Does not establish memory.
- e.g. gammaglobulin shots (pooled human IgG).

How do vaccines work?

- Vaccines are active immunization to provide protection from disease by establishing memory T and B cells.
- Some vaccines prevent disease but not infection.

Preventive vs Therapeutic vaccines

**Preventive**
- Most vaccines in use now provide protection from primary infection or prevent disease.

**Therapeutic vaccines**
- Given to infected people to prevent disease, reduce effects of chronic infection, or stimulate anti-tumor response.

Smallpox---Vaccine Success

Successful eradication of smallpox last known case in world in 1977. Smallpox vaccine is Vaccinia virus.

**Reasons for the smallpox success story**
- No animal reservoir.
- Lifelong immunity.
- One serotype (no antigenic variation).
- Effective attenuated vaccine.
Issues for Vaccine Design

Establishing Protective Immunity

◆ Which antigens are immunodominant?
◆ What type of immune response provides protection from disease?
◆ How to elicit long-term immune protection?

Issues for Vaccine Design

Prevent potential pathogenesis

◆ Disease often a result of an immune response.
◆ Some vaccine trials actually resulted in worse disease.
◆ Vaccines must avoid immune pathology.

Issues for Vaccine Design

Route of immunization

◆ Immunization site will influence where immune responses are elicited.
◆ Important to know route of infection in order to elicit protective immunity.
◆ Primary vaccine routes
  – Intramuscular (IM)
  – Intravenous (IV)
  – Oral

Issues for Vaccine Design

Adjuvants

Added to non-replicating vaccines in order to enhance immunogenicity.
(Bind TLRs, provide inflammatory response, and activate APCs)
◆ Inorganic salts are routinely used in humans.
  • Aluminum hydroxide
  • Aluminum phosphate
  • Calcium phosphate
◆ New lipid adjuvants
  • Liposomes
  • Immune stimulating complexes (ISCOMs)
Other ways to enhance immunogenicity

◆ Inject vaccine with other pathogen to provide adjuvant-like effect
  E.g. *Bordetella pertussis* (whooping cough) is given with tetanus toxoid and diphtheria toxoid.

◆ Inject cytokines with vaccine
  E.g. GM-CSF injected with vaccine or inserted in plasmid.

Issues for Vaccine Design

Antigenic Variation

Viruses have different antigenic subtypes and high mutation rates.

- Example: Antigenic drift of influenza usually means a new vaccine formulation each year.

NOTE**: any potential HIV vaccine will have to deal with different serotypes and high mutation rate.

Types of Vaccines

Attenuated vaccines
aka "Live Vaccines"

◆ Attenuated vaccines are made by growing pathogen in non-human cell culture.
◆ Less virulent in humans.
  - Examples Sabin Oral polio vaccine (OPV), Measles, Mumps, Rubella, Varicella zoster virus (VZV).

Types of Vaccines

Attenuated vaccines

◆ Advantages:
  - Self-replicating
  - Authentic antigen presentation
  - More effective at eliciting CTLs

◆ Disadvantages:
  - Reversal of virulence
  - One lab-adapted strain does not deal with strain variability

Types of Vaccines

Inactivated Vaccines

◆ Whole, killed, non-replicating organism

◆ Inactivated by heat, chemicals, or irradiation
  - Examples Influenza, Hepatitis A virus, Pertussis, Salk inactivated polio vaccine (IPV)
Types of Vaccines
Inactivated Vaccines

◆ **Advantages:**
  – No virulence
  – All antigens present

◆ **Disadvantages:**
  – No replication of pathogen
  – Poor antigen presentation for CMI

Types of Vaccines
Inactivated Flu Vaccine

◆ **Traditional approach:** Cell culture
  – Identify target "new virulent" strains
  – Grow in eggs with "harmless" flu strain
  – Genetic reassortment--expand and inactivate

◆ **New approaches:**
  ◆ Reverse genetics = clone in virulent H or N
  ◆ Recombinant H grown in insect cells

Flu Vaccine Issues in US

◆ Standard Inactivated vaccine.
  – Usually 100 million doses available each year.
◆ Flu-mist
  – Live vaccine and only 1-2 million doses.
◆ Recombinant vaccine still in clinical trials.
◆ Many H5N1 vaccines in the works.

Why have attenuated vaccines been so successful?

◆ **Advantages of replicating live vaccines:**
  – low cost, single dose, no adjuvant, generates IgG, IgA, and cell mediated immunity.

◆ Big disadvantage is potential for revirulence.

Attenuated (self-replicating/ live) vs Inactivated (non-replicating/ killed)

<table>
<thead>
<tr>
<th>Attenuated Vaccine</th>
<th>Inactivated Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Attenuated pathogens in vivo under specific conditions are grown in a suitable host (typically embryonated eggs) and inactivated.</td>
</tr>
<tr>
<td>Type of immunity induced</td>
<td>Produces both humoral and cell-mediated immunity.</td>
</tr>
<tr>
<td>Sabin tendency</td>
<td>Attenuated vaccine in stool.</td>
</tr>
</tbody>
</table>

Success of Polio Vaccination

<table>
<thead>
<tr>
<th>Attenuated Oral Polio Vaccine (OPV)</th>
<th>Sabin 1954</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated Polio Vaccine (IPV)</td>
<td>Salk 1957</td>
</tr>
</tbody>
</table>

(Sabin OPV can have reversal of virulence causing paralytic disease 1:4 million)
Types of Vaccines
Recombinant proteins/synthetic peptides

◆ Identify immunogenic proteins.
  – Usually envelope or outer membrane proteins.
◆ Produce large quantities for immunization.
  – Adjuvant to get immune system to notice proteins.

◆ Advantages:
  – Potentially less expensive production
  – No reversion
◆ Disadvantages:
  – No replication of pathogen, need adjuvant
  – Poor for CMI
  – Short lived immunity?

Human Papilloma virus (HPV) vaccine
(cause warts and cervical cancer)

◆ Vaccinia with HPV capsid proteins used in culture to make "virus-like particles" (no HPV viral DNA).

◆ Vaccine is empty viral capsids + alum.

Subunits in live vectors

Insert genes from pathogen into a well characterized vaccine vector.

(Bacterial or viral vectors: e.g. Vaccinia, Adenovirus, Salmonella, BCG).

Types of Vaccines
Subunits in live vectors

◆ Advantages:
  – Self replicating vectors.
  – Vector acts as adjuvant.
  – Good for CTLs.
◆ Disadvantages:
  – Infecting with other virus or bacterium.
  – May be less efficient for antibodies.

Types of Vaccines
HIV Canarypox vaccine

◆ Insert HIV genes into canarypox genome.
◆ Canarypox is non-human pathogen but can replicate thus vaccine elicits both CTL and some ab responses.
◆ Tested in humans with boost of recombinant HIV protein to increase ab levels.
Types of Vaccines

**DNA vaccines**

- **Advantages:**
  - Elicits both antibody and CMI immune response.
  - Cheap, easy to inject, stable.
  - Unmethylated CpG DNA in vector may provide its own adjuvant effect.

- **Disadvantages:**
  - Immune response not well characterized yet.
  - Potential for immunopathology.

Vaccines currently in use

Most vaccines are whole organism either live attenuated or inactivated vaccines. Some are recombinant proteins or purified macromolecules.

General Issues to Consider in Vaccine Development

- **Efficacy.** How well the vaccine protects the immunized population as a whole.
  - Influenza virus vaccine is only 70% protective. Most vaccines more than 95% protective.
  - How efficacious does a vaccine need to be?

General Issues to Consider in Vaccine Development

- **Cost.** Original vaccines were incredibly cheap. Number of people vaccinated versus cost to manufacture.
  - The WHO BIG SIX: DTP, polio, measles, and BCG cost <$1/person. Vaccinated ~80% of world population.

- **Safety.**
  - Potential revirulence and or increased pathology.

- **Stability of antigen and/or adjuvants.**

- **Drug resistance.**
  - New drug resistance by many bacteria has increased urgency for bacterial vaccines.