Vaccination Strategies
Protective Humoral Immune Responses

Bio 160 lecture

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Pathway to infectious disease

- **Exposure --> infection --> disease --> death**
- Host Immunity operates at two levels to restrict progression to disease & death. These are termed **innate** and **adaptive** immunity. Vaccines are designed to accelerate or augment adaptive response.
- **Exposure -//-> infection**
- **Exposure --> infection -//-> disease**
- **Exposure --> infection --> disease -//-> death of host**
- Virulence of infectious organism is also a factor!

Pathway to neoplastic disease (cancer)

- **Excitation --> neoplasia --> disease --> death**
- Adaptive immune responses act to eliminate neoplastic cells if "unusual antigens" appear. Vaccines are therapeutic since cancer antigens are unpredictable in many cases.
- **Excitation --> neoplasia**
- **Excitation --> neoplasia -//-> disease**
- **Excitation --> neoplasia --> disease -::-> death of host**
- Escape mechanisms of cancer cells also a factor!

Vaccines & immune responses to infectious diseases (Antigen elimination)

- **Immunization**: a procedure designed to increase concentrations of antibodies and/or effector T-cells which are reactive against infection or cancer. Immunization procedure called vaccination and the immunizing agent called vaccine (or “serum” in historical references)..
- When performed before exposure to an infectious agent (or soon after exposure in certain cases), it is called **immuno-prophylaxis**, intended to ***prevent*** the infection.
- When performed during an active infection (or existing cancer), it is called **immunotherapy**, intending to ***cure*** the infection (or cancer).

Immunization

- Two mechanisms by which immunization can be achieved.. **(Kuby:Table 18-1)**
- **Passive immunization**:
  Protective Abs --> non immune recipient*
  No immunological memory w/o Th cells.
  *in animal models of cancer, transfer Th or Tc cells.
- **Active immunization**:
  Induction of adaptive immune response, with protection and memory.

Table 18-1 **ACQUISITION OF IMMUNITY THROUGH PASSIVE AND ACTIVE IMMUNIZATION**

TYPE	ACQUIRED THROUGH
Passive Immunization	- Natural maternal serum/milk - Artificial immune serum
Active Immunization	- Natural infection - Artificial infection: Attenuated organisms Inactivated organisms DNA Purified microbial macromolecules Cloned microbial antigens Synthetic peptides Anti-idiotype antibodies Multivalent complexes

[Artificial refers to steps involving human intervention]

Passive immunization

- **Naturally** - transplacental transfer of maternal IgG Abs to developing fetus; transfer of IgG + IgA Abs in milk during breast-feeding of newborn..
- **Medically** - injection of immune globulin, [from same species, if possible (why?)]. Performed prophylactically, either after diagnosis of exposure to toxin/virus or as a short term preventive procedure, e.g. if one is traveling to an endemic area. **Table 18-2**
- **Blocking** - prevent hemolytic anemia of the newborn: Rhogam injected into pregnant Rh^- mother prior to delivery of each baby conceived with Rh^+ father. (Fig. 17-13)

Table 18-2

COMMON AGENTS USED FOR PASSIVE IMMUNIZATION

DISEASE	AGENT
Black widow spider bite Snake bite	Horse antivenin
Botulism Diptheria	Horse antitoxin
Hepatitis A and B Measles Rabies Tetanus	Pooled human **i**mmune **g**lobulin

Active immunization

- **Naturally** - following exposure to an infection….
- **Medically** - by vaccination: Performed either by i.m. injection of killed or attenuated antigens (often with adjuvant) or by ingestion of attenuated live organisms.
- **Blocking -** Reversal of auto-immune response (anti-Vß).
- **Anti-cancer** - Reactivation of tumor-stimulated T lymphocytes.
- **Tables 18-3 & -4** examples of vaccines to infections

Table 18-3

RECOMMENDED VACCINATION SCHEDULE (INFANTS & CHILDREN)

AGE	VACCINE
Birth--2 mos.	Hepatitis B (recombinant surface Ag)
2 mos.	Diptheria, tetanus, acellular pertussis (DTaP)
	Inactivated Polio virus (IPV)
	Haemophilus influenzae b (Hib-conjugate)
	att Rotavirus (Rv) (primate/human reassortant)
2-4 mos.	Hep B
4 mos.	DTaP, IPV, Hib, Rv
6-18 mos.	Hep B, DTaP, Oral Polio (OPV), Hib, Rv
12-15 mos.	DTaP, Hib
	att Varicella zoster/chicken pox (VZV)
	att Measles, mumps, rubella (MMR)
4-6 yrs	DTaP, OPV, MMR
11-12 yrs	DT

SOURCE: Centers for Disease Control, 1999 Guidelines.

Table 18-4 **CLASSIFICATION OF COMMON VACCINES FOR HUMANS**

DISEASE OR PATHOGEN	TYPE OF VACCINE
WHOLE ORGANISMS	
Bacterial cells:	
Cholera	Inactivated
Plague	Inactivated
Tuberculosis	Attenuated BCG*
Salmonella typhi	Attenuated
Viral particles:	
Influenza	Inactivated
Measles	Attenuated
Mumps	Attenuated
Rubella	Attenuated
Polio (Sabin/OPV)	Attenuated
Polio (Salk/IPV)	Inactivated
V. zoster (chickenpox)	Attenuated
Yellow fever	Attenuated

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

Table 18-4 (continued)

DISEASE OR PATHOGEN	TYPE OF VACCINE
(PURIFIED) MACROMOLECULES	
Toxoids:	
Diptheria	Inactivated exotoxin
Tetanus	Inactivated exotoxin
acellular Pertussis	Inactivated exotoxins
Capsular polysaccaride:	
Haemophilus influenzae b	Polysaccaride + protein carrier
Neisseria meningitidis	Polysaccaride
Streptococcus pneumoniae	23 distinct capsular polysaccarides
Surface antigen:	
Hepatitis B	Recombinant surface antigen (HbsAg)

Vaccine Issues

- Have *protective Ags* been included and are epitopes intact?
- Have the appropriate Abs been induced?
  e.g. anti-cholera toxin & other intestinal infections requires IgA
- Has T-cell immunity been stimulated?
  class I v. class II MHC; Th1 v. Th2
- Has memory been induced?
- Human v. veterinary vaccines?
- Vaccinees = children: Persistence of maternal Ab; "immature" imm. system
  Vaccinees = elderly: Immune deficiencies; autoimmunity
- Side effects (reversal of attenuation, auto immunity);
  Impurities (other viruses, other tissue Ags).
- Vaccine stability; costs; distribution; etc.

Vaccine Strategies

•Vaccination is a cost-effective means of disease prevention..
•Since the advent of widespread vaccinations, the incidence of many diseases such as measles, mumps, rubella, diphtheria, pertussis, and poliomyelitis has dropped significantly.
•One of the great triumphs for vaccines has been the eradication of smallpox during the 1970's.

Ideal Vaccines

•The goal of vaccination is to prime the recipient's immune system, to generate immunological memory. Upon subsequent exposure to the true pathogen, the memory cells specific for this particular pathogen will provide an accelerated response, to attack and clear the pathogen before it harms the host.
•The ideal vaccine would confer lifelong immunity with a single immunization, have no side effects, and be over 95% effective in all cases. In addition, to make vaccines available to all parts of the world, vaccines should be simple, inexpensive to manufacture, easily transportable, and stable in extreme heat or moisture.

A. Inactivated whole microbe vaccines

•An inactivated whole organism vaccine uses pathogens that are killed and are no longer capable of replicating within the host..
•Pathogens are inactivated by heat or chemicals while assuring the surface antigens are intact. However, heat inactivation causes extensive protein* denaturation, so usually chemicals such as formaldehyde are used to inactivate the pathogen. (*polysaccharides stable)
•Preparations of the inactivated whole organism are then administered by injection to the host.

Advantages of inactivated whole organisms

•By administering whole organism as a vaccine, it is easily phagocytosed and its antigens are presented to the Th cells. The full range of exogenous antigens is presented, ensuring that a broad immune response is generated..
•Since the organism is dead, there is no chance of disease occurring in the host.
•The vaccine is relatively heat stable, which is advantageous is places where refrigeration is not available.

Disadvantages of inactivatd whole organisms

• Inactivated vaccines produce a strong humoral immune response, but a weak CTL-mediated response...
• Since inactivated pathogen isn't replicating in the host, presentation of Ags is short-lived, requiring booster vaccinations.
• Endotoxins in whole killed bacterial vaccines can cause serious side effects, while not actually causing the disease.
• Inadequate killing of the pathogenic organism can result in occurrence of the disease. In an early lot of Salk inactivated polio vaccine (IPV) viruses were incompletely killed, causing vaccinees to acquire paralytic polio.

Examples & Future

Examples of whole inactivated organism vaccines are the Salk polio vaccine (IPV), pertussis vaccine (discontin'd), influenza vaccine, and cholera vaccine.

Future

While inactivated vaccines have proven to be successful in the past, the hazards associated with such vaccines remain an issue. Current research is turning towards recombinant and attenuated vaccines, which avoid many of these drawbacks.

B. Attenuated whole organism vaccines

• An attenuated whole organism vaccine uses a non-pathogenic form of the infectious organism, limited in its ability to replicate in the host and therefore unable to cause disease….

• Essentially, the attenuated microbe simulates an infection without causing the actual disease.

• Two ways of creating an attenuated vaccine:

• use a strain of the organism that is pathogenic in animals but not humans (e.g., cowpox)

• create mutants of the infectious organism that will not cause disease (growth in abnormal cond'ns; mutagenesis)

Advantages of attenuated vaccines

• attenuated organism vaccines generate vigorous humoral and cell-mediated immune responses. Since the whole organism is administered, pathogen is readily phagocytosed and its full range of antigens presented, ensuring a broad immune response..

• attenuated organism is able to replicate, persisting in the host for a time sufficient to induce immune memory. Single exposure is advantageous in areas where health care access limited.

• the vaccine can be administered at the normal route of entry, ensuring protection at this site. (Especially advantageous for pathogens that enter mucosally, as such a vaccine will elicit the specialized mucosal immune response.)

Disadvantages of attenuated organisms

• Because a live organism is used, there is the danger that the attenuated form could revert back to the virulent form. (e.g., Sabin oral poliovirus vaccine is known to produce one revertant per million viruses grow & are the source of vaccine-induced polio.)..
• Attenuated strain could recombine with a natural pathogenic strain, resulting in a new form of the organism that the vaccine may not be effective against.
• For vaccines created by growth in abnormal conditions, it is always possible that the growth culture could be contaminated with another substance. (Early batches of polio virus vaccines were contaminated with a monkey virus, SV40, since the polio was grown in monkey kidney cells. Fortunately, this murine oncovirus does not seem to cause disease in humans.)

Examples of attenuated vaccines

The Sabin polio vaccine is an attenuated vaccine created with growth in abnormal conditions, while the oral polio vaccine being administered currently is an example of a genetically engineered attenuated vaccine.
Other attenuated vaccines include the measles, mumps, rubella viruses for MMR vaccine; and the Varicella zoster virus vaccine (VZV) for chickenpox. An example of an attenuated *chimeric* vaccine is the rotavirus vaccine (Rv), which is composed of genes from the human and simian rotaviruses.
The Bacillus-Calmette Guerin (BCG) vaccine for tuberculosis is Mycobacterium bovis; Ty21a (attenuated S.typhi).