

Vaccines

- **Active vs Passive Immunization**
 - Active is longer acting and makes memory and effector cells
 - Passive is shorter acting, no memory and no effector cells
 - *Both can be obtained through natural processes:*
 - *Getting antibodies from mother*
 - *Directly getting the disease*
 - *Or by unnatural processes*
 - *Being given pre-formed antibodies (gamma globulin shot)*
 - *Altered (attenuated) vaccines, toxoids*
 - Immunity elicited in one animal can be transferred to another animal by injecting the recipient animal with serum from the immune animal
 - *Passive immunization= pre-formed antibodies given from one individual to another (across placenta, gamma globulin injection)*

Why use passive immunity?

- Deficiency in synthesis of Ig because of congenital or acquired defects
- When a susceptible person is likely to be exposed to disease
- When time does not permit adequate protection through active immunization
- When a disease is already present and Ig may help to ameliorate or help to suppress the effects of toxin (tetanus, diphtheria or botulism)
 - Passive Immunity-
 - *Natural maternal Ab & Immune globulin & Antitoxin*
 - Active Immunity-
 - *Natural Infection*
 - *Vaccines (attenuated & inactivated organisms & purified microbial proteins, cloned microbial antigens & toxoids)*

- **Tetanus- horse serum (horses do NOT get tetanus and can be injected with tetanus toxin)**
 - Horse produces antibodies to toxin and when injected into person they act to neutralize toxin to prevent binding (serum sickness to horse albumin possible)
 - *People can be given a toxoid (altered form of toxin that still has antigenicity) be this active immunity takes too long to achieve a high antibody titer*
 - *Passive immunization also given to people exposed to botulism, tetanus, diphtheria, hepatitis, measles, and rabies*
 - *Gives immediate protection against spider bites*
 - *For RSV (respiratory syncytial virus) {causes acute respiratory failure in children} can give mouse monoclonal antibodies that have been "humanized" by splicing the constant regions of human IgG to the mouse variable regions (PREVENTS SERUM SICKNESS—Type III or anaphylaxis-- UPON SECOND INJECTION)*

Active Immunization

- **To elicit protective immunity and memory**
 - **2nd exposure elicits a faster, more highly specific (greater affinity antibodies) response**
- **Vaccination of children begins at 2 months:**
 - *Hepatitis B vaccine (birth → 2 months, 1-4 mo, 5-19 mo)*
 - *Diphtheria-pertussis-tetanus (DPT) combined vaccine (15→ 19 mo)*
 - *Trivalent (Sabin) oral polio vaccine (OPV) and inactivated (Salk) polio vaccine (IPV) (5→ 19 mo IPV (2X, followed by) OPV 12-18 mo and 4-6 yrs)*
 - *Measles-mumps-rubella (MMR) combined vaccine (11→ 15 mo)*
 - *Haemophilus influenzae (Hib) vaccine (11→ 16 mo)*
 - *Varicella zoster (Var) vaccine for chicken pox*
 - *Rotavirus (Rv) vaccine for infant diarrhea (new)*
- **Need repeated booster shots at specific times– may be because of maternal circulating Ab's that prevent optimal response of vaccines**

- **Not all vaccines 100% effective**
 - **Some people respond poorly**
 - *Disease*
 - *Decreased immune response (drugs, ...)*
 - *Old age*
 - **Herd Immunity- those who are not vaccinated or those who responded poorly will have a LOW chance of coming in contact with an infected individual that the person without immunity will not become infected**
 - *individuals can become immune by getting the weakened strain from infected individuals*

Designing Vaccines

- **An immune response does not mean that protection has been achieved**
 - Differences between activation and protection of cellular versus humoral branch
 - Important consideration is memory formation
 - *Depends on incubation period of pathogen*
 - *Influenza has 2-3 day incubation period and becomes disease causing before memory cell response occurs*
 - *Therefore must maintain high level of Ig titers rather than relying on effective response by memory cells (may involve booster shots)*
 - *For polio, incubation is greater than 3 days allowing memory response to occur: therefore vaccine designed to induce high levels of immunologic memory*

Whole Organism Vaccines

- **Inactivated (killed) or live but attenuated (avirulent) vaccines (bacterial and viral)**
 - Attenuated vaccines must lose pathogenicity but retain antigenicity and capacity for transient growth in inoculated host
 - *Attenuation- obtained by growing pathogenic bacterium or virus pro long periods under abnormal culture conditions (selects mutants that are better suited for growth under abnormal conditions than normal condidtions)*
 - *Bacillus Calmette-Guerin (BCG)- after 13 years of growth on abnormal media was selected for as suitable for inoculation [problems with potential back mutations]*
 - *Attenuated vaccines better because of:*
 - *Prolonged exposure to Ag'ic epitopes (booster)*
 - *Leads to high affinity Abs and memory*

Sabin Vaccine

- **Consists of 3 attenuated strains of poliovirus**
 - *Colonize intestine and sets up IgA protection*
 - *Also induces IgM and IgG*
 - *3 inoculations to induce good immunity*
 - *First immunization induces good response against one strain and other two will induce good responses against others (one will grow faster and immune response will be against this one first, then this will be killed by immune response during 2nd inoculation and one of the other strains will then grow fast to induce an immunogenic response, etc.....)*
 - *Major disadvantage of attenuated vaccines is possibility of reversion (Sabin= 1 case in 4 million)*
 - *Presence of other viruses (contamination)*
 - *Can get around some concerns by genetically engineering the viral genome to remove pieces*

Inactivated Vaccines

- **By heat or by chemical means-- no longer capable of reproducing**
 - Heat causes denaturation of proteins (epitopes)
 - Chemical inactivation with formaldehyde OK
 - Repeated boosters needed
 - Produce primarily humoral response but not IgA response
- **Purified Macromolecules**
 - Polysaccharide vaccines- coating of capsules with anti-Ig to polysaccharides will prevent augment phagocytosis (S. pneumoniae vaccine consists of 23 Ag'ic capsular polysaccharides)-- opsonizing Abs
 - *These vaccines do not activate T_H cells, but do activate B cell in a TI manner (IgM with no class switch, no affinity maturation and no memory cell formation)*
 - *Can induce T_H cells by attaching polysaccharide to tetanus-toxoid (haptens-carrier) {Hib vaccine}*

Toxoid Vaccines

- **Produced against exotoxins (diphtheria and tetanus) to make TOXOID**
 - Obtain purified toxin and treat with formaldehyde
 - *Cannot get sufficient quantities of toxin-- can clone gene in cells*
- **Recombinant Vaccines-**
 - Cloning primary Ag'ic proteins into bacterial, yeast insects or mammalian expression systems, and these are expressed as antigens for vaccine development
 - *Hepatitis B-- cloned gene for major surface antigen of HBV, the HBsAg, in yeast cells. HBsAg purified and induces protective Abs*
- **Recombinant Vector Vaccines-**
 - Genes that encode major proteins of virulent organisms are placed into attenuated bacteria or viruses and expressed on surface

DNA vaccines

- Plasmid DNA encoding Ag'ic proteins is injected into muscle of recipient. DNA taken up by muscle cells and encoded protein antigen expressed by muscle cells (may be maintained as episomal or integrated DNA).
 - Muscle cells express low levels of MHC I and do not express co-stimulatory molecules, and may be dendritic cells that aid in development of antigenic response
 - *Induce both humoral and cellular responses and because of long expression of Ag will create good memory response*
 - *Refrigeration is not necessary for plasmid DNA which lowers cost*
 - *Same technology can be used for many genes*
 - *Can coat gold beads with DNA and use "gene gun" to inject into muscle*

Synthetic Peptide Vaccines

- Peptides not as immunogenic as proteins
- Tend to induce a humoral reaction more than a cellular (T_H) reaction
- Need to develop a synthetic peptide vaccine that contains both immunodominant B-cell and T-cell epitopes
 - If a CTL response is needed the vaccine must be delivered intracellularly so the peptides can be processed and presented together with class I MHC

Multivalent Subunit Vaccines

- **Approaches to accomplish this:**
 - **Prepare "solid matrix-antibody-antigen (SMAA) complexes by attaching monoclonal antibodies to particulate solid matrices and then saturating the antibody with desired Ag (can attach different monoclonal antibodies to solid matrix, and by binding different peptides or proteins you can get epitopes for both T and B cells). This gives very strong responses**

 - **Can produce multivalent vaccine by incorporating protein antigens or synthetic peptides into protein micelles (mix proteins with detergent and then remove detergent: proteins orient in hydrophilic/hydrophobic orientation with center that contains antigens), Liposomes (lipid vesicles). These fuse with cell membranes and place foreign antigens onto cells to stimulate immune response**