<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Immune response</td>
<td>Adaptive immune response or adaptive immunity is the response of antigen-specific lymphocytes to antigen, including the development of immunological memory.</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Any substance that enhances the immune response to an antigen with which it is mixed</td>
</tr>
<tr>
<td>Affinity</td>
<td>The strength of the binding of one molecule to another at a single site,</td>
</tr>
<tr>
<td>Anamnestic response</td>
<td>Anamnestic response is the rapid reappearance of antibody in the blood following introduction of an antigen to which the subject had previously developed a primary immune response.</td>
</tr>
<tr>
<td>Antibody</td>
<td>An antibody is a protein that binds specifically to a particular substance - its antigen. Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, but all antibodies have the same overall structure and are known collectively as immunoglobulins or Igs. Antibodies are produced by plasma cells in response to infection or immunization, and bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes.</td>
</tr>
<tr>
<td>Antibody, Constant region</td>
<td>The part of the molecule that is relatively constant in amino acid sequence</td>
</tr>
<tr>
<td>Antibody, variable region</td>
<td>The antigen binding sites of a molecule and the most variable part of the molecule</td>
</tr>
<tr>
<td>Antigen</td>
<td>An antigen is any molecule that can bind specifically to an antibody. Their name arises from their ability to generate antibodies. However, some antigens do not, by themselves, elicit antibody production; those antigens that can induce antibody production are called immunogens.</td>
</tr>
<tr>
<td>Apc: Antigen presenting cell</td>
<td>Antigen-presenting cells (APCs) are highly specialized cells that can process antigens and display their peptide fragments on the cell surface together with molecules required for T-cell activation. The main antigen-presenting cells for T cells are dendritic cells, macrophages, and B cells.</td>
</tr>
<tr>
<td>Avidity</td>
<td>Avidity is the sum total of the strength of binding of two molecules or cells to one another at multiple sites. It is distinct from affinity, which is the strength of binding of one site on a molecule to its ligand.</td>
</tr>
<tr>
<td>Basic reproduction Number</td>
<td>The average number of secondary infections produced when one infected individual is introduced into a host virgin population</td>
</tr>
<tr>
<td>B Cell</td>
<td>A B cell, or B lymphocyte, is one of the two major types of lymphocyte. The antigen receptor on B lymphocytes, usually called the B-cell receptor, is a cell-surface immunoglobulin. On activation by antigen, B cells differentiate into cells producing antibody molecules of the same antigen specificity as this receptor. B cells are divided into two classes. B-1 cells, also known as CD5 B cells, are a class of atypical, self-renewing B cells found mainly in the peritoneal and pleural cavities in adults. They have a far less diverse repertoire of receptors than do B-2 cells, also known as conventional B cells, which are generated in the bone marrow throughout life, emerging to populate the blood and lymphoid tissues.</td>
</tr>
<tr>
<td>Glossary - page 2</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Booster</strong></td>
<td>A booster immunization is commonly given after a primary immunization, to increase the titer of antibodies</td>
</tr>
<tr>
<td><strong>Cellular response</strong></td>
<td>Changes within the cell membrane</td>
</tr>
<tr>
<td><strong>Clonal selection</strong></td>
<td>The clonal selection theory is a central paradigm of adaptive immunity. It states that adaptive immune responses derive from individual antigen-specific lymphocytes that are self-tolerant. These specific lymphocytes proliferate in response to antigen and differentiate into antigen-specific effector cells that eliminate the eliciting pathogen, and memory cells to sustain immunity.</td>
</tr>
<tr>
<td><strong>Complement-mediated lysis</strong></td>
<td>Activation of plasma proteins to induce an inflammatory response</td>
</tr>
<tr>
<td><strong>Cytoxic T cell response</strong></td>
<td>T cells that can kill other cells are called cytotoxic T cells. Most cytotoxic T cells are MHC class I-restricted CD8 T cells, but CD4 T cells can also kill in some cases. Cytotoxic T cells are important in host defense against cytosolic pathogens</td>
</tr>
<tr>
<td><strong>Engineered vaccine</strong></td>
<td>A preparation of direct manipulation of genes of weakened or killed pathogen, such as a bacterium or virus that upon administration stimulates antibody production or cellular immunity against the pathogen but is incapable of causing severe infection.</td>
</tr>
<tr>
<td><strong>Epitope</strong></td>
<td>An epitope is a site on an antigen recognized by an antibody or an antigen receptor; epitopes are also called antigenic determinants. A T-cell epitope is a short peptide derived from a protein antigen. It binds to an MHC molecule and is recognized by a particular T cell. B-cell epitopes are antigenic determinants recognized by B cells and are typically discontinuous in the primary structure.</td>
</tr>
<tr>
<td><strong>Extrafollicular antibody response</strong></td>
<td>A response outside the molecular wall</td>
</tr>
<tr>
<td><strong>Germinal center</strong></td>
<td>Germinal centers in secondary lymphoid tissues are sites of intense B-cell proliferation, selection, maturation, and death during antibody responses. Germinal centers form around follicular dendritic cell networks when activated B cells migrate into lymphoid follicles.</td>
</tr>
<tr>
<td><strong>Herd immunity/community immunity</strong></td>
<td>Describes a form of immunity that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals who have not developed immunity. Commonly called Community Immunity.</td>
</tr>
<tr>
<td><strong>Humoral response</strong></td>
<td>Humoral immunity is the antibody-mediated specific immunity made in a humoral immune response. Humoral immunity can be transferred to unimmunized recipients by using immune serum containing specific antibody.</td>
</tr>
<tr>
<td><strong>Immunization</strong></td>
<td>Immunization is the deliberate provocation of an adaptive immune response by introducing antigen into the body</td>
</tr>
<tr>
<td><strong>Inactivated vaccine</strong></td>
<td>A vaccine that consists of pathogen particles which are killed</td>
</tr>
<tr>
<td><strong>Live vaccine</strong></td>
<td>A vaccine prepared from live microorganisms that have been attenuated but that retain their immunogenic properties.</td>
</tr>
<tr>
<td><strong>MHC</strong></td>
<td>MHC molecules is the general name given to the highly polymorphic glycoproteins encoded by MHC class I and MHC class II genes, which are involved in the presentation of peptide antigens to T cells.</td>
</tr>
<tr>
<td><strong>Opsonization</strong></td>
<td>Opsonization is the alteration of the surface of a pathogen or other particle so that it can be ingested by phagocytes. Antibody and complement opsonize extracellular bacteria for destruction by neutrophils and macrophages.</td>
</tr>
<tr>
<td><strong>Pathogen</strong></td>
<td>A microorganism that can cause disease when a host is infected.</td>
</tr>
<tr>
<td><strong>Precommited B cells</strong></td>
<td>A cell that responds to a specific antibody</td>
</tr>
<tr>
<td><strong>Protein-polysaccharide conjugate vaccine</strong></td>
<td>Coupling a polysaccharide vaccine with a carrier protein to transform a T-independent antigen into a T-dependent antigen</td>
</tr>
<tr>
<td><strong>T cell</strong></td>
<td>TH1 cells are a subset of CD4 T cells that are characterized by the cytokines they produce. They are mainly involved in activating macrophages, and are sometimes called inflammatory CD4 T cells. TH2 cells are a subset of CD4 T cells that are characterized by the cytokines they produce. They are mainly involved in stimulating B cells to produce antibody, and are often called helper CD4 T cells.</td>
</tr>
<tr>
<td><strong>Thymus</strong></td>
<td>The site of T-cell development, a lymphoepithelial organ in the upper part of the middle of the chest, just behind the breastbone.</td>
</tr>
<tr>
<td><strong>Vaccination</strong></td>
<td>Vaccination is the deliberate induction of adaptive immunity to a pathogen by injecting a vaccine, a dead or attenuated (nonpathogenic) form of the pathogen.</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td>Substances that are delivered to the immune system to induce specific responses that inactivate, destroy, or suppress pathogens</td>
</tr>
</tbody>
</table>

Vaccinology 101

June 16, 2011

Gary S. Marshall, M.D.
Professor of Pediatrics
Chief, Division of Pediatric Infectious Diseases
Director, Pediatric Clinical Trials Unit
University of Louisville School of Medicine

NurseTIP  www.nursetip.org

Vaccinology 101

• Definition of vaccines
• Basic vaccine immunology
• Types of vaccines
• Additional concepts
Objectives

After watching this broadcast participants will be able to:

• Describe the function of antibodies and T cells in vaccine-induced protective immunity.

• Identify the differences between responses to polysaccharide vaccines and protein-polysaccharide conjugate vaccines.

• Classify vaccines into broad functional categories (live and inactivated) and identify the differences between them.

• Describe the function of adjuvants.

• Define the concept of herd immunity

Definitions

• **Immunization**: protecting individuals from disease by making them immune

• **Vaccination**: delivery of antigens to the host for purposes of stimulating an immune response

• **Vaccines**: substances that are delivered to the immune system to induce specific responses that inactivate, destroy, or suppress pathogens

---

Adaptive Immunity: Antibodies

- Produced by differentiated B cells (plasma cells)
- The only pathogen-specific means of preventing infection

Antibody Functions

Neutralization  Opsonization  Complement-mediated lysis
Generation of Antibody Diversity

Central B-cell Tolerance

- Immature B-cells expressing surface IgM and IgD tested for self reactivity in bone marrow
- B-cells that recognize self...
  - Cell-surface antigens
    - Clonal deletion via apoptosis
    - Rescue via receptor editing: receptor activating gene (RAG)
  - Small, soluble antigens
    - Lose surface IgM expression
    - Express only IgD
Precommited B cells

Adaptive Immunity: T Cells

• Clear infection
• Provide help to B cells

www.rockefeller.edu

Ada. Lancet 1990;335:523
Central T-cell Tolerance

- Generation of T-cell receptor (TCR) diversity similar to antibody diversity
- Immature T-cells (CD4+/CD8+) positively selected for binding to MHC molecules in the thymus
  - Those that recognize MHC-II are transformed into CD4+ T-cells
  - Those that recognize MHC-I are transformed into CD8+ T-cells
- Positively-selected immature T-cells tested for self reactivity in the thymus
- Fate of self-reactive T-cells: clonal deletion

T Cell/APC Interactions

- MHC-I expressed on all cells
- Fold around internally-synthesized foreign peptides
- Long protein chain associated with β-2 microglobulin
- Stimulate cytotoxic T cells
- MHC-II expressed on specialized cells
- Two protein chains
- Groove contains endocytosed, digested foreign peptides
- Stimulate helper T cells
Requirements of a Vaccine

- Activation of APCs
- Activation of T and B cells
- Generation of memory cells
- Generation of epitope diversity
- Persistence of antibody production

Ada. Lancet 1990;335:523

The Extrafollicular Reaction

Antigen-specific IgM

B → P

Spleen and lymph nodes
Germline, low affinity antibodies
IgM
Short-lived
No memory

Polysaccharide

The Germinal Center Reaction

Bone marrow
Hypermutated, high
affinity antibodies
IgG, IgA, IgE
Long-lived

Spleen and lymph nodes
Long-term survival
Anamnestic response

Antigen-specific IgM

Co-stimulatory
receptors and
cytokines

MHC-II with peptide

TCR with CD4

Protein

Anamnestic Responses

Primary vaccination

Booster vaccination or
natural infection

Marshall. The Vaccine
Handbook. PCI Books, Inc.;
2010
Adjuvants

• Actions
  – Potentiate immune response
  – Epitope spread
  – Increased avidity

• Possible mechanisms of action
  – Slow release of antigen
  – Enhance delivery of antigen to APCs
  – Interaction with pattern-recognition receptors
    • Induce maturation of APCs
    • Increase uptake of antigen by APCs

Garcon N. Sci Am 2009;301:72; Tritto E. Vaccine 2009;28:3331;

Adjuvants

• Alum (aluminum salts)
  – Activation of inflammasome complex
  – Processing of proinflammatory cytokines

• AS04
  – Aluminum hydroxide plus monophosphoryl lipid A
  – Interacts with TLR4

Garcon N. Sci Am 2009;301:72; Tritto E. Vaccine 2009;28:3331;
### Adjuvants

<table>
<thead>
<tr>
<th>DTaP</th>
<th>Hib-T (ActHIB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap</td>
<td>IIV</td>
</tr>
<tr>
<td>Td</td>
<td>MCV4-D and MCV4-CRM</td>
</tr>
<tr>
<td>DT</td>
<td>MPSV4</td>
</tr>
<tr>
<td>TT</td>
<td>IPV</td>
</tr>
<tr>
<td>Hib-OMPC (PedvaxHIB)</td>
<td>PPSV23</td>
</tr>
<tr>
<td>HepA</td>
<td>JE-MB (JE-VAX)</td>
</tr>
<tr>
<td>HepB</td>
<td>Rabies vaccine</td>
</tr>
<tr>
<td>HPV2 and HVP4</td>
<td>TViPSV</td>
</tr>
<tr>
<td>JE-VC (Ixiaro)</td>
<td></td>
</tr>
<tr>
<td>PCV13-CRM</td>
<td></td>
</tr>
<tr>
<td>Anthrax vaccine</td>
<td></td>
</tr>
</tbody>
</table>

### Protein-Polysaccharide Conjugates

Protein-Polysaccharide Conjugate Vaccines

<table>
<thead>
<tr>
<th>B-cell response</th>
<th>T cell-independent</th>
<th>T cell-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunol pathway</td>
<td>Extrafollicular</td>
<td>Germinal center</td>
</tr>
<tr>
<td>Response in infants</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immune memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Booster effect</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-term protection</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduced carriage</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Herd immunity</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Cytotoxic T Cell Responses

Classification of Vaccines

- Live
  - Classical
    - Bacterial
  - Engineered
  - Whole agent
- Inactivated
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered
Classification of Vaccines

- **Live**
  - Classical
    - Bacterial
    - Viral
  - Engineered
  - Whole agent

- **Inactivated**
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered

- **BCG**
Classification of Vaccines

- **Live**
  - Classical
    - Bacterial
    - Viral
  - Engineered
  - Whole agent

- **Inactivated**
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered

- **Adenovirus (oral)**
- Measles
- Mumps
- Polio (oral)†
- Rotavirus (human, oral; RV1)
- Rubella
- Smallpox
- Varicella
- Yellow fever
- Zoster

†No longer available in the U.S.
Classification of Vaccines

**Live**
- Classical
  - Bacterial
  - Viral
- Engineered
  - Bacterial
  - Viral

**Inactivated**
- Whole agent
  - Bacterial
  - Viral

**Component**
- Toxoid
- Subunit
  - Physically purified
  - Recombinant
    - Non-engineered
    - Engineered

**Cholera (CVD 103-HgR, oral)**†
**Influenza (intranasal)**
**Rotavirus (bovine reassortant, oral; RV5)**
**Typhoid (oral)**

†No longer available in the U.S.
Classification of Vaccines

- **Live**
  - Classical
  - Engineered
    - Bacterial
    - Viral
  - Whole agent
    - Bacterial
    - Viral
  - Inactivated
    - Component
      - Toxoid
      - Subunit
        - Physically purified
        - Recombinant
          - Non-engineered
          - Engineered

- **Cholera (whole cell)**
- **Cholera (WC/rBS, oral)**
- **Pertussis (whole cell)**
- **Plague**
- **Typhoid (whole cell)**

*No longer available in the U.S.*
*Contains both whole agent and recombinant-derived subunit*
Classification of Vaccines

- Live
  - Classical
    - Bacterial
  - Engineered
    - Viral
  - Whole agent
    - Viral

- Inactivated
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered

- Hepatitis A
- Influenza (whole virus)†
- Japanese encephalitis
- Polio (parenteral)
- Rabies

†No longer available in the U.S.
Classification of Vaccines

- Live
  - Classical
    - Bacterial
    - Viral
  - Engineered
  - Whole agent

- Inactivated
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered

Diphtheria
Tetanus
Classification of Vaccines

- **Live**
  - Classical
    - Bacterial
    - Viral
  - Engineered
    - Bacterial
    - Viral

- **Inactivated**
  - Whole agent
    - Bacterial
    - Viral
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
        - Non-engineered
        - Engineered

**Examples**

- Anthrax (cell-free filtrate)
- Hepatitis B (plasma-derived HBsAg)†
- Hib polysaccharide†
- Influenza (split virus)
- Meningococcal B OMPV§
- Meningococcal polysaccharide
- Pertussis (acellular)
- Pneumococcal polysaccharide
- Typhoid (Vi polysaccharide)

†No longer available in the U.S.
§Not yet available in the U.S.
Classification of Vaccines

Live
- Classical
  - Bacterial
  - Viral
- Engineered

Inactivated
- Whole agent
- Component
  - Toxoid
  - Subunit
    - Physically purified
    - Recombinant
      - Non-engineered
      - Engineered

Hib conjugate
Meningococcal conjugate
Pneumococcal conjugate
Classification of Vaccines

- **Live**
  - Classical
    - Bacterial
  - Engineered
    - Viral
  - Whole agent
    - Bacterial
    - Viral

- **Inactivated**
  - Component
    - Toxoid
    - Subunit
      - Physically purified
      - Recombinant
      - Non-engineered
      - Engineered

### Hepatitis B (HBsAg)
- HPV (L1)
- Lyme disease (rOspA)†
- Meningococcal B (reverse genetics)§

*†No longer available in the U.S.*
*§Not yet available in the U.S.*
Generalizations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Live</th>
<th>Inactivated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response</td>
<td>Humoral and cellular</td>
<td>Mostly humoral</td>
</tr>
<tr>
<td>Dosing</td>
<td>One dose may be sufficient</td>
<td>Multiple doses necessary</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Not necessary</td>
<td>May be necessary</td>
</tr>
<tr>
<td>Administration</td>
<td>Parenteral or mucosal</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Duration of immunity</td>
<td>Potentially lifelong</td>
<td>Boosters may be required</td>
</tr>
<tr>
<td>Transmission</td>
<td>Possible</td>
<td>Not possible</td>
</tr>
<tr>
<td>Inactivation by antibody</td>
<td>Likely</td>
<td>Possible</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>May cause disease</td>
<td>Cannot cause disease</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Fetal damage possible</td>
<td>Fetal damage unlikely</td>
</tr>
<tr>
<td>Storage</td>
<td>Maintain viability</td>
<td>Maintain stability</td>
</tr>
<tr>
<td>Simultaneous admin</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Homologous interval</td>
<td>Minimums apply</td>
<td>Minimums apply</td>
</tr>
<tr>
<td>Homotypic interval</td>
<td>Minimums apply</td>
<td>No minimums</td>
</tr>
</tbody>
</table>

Herd (“Community”) Immunity

- Protection of individuals depends on quality, magnitude, and duration of vaccine response
- Individuals can be protected by preventing exposure
- Exposure depends on infected individuals
- Susceptible members of the herd are protected by the presence and proximity of immune members who prevent propagation of infection

Herd Immunity Threshold

- Basic reproduction number
- Mode of transmission
- Microbial ecology
- Endemic versus epidemic occurrence
- Nonrandom mixing
- Vaccine efficacy
- Vaccination disparities