Vaccinology 101
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COLUMBIA | VAGELOS COLLEGE OF PHYSICIANS AND SURGEONS
PROGRAM IN VACCINE EDUCATION

Principles of Vaccination

- Antigen (Immunogen)
  - A live or inactivated substance (e.g., protein, polysaccharide) capable of producing a (protective) immune response

- Antibody
  - Protein molecules (immunoglobulin) produced by B lymphocytes to help process and/or eliminate an antigen

- Cell-mediated response
  - e.g. T-helper or cytotoxic T cell response

Principles of Vaccination

- Active Immunity
  - Protection produced by the person's own immune system in response to infection, exposure or vaccination
  - Usually permanent, but may or may not be complete

- Passive Immunity
  - Protection transferred from another person or animal
  - Temporary protection that wanes with time

Vaccination

- Active immunity produced by a vaccine
  - Immunity and immunologic memory similar to natural infection but without risk or much lower risk of clinical disease

Passive Immunity

- Transfer of antibody produced by one human/animal to another person or animal
- Sometimes called Antiserum
- Temporary protection
- Transplacental maternal antibody is the most important source in infancy

Sources of Passive Immunity

- Almost all blood or blood products
- Pooled human antibody (immune globulin)
- Human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin) from another animal species
- Monoclonal antibody

Immunization Strategy

- Prevention of infection vs. symptoms:
  - HIV vs. Measles
- Temporary vs. Long-lasting Immunity
  - Passive protection: specific antibodies
    - Immediate Protection, but $t_{1/2} \approx 27$ days:
    - Antitoxins
      - Antibodies to Tetanus, Diphtheria, Botulinum toxins
    - Hyperimmune antisera to specific pathogens:
      - Hepatitis B, Varicella, Rabies, RSV
    - Pooled Human Immune Globulin: not specific
      - Immune Serum Globulin & Intravenous IG
  - Active: vaccination (Longer lag time, but long-lasting)
  - Active - Passive (HBIG+Hep B vac.; RIG+Rabies vac.)
- Pre-exposure (Polio) vs. Post-exposure (Rabies)

Target Populations for Immunization

- High-Risk Groups Only (ex: Rabies, Varicella in some countries)
  - No effect on overall disease burden in the general population
  - Vaccine must be highly effective
  - Must be able to reach all members of high-risk group
  - Less expensive in the short term

Target Populations for Immunization

- Universal Immunization (Polio, Rubella, Varicella in USA)
  - Diminishes overall disease burden in general population
  - Pre-emptive immunization of healthy individuals who eventually become high-risk
  - Decreases risk of exposure for everyone
  - Planned access to target population
  - More cost-effective in long term
  - Requires extremely safe vaccines

Immunization of High Risk Groups

- Travel
  - Japanese Encephalitis, Yellow fever, Typhoid….
- Occupation:
  - Hepatitis B, Rabies, Anthrax, Plague, Rubella & Varicella
- Age, illness, immunosuppression
  - High-risk for invasive pneumoccocal disease:
    - Children < 6 years (Pneumococcal conjugate vaccine)
    - Elderly, high-risk kids ≥ 6 years (Pneumococcal polysaccharide vaccine)
  - Influenza: infants, elderly, or cardiac or pulmonary disease, pregnancy, obesity….
  - Severe varicella (live attenuated varicella vaccine):
    - leukemic children & HIV-infected kids with CD4 ≤ 15%
  - HIV-infected children (Inactivated polio vaccine)

Administration

- Route
  - Mimic route of natural infection: Oral polio, Live attenuated Intranasal Influenza vaccines
  - Parenteral (Intramuscular, subcutaneous)
- Age at immunization
  - Age distribution of natural infection:
    - In pre-vaccine era: ≥ 60% of invasive H.influenzae type b infections occurred at ≤ 18 months of age
  - Age-dependent immune response:
    - Polysaccaride antigens (HIB, Pneumo & Meningococcus) are poorly immunogenic at ≤ 2 years of age
  - Ability to access population to be immunized:
    - Hepatitis B & rubella vaccines in infants vs. adolescents

Immune Response to Immunization

- Primary response
  - 1st exposure to the antigen
  - 7-10 day lag time between exposure and production of antibody and cell-mediated responses
  - Initial antibody response is IgM, later switch to IgG
  - Establish populations of memory T & B cells
- Secondary response
  - After a repeat exposure to the antigen (or pathogen)
  - Shortened lag time between exposure and production of antibody and cell-mediated responses
  - Antibody response is almost all IgG
  - Rapid expansion/ Memory T & B cell populations

What Is Immunologic Memory? B cell Clonal Expansion

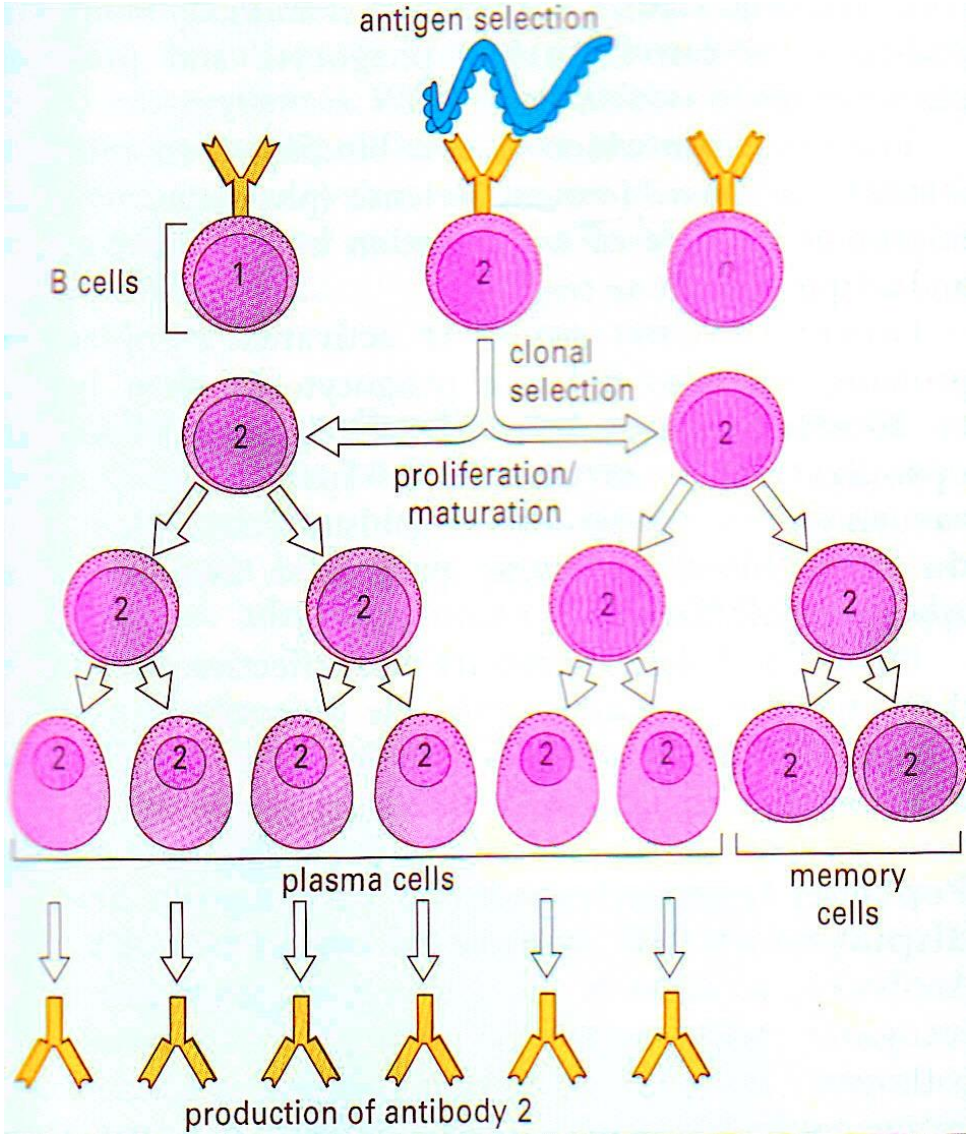

Fig. 1.13, Immunology, 8th ed, Male, et. al. 2013

Factors That Influence Vaccine Effectiveness

- HLA types
- Physiologic condition of vaccinee
  - Age, nutritional status, immune status
- Type of vaccine
  - Live attenuated vs. killed
- Dose and route of administration
- Adjuvants

Influence of Host Genetic Factors on Response to Vaccination

- 5–10% of healthy subjects do not mount an antibody response (anti-HBs) to Hepatitis b Vaccine

- Non-response is associated with different HLA-DR alleles and impaired Th(1?) cell response:
  - increased incidence of non-responsiveness in subjects with HLA-DR3(+) or -DR7(+) haplotypes

Current Technology

- **Inactivated whole organism:**
  - Whole cell Pertussis, eIPV, Hepatitis A, Rabies, Influenza(detergent-treated), plasma-derived Hepatitis B (no longer available in US)
- **Live organism from a related or different species:**
  - Vaccinia, Bacille Calmette-Guerin (BCG, also attenuated by serial passage)
- **Live attenuated organism:**
  - Oral Polio, Measles, Mumps, Rubella, Varicella, Cold-adapted Influenza, Yellow fever
  - Attenuated by passage in tissue culture
- **Toxoids:** inactivated Diphtheria, Tetanus toxins
- **Combination Vaccines:**
  - DTP, MMRV, DTP-HIB, HIB-Hep.B, DTaP- Hep.B-IPV

Current Technology

- **Specific subunit/antigen(s), extracted, purified:**
  - **Acellular Pertussis Vaccines:**
    - PT (Pertussis toxoid), FHA (filamentous hemagglutinin), Pertactin, Agglutinogens
  - **Polysaccarides (T-cell independent antigens):**
    - Hæmophilus (no longer available), Meningococcus, Pneumococcus
  - **Influenza surface glycoproteins (HA, NA)**

- **Conjugated antigens (T-cell dependent):**
  - **HiB:** PRP-D, PRP-T, PRP-OMP, HBoC (crm197)
  - **Pneumococcal Conjugate-13 valent**: CRM 197- 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
  - **Meningococcus A, C, W-135 & Y** conjugated to diphtheria toxoid

Current Technology

- Recombinant antigens:
  - HBsAg/ yeast
  - Meningococcus B:
    - Bexsero: recombinant proteins adhesin A, Heparin Binding Antigen, factor H binding protein, Outer Membrane Vesicles, aluminum hydroxide
    - Trumemba: recombinant lipidated factor H binding protein variants from serogroup B, subfamilies A & B, aluminum phosphate

Current Technology

- **Virus-like particles:**
  - **HPV Quadrivalent Vaccine:**
    - Major capsid proteins of human papillomavirus(HPV) serotypes 6, 11, 16 & 18 expressed in eucaryotic cells
    - 99-100% vs HPV 16/18 related Cervical Intraepithelial Neoplasia (CIN) 2/3 in uninfected women
    - 27% efficacy in women who are recently infected
    - No efficacy in those with established infection
    - FDA-approved for use in females 9-26 years in 2006
      - **Males and a bivalent 16/18 vaccine** later on
      - **Younger age groups to follow**

Rotavirus Vaccine

- **RotaTeq Vaccine Study**:
  - **Pentavalent bovine-human reassortant vaccine**
    - VP7 genes of serotypes G1, G2, G3, G4 and P-type P1A)
  - **70,000 placebo-controlled study**:
    - 70% efficacy vs. any vaccine-serotype-related disease
    - 98% vs. severe disease
    - 85, 94, 96% ↓ in office visits, ED & hospitalizations
    - Intussuception:
      - 6 & 5 cases in the overall vaccine & placebo groups
      - 0 & 1 in vaccine & placebo groups after the 1st dose
  - **3 doses at 2, 4, & 6 months of age**
  - **Added to the 2007 Recommended childhood schedule**

Zoster Vaccine Recombinant Adjuvated (Shingrix)

- Varicella virus recombinant gE antigen component + AS01B adjuvant suspension
- FDA-approved on Oct. 20, 2017
- Indication: adults ≥50 years of age including all who received prior live attenuated Zoster vaccine (Zostavax)
- 2 doses, with 2nd dose 2-6 months after the 1st

Adjuvants

- **Non-pathogen related additives that improve immunogenicity**
- **Aluminum salts are most common**
  - Hepatitis b vaccine, tetanus and diphtheria toxoids
- **Mechanisms of action?**
    - **Formation of an antigen depot at the inoculation site**
      - Water/oil emulsions & alum
    - **Mobilization of Th cell response:**
      - Protein carriers, polyA/polyU
    - **Up-regulation of Ig receptors on B cells:**
      - B-cell mitogens, antigen polymerizing agents
    - **Increased uptake by Antigen-presenting cells:**
      - MDP (muramyl dipeptide) derivatives, LPS, Lipid A
    - **Cytokine induction & secretion**

Impact of Vaccines in the 20th & 21st Centuries

Comparison of 20th Century Annual Morbidity & Current Morbidity

Disease	20th Century Annual Morbidity*	2017 Reported Cases†	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	15,808	92%
Tetanus	580	31	95%
Polio (paralytic)	16,316	0	100%
Measles	530,217	122	>99%
Mumps	162,344	5,629	97%
Rubella	47,745	9	>99%
CRS	152	2	99%
Haemophilus influenzae	20,000 (est.)	22§	>99%

* *JAMA*. 2007;298(18):2155-2163

† CDC. *National Notifiable Diseases Surveillance System, Week 52, 2017 Weekly Tables of Infectious Disease Data*. Atlanta, GA. CDC Division of Health Informatics and Surveillance, 2018. Available at: www.cdc.gov/nndss/infectious-tables.html. Accessed on January 4, 2018.

§ *Haemophilus influenzae* type b (Hib) <5 years of age. An additional 11 cases of Hib are estimated to have occurred among the 237 notifications of Hi (<5 years of age) with unknown serotype.

Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate

Disease	Pre-Vaccine Era Annual Estimate	2015 Estimate (unless otherwise specified)	% Decrease
Hepatitis A	117,333*	2,500†	98%
Hepatitis B (acute)	66,232*	19,200†	71%
Pneumococcus (invasive) All ages <5 years of age	 63,067* 16,069*	 29,000¶ 1,800¶	 54% 89%
Rotavirus (hospitalizations <3 years of age)	62,500‡	11,250§	82%
Varicella	4,085,120*	126,639††	97%

* *JAMA*. 2007;298(18):2155-2163

† CDC. Viral Hepatitis Surveillance – United States, 2014

¶ CDC. Unpublished. Active Bacterial Core surveillance. 2015

‡ CDC. *MMWR*. February 6, 2009 / 58(RR02); 1-25

§ New Vaccine Surveillance Network 2015 data (unpublished); U.S. rotavirus disease now has biennial pattern

†† CDC. MMWR. November 25, 2016 / 65(46);1306-1321 (2015 final data)