Vaccinology 101

January 12, 2021

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History of Vaccine development

- Concept of Vaccination as a Public Health Tool
- Immunology of Protection
  - Development of Protection
  - Life-long vs. Transient immunity
  - Types of immunogens:
    - Live vs. killed; whole vs. selected antigen; adjuvant; conjugated and combination vaccines
    - Mimic the natural route of infection vs. systemic administration
  - Active vs. passive protection
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
Principles of Vaccination

**General Rule:** the more similar a vaccine is to the disease-causing form of the organism, the “better” the immune response to the vaccine.

**Current Trend:** targeted immune response by exploiting conjugated carrier molecules, adjuvants, cytokines.....
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 pneumococcal 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
Primary and secondary antibody responses

- Primary antigen challenge
- Secondary antigen challenge

Log Ab titer vs. days

IgM and IgG response over time:
- Primary response
- Secondary response

Fig. 9.14, Immunology, 8th ed, Male, et al. 2013
How Does Immunization Strategy Influence the Choice of Vaccine?

Antibody responses to live and killed polio vaccine

Fig. 18.10, Immunology, 8th ed, Male, et. al. 2013
What Happens When a Vaccinee is Exposed to a Pathogen after being Immunized?
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:**
Current Technology

• Specific subunit/antigen(s), extracted, purified:
  - Acellular Pertussis Vaccines:
    • PT (Pertussis toxoid), FHA (filamentous hemagglutinin), Pertactin, Agglutinogens
  - Polysaccharides (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
    - Intussusception:
      - 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 $\geq 50$ years of age including all who received prior live attenuated Zoster vaccine (Zostavax)
- 2 doses, with 2$^{nd}$ dose 2-6 months after the 1st
Newer Vaccine Technologies

• 2015: Malaria (RTS,S/AS01)
  - Repeat T-cell Epitope, HBsAg/Adjuvant

• 2019: Ebola vaccines
  - rVSV-ZEBOV: VSV replication competent vectored-expressing Kikwit strain surface glycoprotein
  - Ad26.ZEBOV/MVA-BN-Filo:
    • Prime (adenovirus expressing Mayinga variant surface glycoprotein)
    • Boost (Modified Vaccinia Ankara expressing expressing GP from EBOV, SUDV, and MARV as well as TAFV NP

• 2019: COVID-19 vaccines:
  - mRNA constructs
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
Invasive Pneumococcal Disease

FIGURE 1. Changes in incidence rate* of invasive pneumococcal disease (IPD) among children aged <5 years before and after introduction of 7-valent pneumococcal conjugate vaccine (PCV7), by age and year — Active Bacterial Core surveillance, eight states,† 1998–2005

FIGURE 2. Projected number of invasive pneumococcal disease (IPD) cases prevented among children aged <5 years by 7-valent pneumococcal conjugate vaccine (PCV7), by age and direct or indirect effects — United States, 2005

*National projections of IPD cases calculated applying ABCs age- and race-specific rates to the age and racial distribution of the U.S. population using U.S. Census 2000 data.
†Calculated as a product of national projections of PCV7-type IPD cases among children aged <5 years in 1998–1999, PCV7 coverage (≥3 doses) for each birth cohort in 2001–2005, and PCV7 efficacy against PCV7-type IPD.
‡Calculated by subtracting national projections of PCV7-type cases in 2005 from average national projections of PCV7-type IPD cases in 1998–1999 and then subtracting PCV7-type IPD cases prevented directly.
§Calculated by subtracting national projections of non-PCV7-type cases in 2005 from average national projections of non-PCV7–type IPD cases in 1998–1999.

* Also pneumonia, otitis media
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<th>Disease</th>
<th>20th Century Annual Morbidity†</th>
<th>2019 Reported Cases ‡‡</th>
<th>Percent Decrease</th>
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<td>Smallpox</td>
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<td>Diphtheria</td>
<td>21,053</td>
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<td>Measles</td>
<td>530,217</td>
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<td>Mumps</td>
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<td>Pertussis</td>
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<td>Congenital Rubella Syndrome</td>
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<td>Tetanus</td>
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<td><em>Haemophilus influenzae</em></td>
<td>20,000</td>
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† JAMA. 2007;298(18):2155-2163
* Haemophilus influenzae type b (Hib) < 5 years of age. An additional 12 cases of Hib are estimated to have occurred among the 243 notifications of Hi (< 5 years of age) with unknown serotype.
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<th>Disease</th>
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<td>Hepatitis A</td>
<td>117,333 †</td>
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<td>Hepatitis B (acute)</td>
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<td>all ages</td>
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<td>&lt; 5 years of age</td>
<td>16,069 †</td>
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<td>Rotavirus (hospitalizations, &lt; 3 years of age)</td>
<td>62,500 † †</td>
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<td>Varicella</td>
<td>4,085,120 †</td>
<td>102,128 ###</td>
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† JAMA. 2007;298(18):2155-2163
†† CDC. MMWR. February 6, 2009 / 58(RR02):1-25
* CDC. Viral Hepatitis Surveillance - United States, 2016
# CDC. Unpublished, Active Bacterial Core Surveillance, 2016
## New Vaccine Surveillance Network 2017 data (unpublished); U.S. rotavirus disease now has biennial pattern
### CDC. Varicella Program 2017 data (unpublished)
Questions?
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<th>DTP 3+</th>
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Figure 5. Flu Vaccination Coverage Comparisons, United States, 2011–2019

The 2018–19 NHIS estimates are projected estimates of coverage through May 2019 based on estimated vaccinations received July–November 2018 using NHIS interviews conducted August–December 2018 and 2017–18 NHIS estimates by month.

https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm
### Table 1–A: Influenza vaccination coverage estimates by age group — United States,* 2007–08 through 2010–11

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<th>Estimate†</th>
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<th>2008-09†</th>
<th>2009-10 Seasonal (Trivalent)‡</th>
<th>2010-11</th>
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<td>%</td>
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