Vaccinology 101
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Course Number PB-VI01P: Development of a Vaccine During a Pandemic
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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 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
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 ≥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

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

* JAMA. 2007;298(18):2155-2163
§ *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.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Vaccine Era Annual Estimate</th>
<th>2015 Estimate (unless otherwise specified)</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>117,333*</td>
<td>2,500†</td>
<td>98%</td>
</tr>
<tr>
<td>Hepatitis B (acute)</td>
<td>66,232*</td>
<td>19,200†</td>
<td>71%</td>
</tr>
<tr>
<td>Pneumococcus (invasive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>63,067*</td>
<td>29,000‡</td>
<td>54%</td>
</tr>
<tr>
<td>&lt;5 years of age</td>
<td>16,069*</td>
<td>1,800‡</td>
<td>89%</td>
</tr>
<tr>
<td>Rotavirus (hospitalizations &lt;3 years of age)</td>
<td>62,500‡</td>
<td>11,250§</td>
<td>82%</td>
</tr>
<tr>
<td>Varicella</td>
<td>4,085,120*</td>
<td>126,639††</td>
<td>97%</td>
</tr>
</tbody>
</table>

* 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)