Vaccines

Smallpox

Edward Jenner
Variolation
Cowpox – Vaccination

Vaccines – active immunization
killed
subunit
live attenuated
toxoid

Passive immunization
injection of antibodies

Diphtheria
Disease due to local and disseminated action of bacterial toxin

*Corynebacterium diphtheriae*
Therapy – Antitoxin
Prevention – Toxoid vaccine
Epidemic in Russia due to falling vaccine coverage

*Haemophilus influenzae* B
Meningitis and sepsis in infants, significant mortality
Pathogenesis involves antiphagocytic capsular polysaccharide
Polysaccharide protein conjugate vaccine has essentially eliminated invasive *H. influenzae* disease

Polysaccharide antigens elicit poor antibody response, especially in young infants, limited memory response.
Protein-polysaccharide conjugate antigens elicit helper T cell activity resulting in good antibody response and memory cell production
Permits effective vaccines against bacterial pathogens with antiphagocytic capsular polysaccharides including *Streptococcus pneumoniae, Neisseria meningitidis*

Pertussis – Whooping cough

*Bordetella pertussis*
Can be fatal in infants under 3 months of age
Colonization of respiratory tract, production of multiple toxins that inhibit ciliary action and immune cell function
Killed whole cell (old) and acellular (current) vaccines
Concern about potential association with fatal seizures (later proven false) in ‘70s caused vaccine cessation in some countries resulting in massive pertussis epidemics
Beginning of “modern era of vaccine refusal” due to scientifically unjustifiable fear of vaccines
Major pertussis epidemic in Washington 2012
In US, vaccine refusal associated with increasing incidence of pertussis
Increase may also be due to reduced efficacy of acellular vaccine relative to older killed whole cell vaccine
Smallpox – a viral disease spread by respiratory route
- Variola major = smallpox virus
  - Begins with a high fever, skin rash progresses through vesicular and pustular forms
  - Mortality 10-30%
- Highly contagious – 30-80% of household contacts infected
- Large epidemics occurred
- Eradicated by vaccination - last known natural case occurred in Somalia in 1977

Variolation = inoculation
- Intentional infection with smallpox virus
- Origins uncertain, known in India and China since Eighth Century
- Introduced in England and the American Colonies in 1721
- Performed by rubbing material taken from a pustule of a smallpox patient into a scratch on the hand
- Variolated persons got the disease, but in a milder form
  - Likely due to route of infection (skin lesion vs. respiratory)
- Problems
  - Significant mortality associated with variolation
  - Variolated individuals were source of natural infections to others

Dr. Edward Jenner
- British physician noted milkmaids acquired a mild rash illness from cattle, cowpox, and did not acquire smallpox
- In 1796-1797, there was an outbreak of cowpox, and Jenner inoculated subjects with material prepared from human cowpox lesions, then intentionally infected (challenged) the subjects with smallpox material
- These subjects were completely protected from disease
- The practice of “vaccination” (from Latin vacca cow) quickly spread throughout Europe and by 1850 was mandated by law in a number of countries.

Vaccines – Active Immunization
- Vaccine - material derived from a microbial pathogen that induces an immunologically mediated resistance to disease
- Vaccine types:
  - killed + inactivated
    - many successful viral vaccines
    - whole bacteria likely to produce febrile reactions, no longer used in U.S.
  - subunit = acellular
    - specific factors which elicit immunity
      - polysaccharides, proteins,
      - conjugate vaccines-polysaccharides conjugated to a protein
  - live attenuated
    - multiple doses may be required
    - storage and maintenance of viability can be more difficult
  - toxoid
    - chemically inactivated (or mutated) toxin which retains antigenicity

Passive Immunization
- Injection of human or animal antibodies capable of providing immunity to a microbial pathogen
- Immunity is immediate, but short lasting
- Examples
  - Diphtheria, tetanus, botulinum antitoxins
  - Pooled human immunoglobulin to prevent hepatitis A virus infection
  - Human anti-rabies immunoglobulin for post exposure prophylaxis
  - Human Varicella-zoster immunoglobulin (VZIG) for post-exposure prophylaxis in high risk individuals
  - Human anti-hepatitis B immunoglobulin (HBIG) for post exposure prophylaxis

Diphtheria
- Corynebacterium diphtheriae
  - Gram-positive bacillus, member of normal human microbiota
  - Diphtheria
    - Acquired by respiratory route
    - Pharyngitis, respiratory obstruction, myocarditis
    - Mortality ~10% in infants, lower in older children and adults
  - Pathogenesis
    - Bacteria colonize the oropharynx
    - Produces a toxin that inhibits protein synthesis respiratory epithelium, heart muscle
  - Therapy
    - Maintain airway, provide antitoxin, treat with antibiotics
  - Prevention
    - Toxoid vaccine
      - Diphtheria toxin is chemically inactivated, but will elicit the production of antibodies capable of neutralizing active toxin
**Haemophilus influenzae B**

- *Haemophilus influenzae*
  - Gram-negative bacillus
  - Normal microbiota acquired by respiratory route
  - Meningitis, pneumonia, sepsis in infants 6–18 months of age
  - Mortality ~10% in infants
- Pathogenesis
  - Bacteria colonize the nasopharynx and respiratory tract
  - Bacterial invasion of respiratory epithelium
  - Capsular polysaccharide protects bacteria from opsonization by complement components
- Therapy
  - Antibiotics
- Prevention
  - Polysaccharide–protein conjugate vaccines
    - Purified polysaccharides are usually non-immunogenic in infants, immune response is poor in children and adults
    - Protein attached to polysaccharide antigen elicits helper T cells, allows a good response against the polysaccharide

**Polysaccharide-protein conjugate vaccines**

- 1988 *Haemophilus influenzae B*
- 2001 *Streptococcus pneumoniae*
- 2005 *Neisseria meningitidis*

**Pertussis**

- *Bordetella pertussis*
  - Gram-negative bacillus, difficult to isolate
  - Pertussis = whooping cough
    - Acquired by respiratory route
    - Prolonged severe coughing, vomiting, seizures, pneumonia
    - Mortality ~1% in infants under 3 months of age
- Pathogenesis
  - Bacteria colonize the nasopharynx and respiratory tract
  - Produce toxins that inhibit ciliary action of epithelium, and inhibit immune cell function
- Therapy
  - Supportive (oxygen, nasotracheal suctioning), antibiotics
- Prevention
  - Killed whole cell vaccine (no longer used in US, still in use in many countries)
  - "Acellular" vaccine: purified surface proteins, toxoids

**Hypotheses for basis of current pertussis epidemics in developed countries**

- Vaccine refusal
- Acellular vaccine not as effective
- Emergence of more virulent strains
  - Strains with mutation in toxin gene promoter produce increased amounts of toxin have appeared in US, Europe, Australia