Introduction to Vaccinology

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Immunity

- Immunity is the ability of the body to tolerate that is indigenous to it and eliminate material that is foreign
- Active Immunity
- Passive Immunity

Types of vaccines

- Live attenuated vaccines
- Inactivated vaccines
- Subunit vaccines
- Recombinant Vector vaccines
- DNA vaccines

Smallpox vaccine

Milestones in Vaccine Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1885</td>
<td>First use of live attenuated viral vaccine (variola) in humans</td>
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<tr>
<td>1909</td>
<td>First live attenuated bacterial vaccine (Bacillus Calmette-Guerin, or BCG) created for use against tuberculosis</td>
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<tr>
<td>1921</td>
<td>Diptheria toxoid developed</td>
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<td>1924</td>
<td>Tetanus toxoid produced</td>
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<td>1930s</td>
<td>Pertussis vaccine developed</td>
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<td>1952</td>
<td>Yellow fever vaccine developed</td>
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<td>1945</td>
<td>Diphtheria-tetanus-pertussis (DTP) combination introduced</td>
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<td>1955</td>
<td>Inactivated polio vaccine introduced</td>
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<td>1963</td>
<td>Live-attenuated oral polio vaccine introduced</td>
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<td>1963</td>
<td>Measles vaccine introduced</td>
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<tr>
<td>1986</td>
<td>First recombinant vaccine (Hepatitis B) introduced</td>
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<td>1990</td>
<td>First polysaccharide conjugate vaccine (Haemophilus influenza type b) introduced</td>
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Types of Vaccine

- Live attenuated
  - Viral, e.g., oral polio vaccine (OPV), measles, yellow fever
  - Bacterial, e.g., BCG

- Inactivated
  - Whole
  - Viral, e.g., inactivated polio vaccine (IPV)
  - Bacterial, e.g., whole-cell pertussis
  - Fractional
  - Protein-based
  - Subunit, e.g., acellular pertussis
  - Toxoid, e.g., diphtheria and tetanus
  - Polysaccharide-based
  - Puriﬁed, e.g., meningococcal
  - Conjugate, e.g., Haemophilus inﬂuenzae type b (Hib)

- Recombinant, e.g., Hepatitis B
Vaccines of the future

- Milk
- Bananas
- Tomatoes
- Patch
- DNA attached to gold micro-molecules
- Nasal spray vaccines

Vaccines in water?

CONCLUSION
In this hypothetical population consisting of only susceptible individuals, the disease can spread through the population exponentially, eventually infecting everyone because everyone will come in contact with an infected individual. Therefore, the growth rate of the infection is held in check with only a 75% immunization coverage rate.

Global Estimated Deaths Occurring and Prevented, 2000:
Measles, Neonatal Tetanus and Pertussis

Despite the slowdown of progress in the 1990s, over two million deaths were prevented in the past 10 years as a result of measles, pertussis, and tetanus immunizations alone (see graph). Clearly, however, the job is far from complete; approximately 900,000 children die each year from measles, 400,000 from pertussis, and 200,000 from tetanus.
Vaccines as a Practical Tool in Public Health

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Lecture 1

Two examples in world history of the successful deliberate eradication of human disease

Smallpox and Poliomyelitis

Smallpox: The Virus
- Variola virus
- "Crowd disease" - requires a large, densely populated area in order to propagate extensively (BRR=4)

Basic Reproductive Rate
- Number of new infections from single infected person
- Examples
  - High: Measles, BRR=>30
  - Moderately High: Rubella, BRR=12
  - Moderate: Smallpox, Polio, BRR=4
  - Low: Malaria in the USA or Italy, BRR=1.1

Smallpox Transmission
- Moderately contagious
- Transmitted through saliva or by direct contact with the lesions on the skin
- People with cough most infectious

Symptoms
- After 12-14 day incubation period
  - Fever to 41°C.
  - Chills
  - Back/Headaches
  - Nausea
- Four days later
  - Some relief
  - Rashes appear on face, chest, arms, back, and legs
- Next few days
  - Spots change to raised, blister-like pustules
- Nine days
  - Postulates split open, dry up, and form scabs, which will fall off and leave scars
Treatment

- No medicines available to treat smallpox once lesions begin to develop
- Vaccine available since 1796

Smallpox History - I

- Believed to have appeared at the time of the first agricultural settlements in northeastern Africa, around 10,000 BC
- Earliest evidence of skin lesions resembling those of smallpox found on mummies from the time of the 18th-20th Egyptian Dynasties (1570 to 1085 BC) and in the mummy of Ramses V, a young man who died in 1157 BC

Smallpox History - II

- Smallpox epidemic recorded in 1350 BC during the Egyptian-Hittite war
- Smallpox described in 910 AD in De variolis et morbillis commentarius
  - Disease survivors were later immune to it
  - Illness transmitted from person to person
  - First theory of acquired immunity: Rhazes explanation of why survivors of smallpox do not develop the disease again

Smallpox History - III

- The large-scale epidemic, “the plague of Antonine,” killed 3.5-7.0 million persons in AD 180 contributed to the fall of the Roman Empire
- Introduced into the Americas by Spanish and Portuguese conquistadors
  - When Spanish arrived in 1518, Mexico had 25 million inhabitants; by 1620, population was 1.6 million

Smallpox Case-Fatality Rate

- Variable CFR
  - Variola minor <2%
  - Variola major 20-70%
  - Fulminating smallpox 99%
- Among children <5 years of age with smallpox in the 18th century, 80% died in London, 98% in Berlin

Smallpox History - IV

- As recently as 1970
  - Smallpox endemic in 31 countries
  - 10-15 million persons developed smallpox yearly
  - >2 million persons died of smallpox each year
The Art of Variolation - I
- Material from vesicles, pustules, or scabs from mild patients introduced into others via the nose or skin
- Introduced into England by Lady Montague in 1721 from her Constantinople experience

The Art of Variolation - II
- 2-3% of variolated persons...
  - Died of smallpox
  - Became the source of a new epidemic; or
  - Developed other illnesses from the lymph of the donor, such as tuberculosis or syphilis
- Yet CFRs 10 times lower than with naturally occurring smallpox

Edward Jenner (1749-1823)
- Observation: milkmaids with past cowpox had fair skin, i.e., no pock scars
- In 1796, Jenner used cowpox fluid pustule from Sarah Nelmes to inoculate 8-yr-old James Phipps via two half-inch arm incisions
- Six weeks later, Jenner variolated the child with no reaction

Inquiry: The Causes and Effects of the Variolae Vaccinae
- Article sent to the Royal Society rejected
- Decided to finance its publication himself
- Described 10 vaccinees and 13 persons with past cowpox in whom variolation was unsuccessful

Smallpox Eradication
- Last recorded "wild" case of smallpox
- Somalia October 1977
- Ali Maalin (23yrs)

Smallpox Eradication
- Last human smallpox in U.K in 1978
- Virology laboratory with very poor safety precautions
- Viral airborne transmission to closed space, a dark room, two flights away where a hospital photographer was infected and died
- (Virology lab director committed suicide)
**Why were we successful with smallpox? - I**
- Relatively low BRR
- Herd immunity feasible with relatively low overall coverage
- Excellent vaccine, lyophilized, stable Vaccinia incubation period 2 days less than variola

**Why were we successful with smallpox? - II**
- No animal reservoir
- Pock mark scars facilitate epidemiology
- One serotype, no mutations
- Seasonal transmission with natural nadir enabling surveillance-containment strategy

**Why were we successful with smallpox? - III**
- Obvious clinical syndrome
- Global collaboration despite cold war
- Strong national and international commitments of expertise and $$
- Motivated local populace

**Two examples in world history of the successful deliberate eradication of human disease**

Smallpox and Poliomyelitis

**History of Polio - I**
- 3700 B.C.: Earliest evidence of polio in the bone formation of an Egyptian skeleton
  - Polio was rare in ancient times due to poor sanitation and infection of very young infants who do not get paralytic disease but acquire immunity
  - Polio epidemics in 20th century, mainly in industrialized countries
History of Polio - II

- 1908: Landsteiner determines that polio is a virus rather than bacteria.
- 1916: One of the largest epidemics of the century occurs, paralyzing 27,000 people and killing 9,000.
- 1952: 558,000 people contract polio, leaving thousands permanently afflicted.

History of Polio - III

- 1954: Nobel Prize awarded to Enders, Weller and Robbins for culturing poliomyelitis viruses
- 1954: First inactivated polio vaccine announced by Dr. Jonas Salk
- 1.8 million school children participate in trials of the inactivated vaccine
- 1961: Dr. Albert Sabin’s oral polio vaccine approved for use by the AMA based on Russian clinical trials

Polio Vaccine: Salk

- Killed virus vaccine
- Safer than the live virus vaccine
  - In 1955, 204 cases or 0.01% of the total vaccinated children developed polio
  - 3% of the cases were paralytic
  - 11 of the victims died
  - All attributed to seven sets of the vaccine produced in by Cutter Laboratories in California
- Requires multiple shots to achieve full immunity

Polio Vaccine: Sabin

- Live attenuated oral vaccine
- More effective than killed vaccine
  - Oral dose with partial immunity from even one vaccine excellent for developing countries
- In 1957, twenty field trials were conducted of the three oral vaccines, Sabin’s included – all were approved by the WHO in 1964
- The most dramatic effect of the Sabin type vaccine was shown in the US
  - Annual polio incidence of 37,864 from 1951-1955 fell to 570 from 1961-1965, a decrease of 99.98%
Global Polio Eradication Strategy

- High routine TOPV immunization coverage
- Supplementary immunization with national immunization days (NIDs)
- Effective surveillance for Acute Flaccid Paralysis and wild virus
- Door-to-door immunization (“mopping up” campaigns)

Polio Eradication

- Last case in United States in 1979
- Last case in Western Hemisphere in 1991 until DR/Haiti cases in 2000
- Western Hemisphere certified polio free (sic) in 1994
- Global eradication goal by 2000—now anticipated to occur in 2002 or later in decade

Countries reporting wild poliovirus in 2000, as of 30 Oct 2000

- Certified or polio-free
- Zero wild viruses
- Less than 99 wild viruses
- 10 to 99 wild viruses
- More than 99 wild viruses
Polio Eradication Milestones
- Development of systematic genomic sequencing
- Mass vaccination
  - 76 million children immunized in 17 West and Central African countries during "synchronized" NIDs in 2000
  - 152 million children immunized in India in December of 2000
- Largest coordinated network of public health laboratories

Priority Countries
- Poliovirus reservoirs with high transmission rates
  - Bangladesh
  - Ethiopia
  - India
  - Nigeria
  - Pakistan
- Conflict impedes vaccination and surveillance activities
  - Afghanistan
  - Angola
  - Democratic Republic of Congo
  - Somalia
  - Sudan

Why will we be successful with polio? - I
- Relatively low BRR
- Herd immunity feasible with relatively low overall coverage
  - "free vaccines" due to fecal-oral spread
- Excellent trivalent vaccine, oral, stable if frozen

Why will we be successful with polio? - II
- Three serotypes, no mutations
- No animal reservoirs
- Obvious clinical syndrome, though most cases asymptomatic

Why will we be successful with polio? - III
- Global collaboration despite cold war (to 1989)
- Strong national and international commitments of expertise and $$
- Motivated local populace
- Public-private partnerships with Rotary International