History of vaccination

- Vaccination is a practice of deliberately stimulating immune system in order to protect individuals against a disease.
- Vaccination is used worldwide and have resulted in eradication or low incidences of many diseases such as smallpox, measles, whooping cough, mumps and poliomyelitis.
- It was recognized that individuals who recovered from a diseases such as smallpox rarely contracted it a second time.
- Old Chinese writing describes the procedure of 'variolation'.
- In variolation, small amount of the powered crusts of small pox pustules were inhaled or placed in a scratch made in the skin. And this resulted in a permanent immunity to small pox.

History of vaccination

- Edward Jenner noted that milkmaids who suffered from cowpox rarely suffered from smallpox.
- Using this observation, he conducted a classic experiment in which he deliberately transferred material from a cowpox lesion from a maid to a scratch in the arm of a young boy.
- Six weeks later he exposed the boy to the pus from a smallpox victim, but boy did not develop the disease and became immune to smallpox.
- Using this less dangerous cowpox material in place of the pustules from smallpox cases, Jenner and others worked to spread the practice of variolation.
- Later, Pasteur used the word vaccination to describe any type of protective inoculation.

History of vaccination cont'd

- WHO initiated a program of intensive smallpox vaccination in 1967.
- As there is no animal hosts and no non-immune humans to whom small pox could be spread, the disease died out and in 1979 WHO declared the world free of smallpox.
- Smallpox is a matter of concern for bioterrorism because of largely unprotected populations of the world.
- Vaccinia virus used for vaccination against smallpox in recent years is neither the cowpox nor the small pox virus and it is not clear where this virus originated.
- Some scientists think that vaccinia virus is a hybrid of the cowpox and smallpox viruses.
- Vaccinia virus has been genetically engineered in recent years to make experimental vaccines against other diseases such as AIDS and viral hepatitis.

Principles of immunization

- Naturally acquired immunity is the acquisition of adaptive immunity through normal events such as an exposure to infectious agent.
- Immunization mimics those same events, protecting against disease by inducing artificially acquired immunity.
- The protection acquired by immunization can be active or passive.
- Active immunity is the result of an immune response upon exposure to an antigen. It provides immunological memory.
- Passive immunity can occur both naturally (mother to fetus) or artificially and provides no memory e.g. antitoxin, antiserum etc.
- 'Immune serum immunoglobulin' or 'gamma globulin' (IgG) is given to travelers and immunosuppressed people.
- Hyperimmune globulin is used to prevent and treat specific diseases such as tetanus, rabies, hepatitis A and B.

Principles of immunization

	Active	Passive
Natural	Natural exposure to antigen induces an immune response; immunity following an attack of measles.	Transfer of antibodies or cells produced by others; temporary immunity from antibodies of the mother transferred to infant across the placenta or in milk.
Artificial	Deliberate exposure to antigen induces an immune response; immunization of children.	Antibodies in immune serum are introduced into body; injection of rabies immune globulin after a dog bite.

Vaccines and immunization procedure

- A vaccine is a preparation of a disease-causing agent or its products used to induce active immunity.
- Vaccines not only protect an individual against disease, they can also prevent diseases from spreading in a population.
- When a critical portion of a population is immune to the disease, either through natural immunity or vaccination, phenomena is called herd immunity.
- Herd immunity help in preventing the spread of an infectious disease because of lack of susceptible hosts.
- Herd immunity is responsible for dramatic declines in childhood diseases.
- Unfortunately, some of the diseases reappear and spread as a direct consequence of parents failing to have their children vaccinated.

Vaccines

- Effective vaccines should be
  - safe with few side effects
  - Low in cost
  - Stable with a long shelf-life
  - Easy to administer.
  - should give long lasting immunity against specific disease
  - should induce specific antibodies or immune cells, or both
  - Example, polio vaccine should induce antibodies which can neutralize polio virus while effective tuberculosis vaccine should induce cellular immunity that can limit the growth of the intracellular bacteria.
- Vaccines falls in two general categories
  - Attenuated vaccines
  - Inactivated vaccines

Attenuated vaccines

- An attenuated vaccine is a weakened form of the disease-causing microorganisms generally unable to cause disease.
- The attenuated strains replicates in the vaccine recipient, causing an infection with detectable or mild disease that typically results in long-lasting immunity.
- Generally induces appropriate immunity required for the control of infection.
- Usually involves successively culturing of microbes under a given set of conditions, resulting in a gradual accumulations of mutations that make it less able to cause disease.
- Example: Pasteur used anthrax and chicken cholera grown at higher than normal temperatures. Human viruses may be attenuated by growing in cells of a different animal species.
- Genetic manipulation is now used to produce strains with low virulence as wild type-genes replaced with mutated genes which can not revert to wild type.
- Genes can be deleted from vaccine virus strains to make them safer and to differentiate them from wild type.

Attenuated vaccines

- Attenuated vaccines have several characteristics that make them more desirable than their inactivated counterparts.
  - single dose is sufficient to induce long-lasting immunity,
  - provide greater amounts of antigen as organisms multiply or replicate
  - longer exposure of immune system to antigen
  - has added potential of being spread from an individual being immunized to other non-immune people.
- Disadvantages of attenuated vaccines are
  - potential to cause disease in immunosuppressed people,
  - rarely they can revert or mutate to strains that cause serious disease
  - Avoid giving to pregnant women, because microbes can cross placenta and can cause damage or disease in fetus.
  - need refrigeration to keep them active.
- Attenuated vaccines which are in widespread use include Sabin polio vaccine, measles, mumps, rubella and yellow fever vaccines

Inactivated vaccines cont'd

- An inactivated vaccine is unable to replicate but retains the immunogenecity of the infectious agent or toxin.
- Inactivated vaccines fall in two categories:
  - Whole agents
  - fractions of the agent.
- The advantage of inactivated vaccines is that they cannot cause infections or revert to dangerous forms.
- Disadvantages:
  - As they do not replicate, the magnitude of immune response is limited
  - they have to be administered several times to induce protective immunity.

1. Inactivated whole agent vaccines: contain killed microorganisms or inactivated viruses. They are prepared with a chemical such as formalin which does not significantly change the surface epitopes.
   - Examples: cholera, plague, influenza, rabies and Salk polio vaccine.

Inactivated vaccines cont'd

2. Toxoids: are inactivated toxins. They are prepared by destroying toxic part of the molecules while retaining antigenic epitopes.
   - Diphtheria and tetnus vaccines are toxoids. An initial series of doses given in childhood, followed by booster vaccines every 10 years.
3. Protein subunit vaccines: are composed of important proteins or antigenic fragments of an infectious agent which are considered important in inducing protective immunity, rather than whole cells or viruses.

- Advantage of subunit vaccines is that parts of the microbes that sometimes cause undesirable side effects are not included in the vaccines.
- Example: Whooping cough (pertussis) killed vaccine previously used in children caused serious side effects. But a subunit vaccine, referred as acellular pertussis (aP) vaccine does not cause side effects and has now replaced the killed whole cell vaccine.

Inactivated vaccines cont'd

4. Recombinant vaccine: is a subunit vaccine produced by genetically engineered microorganisms.
   - Example: Vaccine against Hepatitis B virus.
5. Polysaccharide vaccines: are composed of the polysaccharides that make up the capsule of certain organisms.

- They usually elicit IgM response, provide no memory and elicit a poor response in children.

6. Conjugate vaccines: represent an improvement over purified polysaccharide vaccines because they are effective in young children.

- Polysaccharides are intentionally converted into T-dependent antigens by conjugating to proteins. Example: *Heamophilus influenzae* type b and *Streptococcus pneumoniae*.

Inactivated vaccines cont'd

- Many inactivated vaccines contain an adjuvant, a substance that enhances the immune response to antigens.
- Adjuvants are necessary additives as purified antigens such as toxoids and subunit vaccines are often poorly immunogenic by themselves as they lack danger signals, the pattern associated with tissue damage or invading microbes.
- Adjuvants are thought to work by providing the danger signals to antigen presenting cells such as dendritic cells.
- Some adjuvants appear to absorb the antigen and release it at a slow but constant rate to the tissues and surrounding blood vessels.
- Unfortunately, many effective adjuvants cause an intense inflammatory response, making them unsuitable for use in human vaccines.
- Currently the only adjuvant approved in US for use in human vaccines is alum (aluminum hydroxide and aluminum phosphate)

Table 17.2 A Comparison of Characteristics of Attenuated and Inactivated Vaccines

Characteristic	Attenuated Vaccine	Inactivated Vaccine
Antibody response	IgG; IgA if administered orally	IgG
Cellular immune response	Good	Poor
Duration of protection	Long-term	Short-term
Need for adjuvant	No	Yes
Number of doses	Usually single	Multiple
Risk of mutation to virulence	Very low	Absent
Route of administration	Injection or oral	Injection
Stability in warm temperatures	Poor	Good
Types	Attenuated viruses, attenuated bacteria	Inactivated whole agents, toxoids, subunit vaccines, polysaccharide vaccines

Table 17.1 Some Important Immunizing Agents for Humans

Disease	Type of Vaccine	Persons Who Should Receive the Vaccine
Anthrax	Acellular	People in occupations that put them at risk of exposure, such as military personnel
Diphtheria	Toxoid	Children; adults receive a booster every 10 years
Haemophilus influenzae type b infections	Polysaccharide-protein conjugate	Children
Hepatitis A	Inactivated virus	Children who live in selected regions, people traveling to certain parts of the world
Hepatitis B	Protein subunit is produced by genetically engineered *Saccharomyces cereviseae* and purified	Children, adults in high-risk groups such as IV drug abusers, health care workers who might be exposed to infected blood, and contacts of infected people, homosexual men, and people who have multiple sexual partners
Influenza	Inactivated virus, usually given by injection in the United States, but as a nasal spray in parts of Europe	Adults over age 50, medical personnel, and people at increased risk for complications; given yearly, as the antigens of the virus change frequently
Measles	Attenuated virus	Children, people entering college, adults born after 1956 who have not been immunized, travelers to foreign countries, and HIV-infected people without severe immunosuppression
Meningococcal disease	Purified polysaccharide (4 serotypes)	Children and adults with certain conditions that put them at greater risk (for example, those without a spleen or who have certain complement system defects); people traveling to sub-Saharan Africa

Table 17.1 Some Important Immunizing Agents for Humans

Disease	Type of Vaccine	Persons Who Should Receive the Vaccine
Mumps	Attenuated virus	Same as measles
Pertussis (whooping cough)	Acellular vaccine given together with diphtheria and tetanus toxoids (DTaP)	Children
Pneumococcal infection	Two forms—purified polysaccharide (PPV) and polysaccharide-protein conjugate (PCV)	Children should receive PCV; adults over 65, people with certain chronic infections, and others in high-risk groups should receive PPV
Rabies	Inactivated virus grown in human or rhesus monkey cells	People exposed to the virus, people at high risk for exposure, such as veterinarians and other animal handlers
Rubella (German measles)	Attenuated virus	Children, adults (particularly women) who are susceptible, health care workers who are at high risk of exposure
Tetanus	Toxoid	Children; adults receive a booster every 10 years
Tuberculosis	Attenuated BCG strain of tuberculosis bacteria	Used only in special circumstances in the United States; widely used in other countries
Typhoid fever	Two forms—attenuated bacteria (taken orally) and purified polysaccharide	People traveling to certain parts of the world
Varicella-zoster (chickenpox)	Attenuated virus	Children; may also be given to susceptible adults
Yellow fever	Attenuated virus	Travelers to affected areas

Vaccination strategy for poliomyelitis

- Polio virus enters the body orally and infects the throat and intestinal tract and then enter blood stream. From there, it may invade nerve cells and cause disease poliomyelitis.
- There are three types of polio virus and any one of them can cause poliomyelitis.
- The Salk vaccine developed in mid 1950s consists of all three types of inactivated viruses.
- This vaccine was quite successful in lowering the rate of disease but it had disadvantage of requiring multiple of injection over a period of time.
- In 1961, the Sabin vaccine, attenuated vaccine became available with the advantage of cheaper oral vaccination.
- But Sabin vaccine although it replicates in intestine still need three doses rather than one because of interactions among the three types of viruses present in the vaccine.
- Both attenuated and inactivated polio vaccines induce circulating antibodies and prevent viral invasion of central nervous system and consequently paralytic poliomyelitis.

Vaccination strategy for poliomyelitis

- The Sabin vaccine has the advantage that it induces mucosal immunity and potentially provides herd immunity.
- Polio vaccination was so successful that by 1980, US was free of wild-type poliovirus.
- However, poliomyelitis still occurred occasionally, caused by the vaccine strain; ~one case for every 2.4 million doses of Sabin vaccine. And only way was to avoid Sabin vaccine in favor of Salk vaccine.
- But situation was not as simple as it might seem.
- The Sabin vaccine, unlike Salk vaccine, prevents transmission of the wild-type virus should it ever be reintroduced to the population.
- If only the inactivated vaccine is given, the virus can still replicate in GI tract and be transmitted to others, rapidly spreading in a population.

Vaccination strategy for poliomyelitis

- A campaign to eliminate polio was so successful that by 1997, the worldwide incidence of polio decreased substantially.
- A vaccine strategy to capture the best of both vaccines was adopted.
- Children first received doses of the Salk virus, protecting them from poliomyelitis; following these doses the Sabin vaccine was given, providing mucosal protection while also boosting immunity.
- Efforts to globally eradicate polio by 2005 are underway.

The importance of routine immunizations

Table 17.3 The Effectiveness of Universal Immunization in the United States

Disease	Cases per Year Before Immunization	Decrease After Immunization
Smallpox	48,164 (1900–1904)	100%
Diphtheria	175,885 (1920–1922)	Nearly 100%
Pertussis (whooping cough)	147,271 (1922–1925)	95.7%
Tetanus	1,314 (1922–1926)	97.4%
Paralytic poliomyelitis	16,316 (1951–1954)	100%
Measles	503,282 (1958–1962)	Nearly 100%
Mumps	152,209 (1968)	99.6%
Rubella (congenital syndrome)	823 (estimated)	99.4%
Haemophilus influenzae type b infections	20,000 (estimated)	99.7%

- But even now, nearly 20% of American children are not fully immunized and many Americans becomes ill or even die every year from diseases that are readily prevented by vaccines.
- One reason some children are not fully vaccinated is that parents have refused to have their children vaccinated, fearing rare chance that immunization procedure might be harmful.

Table 17.4 Recommended Childhood Immunization Schedule in the United States (2002)

Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24mo	4–6 yrs	11–12 yrs	13–18 yrs
Hepatitis B												
Diphtheria, tetanus (Td), acellular pertussis (DTaP)			DTaP	DTaP	DTaP		DTaP			DTaP	Td	
Haemophilus infuenzae type b (Hib)												
Poliovirus (IPV—inactivated polio vaccine)												
Measles-mumps-rubella (MMR)												
Varicella (chickenpox-Var)												
Pneumococcal												

Range of acceptable ages for vaccination indicated by colors:
First dose   Second dose   Third dose   Fourth dose   Subsequent doses   Catch-up vaccinations

Since children need a minimum of 15 separate injections to complete immunization schedule from birth to six years, it is desirable that several vaccines be combined into a single preparation.

Current progress in immunization

- Recent advances in immunology provide researchers with the biological tools required to make safer and more effective vaccines. Progress is occurring in several fronts
  - Enhancement of the immune response to vaccines
  - Development of new or improved vaccines against certain diseases
  - Development of new type of vaccines
- Examples: conjugate vaccine, toll like receptors helping in designing new adjuvants
- Novel vaccine methods: Peptide vaccines, edible vaccines and DNA-based vaccines.
- Some diseases for which new or improved vaccines are sought include

HIV/AIDS	Malaria	Influenza
Strep throat	Genital Herpes	Hepatitis C
Cancer		