Vaccines in prevention of viral infections

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Vaccine

- A vaccine typically contains an agent that resemble a disease causing microorganisms, and is often made from weakened or killed forms of the microbe, its toxins or its surface proteins.
- The vaccine stimulates the body's immune system to recognize the agents as foreign, destroy it, and remember it, so that the immune system can more easily recognize and destroy any of these microbes that it later encounters.
- Vaccines may be:
  - Prophylactic-prevent/ ameliorate the effect of a future infection.
  - Therapeutic – cancer vaccine
- Term vaccine – Edward Jenner 1796 (cow pox virus against small pox)

Types of Vaccines

- Killed
- Attenuated
- Toxoid
- Subunit
  - Non-recombinant subunit vaccine
  - Recombinant subunit vaccine
- Conjugate
- Recombinant virus vaccines or live recombinant vaccines
- DNA Vaccine
- Edible vaccine

Killed vaccines

- Some vaccines contain killed, but previously virulent, micro-organisms that have been destroyed with chemicals or heat.
- Examples are the influenza vaccine, cholera vaccine, bubonic plague vaccine, polio vaccine, hepatitis A vaccine, and rabies vaccine

Attenuated Vaccine

- Many of these are live viruses that have been cultivated under conditions that disable their virulent properties, or which use closely-related but less dangerous organisms to produce a broad immune response; however, some are bacterial in nature.
- They typically provoke more durable immunological responses and are the preferred type for healthy adults.
- Examples include the viral diseases yellow fever, measles, rubella, and mumps and the bacterial disease typhoid. The live Mycobacterium tuberculosis vaccine developed by Calmette and Guérin is not made of a contagious strain, but contains a virulently modified strain called "BCG" used to elicit an immune response to the vaccine. The live attenuated vaccine containing strain Yersinia pestis EV is used for plague immunization.

Toxoid Vaccine

- Toxoid vaccines are made from inactivated toxic compounds that cause illness rather than the micro-organism.
- Examples of toxoid-based vaccines include tetanus and diphtheria.
- Toxoid vaccines are known for their efficacy.
- Not all toxoids are for micro-organisms; for example, *Crotalus atrox* toxoid is used to vaccinate dogs against rattle snake bites.

Subunit vaccines (non-recombinant and recombinant)

- Non-recombinant subunit vaccine
  - In case of non-recombinant subunit vaccine antigens must be produced and purified by cultivation of pathogen. Example : the subunit vaccine against Hepatitis B virus previously extracted from the blood serum of chronically infected patients.

- Recombinant subunit vaccine
  - These vaccines are those in which genes for desired antigen are inserted into vector, usually a virus. The antigen is purified and injected as vaccine.
  - Hepatitis B vaccine that is composed of only the surface proteins of the virus now produced by recombination of the viral genes into yeast.
  - Virus-like particle (VLP) vaccine represents a specific class of recombinant subunit vaccine that mimic the structure of authentic virus particles.
    - They are recognized readily by the immune system and present viral antigens in a more authentic conformation than other subunit vaccine.
    - They can be synthesized through the individual expression of viral structural proteins which can be then self assemble into virus-like structure. Combinations of structural capsid proteins from different viruses can be used to create recombinant VLPs.
    - Example: human papillomavirus (HPV) that is composed of the viral major capsid protein, and the hemagglutinin and neuraminidase subunits of the influenza virus.

Conjugate Vaccine

- Certain bacteria have polysaccharide outer coats that are poorly immunogenic.
- By linking these outer coats to proteins (e.g. toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen.
- Example: *Haemophilus influenzae* type B vaccine

Recombinant virus vaccines or live recombinant vaccines

- A gene coding for an immunogenic protein from one organism into the genome of other, such as vaccinia virus is introduced.
- The organism expressing that gene is called as recombinant.
- Following injection into the subject, the recombinant will replicate and express sufficient amount of the foreign protein to induce a specific immune response to the protein.
- Can also encode for several antigens from different pathogens, introducing the possibility of a single vaccine for several diseases (Polyvalent vaccine).
- Example vaccine for poultry against fowl pox and new castle disease.

DNA vaccine

- In recent years a new type of vaccine called *DNA vaccination*, created from an infectious agent's DNA, has been developed.
- It works by insertion and expression of viral or bacterial DNA into human or animal cells.
- Some cells of the immune system that recognize the proteins expressed will mount an attack against these proteins and cells expressing them.
- Because these cells live for a very long time, if the pathogen that normally expresses these proteins is encountered at a later time, they will be attacked instantly by the immune system.
- One advantage of DNA vaccines is that they are very easy to produce and store.
- As of 2006, DNA vaccination is still experimental.

Edible Vaccine

- Genes coding for significant antigens are introduced into plants, such that the fruits produced bear foreign antigens.
- This is edible vaccine and is still in experimental stage.
- Transgenic tobacco is successfully engineered for the production of edible vaccines against Hepatitis B antigen using‘s gene of HBV (Hepatitis B Virus). The optimum level of recombinant protein was obtained in leaves and seeds.
- Potato is one of the best sources for vaccine production but the raw potatoes are not palatable and cooking destroys protein antigens. Vaccine for cholera is successfully developed in potato.
- Banana is the ideal plant for oral vaccine production due to its excellent digestibility, palatability and availability throughout the year. Vaccine for hepatitis B is successfully made in banana.

AIDs Vaccine

- The genetic variability of HIV has thus far hampered the development of an AIDs vaccine.

Strategies:

- **Use of antibodies** to envelop protein, gp120 to bock CD4-gp120 interactions and thus block infection.
  - Gene encoding gp120 mutates frequently
- **Subunit vaccines**- genes for several HIV envelop proteins have been engineered into vaccinia virus or adenovirus particle (clinical trials underway)
- **Killed intact HIV**- restricted to use in HIV infected individuals. (100% HIV may not kill during inactivation)
- **Live attenuated vaccines** – HIV2 cause mild form of disease with very long latent period, protect person from infection with HIV1 (associated risk is that integration of virus may cause cancer, mutation might reactivate virulence and so on).

...AIDs Vaccine

- **Anti-idiotype antibodies**- **A vaccine made of antibodies that see other antibodies as the antigen and bind to it**.
- Antibodies to CD4 are used as antigen that raise the antibodies, which resemble the molecular configuration of CD4 (idiotype means binding site).
- Anti-idiotype antibodies could then bind HIV particles by gp12-CD4 type interaction.
- **Soluble CD4**- The CD4 protein itself as an AIDs antagonist (soluble CD4 a product of RDT).
- Soluble CD4 could interact with HIV and block its attachment.
- Not useful for AIDs patients as these individuals lack significant immune function and thus would not respond to a vaccine.

Polio vaccines

- **Polio vaccines** are vaccines used to prevent poliomyelitis (polio).
- Poliovirus infection can provide lifelong immunity against the disease, but this protection is limited to the particular type of poliovirus involved [(Type 1 (Mahoney), 2 (MEF-1), or 3(Saukett)].
- Infection with one type does not protect an individual against infection with the other two types.
- The development of effective vaccines to prevent paralytic polio was one of the major medical breakthroughs of the 20th century.
- Two different kinds of vaccine are available:
  - An inactivated (killed) polio vaccine (IPV) developed by Dr. Jonas Salk and first used in 1955, and
  - A live attenuated (weakened) oral polio vaccine (OPV) developed by Dr. Albert Sabin and first used in 1961.
- Both vaccines are highly effective against all three types of poliovirus.

Inactivated polio vaccine (IPV)

- IPV is produced from wild-type poliovirus strains of each serotype that have been inactivated (killed) with formalin.
- As an injectable vaccine, it can be administered alone or in combination with other vaccines (e.g., diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenza).
- Salk vaccine is produced by growing wild virulent reference strains in a type of monkey kidney tissue culture which are then inactivated with formalin.
- HeLa cells were used by Jonas Salk to test the first polio vaccine in 1950s.
- This immortal cell line was derived from cervical cancer cell taken from Henrietta Lacks, a patient.
- They were easily infected by virus, causing infected cells to die. This made HeLa cells highly derirable for polio vaccine testing since results could be easily obtained.
- 60-70% effective against type 1
- 90% effective aganst PV2 and PV3

Oral polio vaccine (OPV)

- OPV consists of a mixture of live attenuated poliovirus strains of each of the three serotypes, selected by their ability to mimic the immune response following infection with wild polioviruses, but with a significantly reduced incidence of spreading to the central nervous system.
- Produced by passage of virus through non-human cells at a sub-physiological temperature, which produces spontaneous mutations in the viral genome.
- There are 57 nucleotide substitutions which distinguish the attenuated Sabin 1 strain from its virulent parent.
- Two nucleotide substitutions attenuate type 2 Sabin.
- Ten substitutions are involved in attenuating Sabin 3 strain.
- Mutations located in virus's internal ribosome entry site-reduces the ability of poliovirus to translate its RNA template with in the host cell.
- Vaccine contains small traces of neomycin and streptomycin as one vial contain 10-20 doses.

Small Pox Vaccine

- Small pox vaccine was introduced by Edward Jenner in 1796.
- Found hat persons previously infected with cow pox did not later catch small pox.
- Smalpox vaccine is made from vaccinia virus which is another “pox” type virus related to smallpox but cannot cause small pox.
- Until the end of 19th century vaccination was done either directly with vaccine produced on the skin of calves

or

- Particularly in England, with vaccine obtained from calf but then maintained by arm to arm transfer – risk of transfer of other diseases eg.- tuberculosis, tetanus.

… Small Pox Vaccine

- Given the different set of vaccines available:
- **Ist generation vaccine:** used during the eradication campaign and made from the lymph or skin of inocuated animals.
- Contained live vaccinia virus administered by puncturing the skin of upper arm by bifurcated needle.
- **2nd generation vaccine:** produced in tissue culture, contain replication competent virus (used during end of eradication period).
- **3rd generation vaccine:** attenuated vaccine strains specifically developed as safer vaccine at the end of eradication phase by further passage in cell culture or animal.
- **Next generation vaccine:** developed is now focussing in a variety of subunit (protein & RNA based) in order to create safer, yet still efficacious smallpox vaccines.