MODERN VACCINES

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What is a vaccine?

Whole or a portion of the pathogen's structure that upon administration stimulates antibody production or cellular immunity against the pathogen but is incapable of causing severe infection.

The goal of vaccination is to prime the immunity against pathogens (or toxins) without causing disease.
Importance of vaccines

• Vaccines are one of the greatest achievements of medical science

• Vaccines have consigned dreaded diseases like smallpox to history and some others including polio are on the verge of extinction.

• At least 3 million lives are saved every year and if vaccination is available to everyone the number will be 4.5 million.
Components of the Immune System

- **Innate**
  - Humoral: complement, interferon, TNF etc.
  - Cellular: macrophages, neutrophils

- **Acquired**
  - Humoral: antibodies, cytokines
  - Cellular: T & B cells; other effector cells and dendritic cells
Vaccination

It protects a recipient from a pathogenic agent.

Active immunity is produced by vaccines.

Immunity and immunologic memory similar to natural infection but without risk of disease.

General rule

The more similar a vaccine is to the natural disease, the better the immune response to the vaccine
Booster doses

Boosting a vaccine involves revaccination by the same or some other vaccine.

Booster doses help in raising sufficiently large immune response to be effective in protecting against disease.

Boosting helps to replenish the immune response after a long period (e.g., 10 years as is the case for tetanus vaccine).
TYPES OF VACCINES

A. TRADITIONAL VACCINES

A-1. Killed vaccines

A-2. Attenuated vaccines

B. MODERN VACCINES

B-1. Recombinant vaccines

B-2. DNA vaccines

B-3. Conjugate vaccines
A. Traditional vaccines

A-1. Killed vaccines

The pathogen killed by heat or chemical treatment

Activate only humoral response

Generally not as effective as live vaccines

Generally require 3-5 doses

Antibody titer falls over time

Examples

Salk vaccine for polio, whole cell typhoid vaccine,

hepatitis A, rabies, plague
A. Traditional vaccines

A-2. Attenuated vaccines

Live but attenuated pathogen

Pathogenicity suppressed but overall structure and antigenicity remain intact

Advantages

Evoke both humoral and cellular immunity

Because of production of memory cells, usually a single shot is enough

Usually effective with one dose
A. Traditional vaccines

Disadvantages of Attenuated vaccines

- Extensive safety precautions needed
- Inactivation/attenuation must be 100%
- Attenuated strains might revert
- Limited shelf-life and stringent refrigeration requirements
- Unstable and severe reactions possible

Examples

- BCG, oral typhoid, measles, mumps
B. MODERN VACCINES

B-1. Recombinant vaccines

B-2. DNA vaccines

B-3. Conjugate vaccines
B-1. Recombinant Vaccines

Use of molecular methods to produce recombinant micro-organisms or their parts to enhance their immunogenicity.

B-1.1 Subunit vaccines
B-1.2 Peptide vaccines
B-1.3 Recombinant attenuated vaccines
B-1.4 Vector vaccines
B-1.1 Subunit vaccines

Vaccines that use components of a pathogen rather than the whole organism are “subunit” vaccines

**Advantage**

Using a purified protein ensures that the vaccine is safe and stable

**Disadvantages**

Purification may be costly

Isolated protein may not have the same conformation as in the pathogen, so may not have the same antigenicity

**Examples:**

HSV, hepatitis B, influenza, acellular pertussis, typhoid Vi polysaccharide
B-1.1 Subunit vaccines

Example: HSV (Herpes Simplex Viruses)

HSV may cause cancer, encephalitis and severe eye infections

For subunit vaccine, the target antigenic protein is HSV viral envelope glycoprotein D

Modified HSV glycoprotein D is effective against both HSV-1 and HSV-2

Limitations

Single immunogenic domain is not known in all pathogens

Antigenic variation in immunogenic domain
Development of Subunit Vaccine against HSV

- Clone gD gene
- Transfect CHO cell
- Secreted protein
- Purify & concentrate

HSV

Infect

Not Protected

Infect

Protected
B-1.2 PEPTIDE VACCINES

Vaccine from a specific domain of an antigenic protein

Single epitope or antigenic determinant

Peptides need to be linked to another molecule to prevent rapid degradation

Common carrier proteins

Hepatitis B core protein (HbcAg) – highly immunogenic carrier protein – self assemble into small particles

Examples:

Melanoma vaccine, *H. influenzae* protein D
Structure of a peptide vaccine

Diagram showing the structure of a peptide vaccine, with components labeled as follows:
- Carrier Protein
- Short Peptides
- Linker
- HBcAg
B-1.3 Recombinant Attenuated Vaccines

Recombinant DNA techniques permit genetic manipulation for generating attenuated vaccines

**Methods**

A non-pathogenic organism engineered to carry and express antigenic determinants from a target pathogenic agent

A pathogenic organism engineered such that the virulence genes have been modified or deleted

**Benefits**

Only a selected antigenic determinant from the pathogen is put into the non-pathogen so there is no chance of vaccine causing disease
Benefits
Deletion of virulence genes greatly decreases the likelihood of reversion back to virulent form.

Whole organism much more immunogenic than subunit or peptide vaccine.

Examples:
- Engineered Cholera exotoxin *V. cholerae*
- hpaA gene-engineered attenuated *Salmonella Typhimurium*

Engineered *V. cholerae* strain
- A part (gene) of A1 domain is deleted to create non-pathogenic *V. Cholerae*
- No active enterotoxin
- Retains other biochemical features
- 90% protection
B-1.4 VECTOR VACCINES

Live non-pathogenic viruses used as vaccine

Advantages

Antigen is authentic
Virus expresses antigen in the context of viral particle.
Amount of antigen is amplified during replication of the live virus.

Disadvantages

Serious viral infection in immuno suppressed host – AIDS and transplant patients

Example -- Vaccinia virus

Live vaccine used for eradication of smallpox, Genome is ds DNA (187 kbp), Generally benign, Broad host range


**DNA Vaccines**

DNA vaccines consist of naked DNA.

The DNA is introduced into a plasmid. The altered plasmids carry genes specifying one or more antigenic proteins made by a selected pathogen.

In early 1990s, experiments on rodents and primates revealed that DNA vaccines generated both humoral and cellular immune responses.

**DNA vaccines in various stages of trials:**

Tuberculosis, Herpes, Influenza, Hepatitis B, Plasmodium, Japanese encephalitis

Attachment of cancer genes with bacterial genes can enhance the immune response.
B-2 DNA VACCINES

Preparation
- A suitable vector (plasmid) capable of expression in mammalian cells is basic tool.
- It should also have the capacity for introduction of multiple genes.
- Genes of interest are inserted into these vectors by conventional cloning methods.

Delivery
- The plasmids are usually delivered by injection or a device known as gene gun.
- Injection (muscle), puts genes directly into some cells and also leads to uptake by cells in the vicinity of the inserted needles.
- The gene gun propels plasmids into cells near the surface of the body (usually skin).
- Very promising results have been obtained by intraperitoneal,
Scientific American
DNA VACCINES

Advantages

1. Viral and parasitic antigens are presented to the host immune system in native form.

2. They are superior to live vectors.

3. DNA vaccines are more thermostable than other vaccines.

4. Double stranded DNA is poorly immunogenic.

5. Immune response can be boosted substantially by repeat immunization.

6. Utilizing identical or similar vector backbones a wide range of infectious disease and cancer targets can be addressed.

7. DNA vaccines may also be used as a tool for production of poly- and monoclonal antibodies.
DNA VACCINES

SAFETY CONCERNS

1. Don’t know the fate of DNA

2. Hypothetically, production of anti-DNA antibodies or other autoimmune diseases is possible.

3. In very rare cases, malignant transformation of cells that have taken up injected or transfected nucleic acids may occur.

4. Foreign DNA may become chromosomally integrated and the integration event may result in proto-oncogenic activation or tumor suppressor gene inactivation.
B-3 CONJUGATE VACCINES
Lipopolysaccharides

In case of Gram negative bacteria, besides proteins, the lipopolysaccharides (LPS) are also immunogenic.

LPS are highly toxic but the main antigenic component O-specific polysaccharides (OSP) is non-toxic.

However, isolated OSP, are small molecules (less than $3 \times 10^4$ Da) and do not induce serum antibodies at any age and are considered as haptens.

They need adjuvants to be effective.
LIPOPOLYSACCHARIDE

- O-antigen
  - Highly variable area
  - Molecular weight range
    2,000 - 1,000,000 daltons

- Polysaccharide core

- Sugars

- Phosphate

- Lipid A
  - Highly conserved structure
  - Target for EAA™

- Fatty acids
Conjugate vaccines

“Conjugate vaccines are so-called because their production involves the conjugation of the polysaccharide antigen with a protein”.

This conjugation converts the T-cell independent carbohydrate antigen into a T-cell dependent antigen, with all the associated benefits in terms of immunological response.
MULTIVALENT ANTIGEN

multiple different antigenic determinants

POLYVALENT ANTIGEN

multiple identical antigenic determinants
After conjugation of polysaccharide with a protein, following benefits are gained:

Because of protein presence, cellular immune system is evoked leading to better immunity.

Memory cells are formed.

Affinity maturation takes place.
Licensed Conjugate Vaccines

- *Haemophilus influenzae* type b
- *Neisseria meningitidis* type C
- *Streptococcus pneumoniae*

Conjugate vaccines at trial

- *Salmonella enterica* serotype Typhi
- *Pseudomonas aeruginosa*
- *Escherichia coli* O157