

Review Article**Immunological memory as the fundamentals of vaccines**Fatima Haider^{1*}, Amir Sultan² and Hassan Ahmed Khan³¹Capital University of Science and Technology, Islamabad, Pakistan²Comsats University, Islamabad, Pakistan³Abbottabad University of Science and Technology, Abbottabad, Pakistan

*fatima.microbiologist@gmail.com

Abstract:

The immune system also called as the defense system involves many different cells that work as soldiers in an individual. These immune cells provide protection against various pathogens. For better protection of an individual the immune systems has the ability to memorize or remember the pathogen. This ability is known as immunological memory. With the help of immunological memory the immune memory cells remember the antigen and are prepared if there is an encounter with the antigen in future. The immunological memory can be developed against certain strains with the help of different types of vaccines. Such types of vaccines that are currently being used to save lives are, Live attenuated vaccines, Toxoid vaccines, Subunit vaccines, Glyco-conjugated vaccines, and Killed/Inactivated vaccines. These vaccine show different efficiency. Hence, the immunological memory generated after a single vaccination may wear off with time. Multiple numbers of shots are required for the development of long term memory. All these types of vaccines vary from each other in their manufacturing and also in their mechanism of providing long term immunological memory. They show many pros and cons but their advantages are greater than their disadvantages. Thus, are preferred to be used for the betterment of mankind.

Key words:

Immunological memory, Memory cells, Live attenuated vaccines, Toxoid vaccines, Subunit vaccines, Glycoconjugated vaccines, Killed/Inactivated vaccines, Adaptive immunity.

Introduction:

Our immune system provides us immunity against pathogens present in the environment [1]. There are different components that play an important part in immunity such as, different types of White Blood Cells, Dendritic cells, T cells, B cells, CD4+, CD8+ etc [2]. Our immune system is further differentiated into adaptive and innate immunity. They are differentiated on the bases of their function and the mechanism involved provides protection against the pathogen. In easier words innate immunity is inborn and adaptive immunity is developed with the exposure to environment [3].

Immune Response Cells	
Innate Immune System Cells	Adaptive Immune System Cells
Dendritic Cells	B-Cells
Mast Cells	Antibiotics
Macrophage	T-Cells
Granulocytes	CD4+ T-Cells
Complement Protein	CD8+ T-Cells
Gamma-delta T-Cells	Gamma-delta T-Cells
Natural Killer(NK) Cells	Natural Killer(NK) Cells

Table 1: Cells involved in both Innate and Adaptive Immune Cells [2]

There are various types of vaccines that play an important role in immunological

memory. Immunological memory is the capability of the immune system to remember the antigen for future protection of individual [2]. Different vaccines show use different mechanism. Live attenuated viruses, conjugated vaccines and adjuvant subunit vaccines are being studied for a long lasting immunological memory [1].

Live attenuated vaccines for long term immunity:

Vaccines that are made up of weak microbes are called live attenuated vaccines [4]. Some examples of such types of vaccines are measles, mumps, rubella, smallpox etc [5]. A research carried out in china and India approximately 1000 AD made small pox vaccine from weakened virus [5]. There are different ways that can utilize attenuated viruses for mankind. One of the ways involves the growth of a population in a host. Measles virus is replicated in fibroblasts of the chicken. This procedure gives various mutant strains. From these strains a specific strain is obtained for manufacturing a vaccine. This is a useful procedure for RNA viruses. Another way that can be used is by growing the strain in an artificial medium. This requires maintains of factors such as, temperature. Optimum conditions are provided so that the strain can replicate fast [5].

Having a look at measles vaccine's mechanism; the virions enter different cells with the help of clathrin-mediated endocytosis. When the cytosol is formed the protein of the virus are degraded. The peptides are placed on MHC type I molecule. The complexed formed is placed on the surface of the cell. The complex on the cell surface is recognized by the cytotoxic T cells. The recognition is done by T cell receptors. This causes the release of cytokines directing apoptosis [6]. Furthermore, the dendritic cells will start the previous process for the release of IgG

antibodies, plasma cells and memory B cells [5].

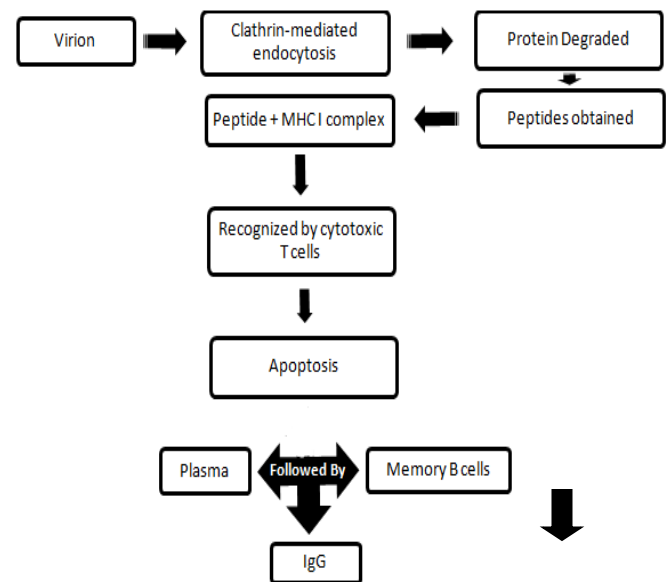


Figure 1: Flow chart showing immunology of LAV [6],[5]

Hence, individual with immunity when exposed to the antigen such as, measles virus show both defense processes. The T cells kill the infected cells whereas; the IgG antibodies are produced in the blood stream. The antibodies attach to the cell surface to prevent disease [7]. One main drawback of the LAV is that it may get reversed and cause infection in an immunized individual. It may also occur in immunosuppressed individual due to the lack of working of the immune system [5]. For having a closer look at molecular level for long time immunity few researches are being carried out on innate immunity. The research showed that involvement of different pathogen recognition receptors such as, CD8+, Macrophages, Cytokines and Chemokines is a way to find out the activity of T-cells. Hence, proposing that adaptive immunity is led by innate immunity. The innate immunity signals are generated by LAV [8].

With the help of different factors mainly environment and genetic [9], effects innate signals towards antigen receptors. The CD4+ T-cells play an important role in

encouraging live long CD8+ T-cells and B-cells response [10]. An early study of innate and CD4+ after the injection of LAV can aid in production of long term immunity [1].

Toxoid vaccine showing long term immunity:

Some microbes harm individual by releasing chemicals. These chemicals are known as exotoxin. Such ability can be seen in microorganisms such as, tetanus and diphtheria. They may cause serious infections on the release of toxins. An example of infection is pertussis [9]. Having an eye on tetanus an example of toxoid vaccine. This strain releases tetanospasmin. This toxin attaches to the receptors on motor nerve. Causing the blockage in production of glycine amino acid. Hence, in return causing abnormal functioning of gamma-Aminobutyric acid (GABA) neurons. Making the infected person get muscle spasms [5].

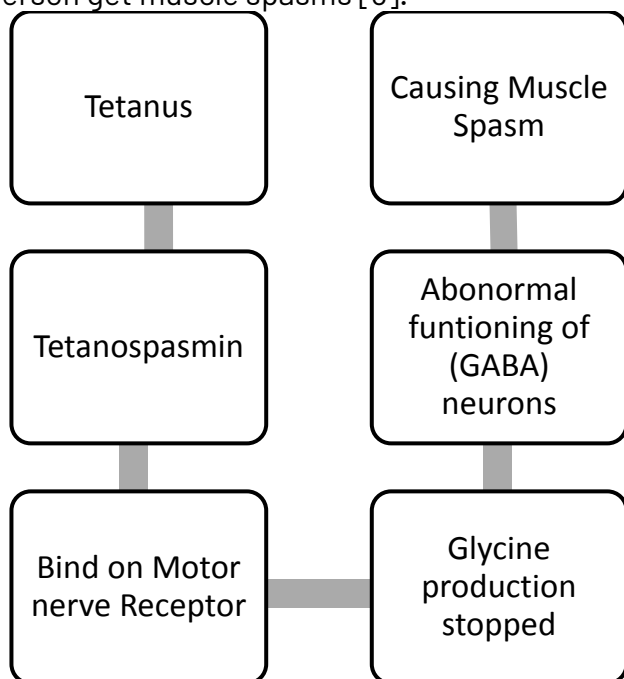


Figure 2: Flowchart showing the effect of tetanospasmin [5]

Immunological memory by adaptive immune response is generated on vaccination, the toxoid is exposed to immature dendritic cells. In the cell they

bind to (MHC II) molecules. The complex formed after binding appears on the cell surface. After this proliferation occurs by the attachment of T_H2 on complex formed. This binding activates T- cell hence, causing proliferation. Some toxoid molecules not taken up by the dendritic cells come in contact with memory B-cells [5, 10]. As observed in the mechanism toxoid vaccine they do not cause infection and they are highly stable towards factors such as, temperature and light. A minor disadvantage of the vaccine is that it needs adjuvant and it may cause temporary inflammation [5].

Subunit vaccine and immunological memory:

In a subunit vaccine adjuvant are needed. These adjuvants are needed for better performance of the vaccine. Adjuvants are substances work against the antigen added in the individual. This is done by improving immune response. [11]. Few examples for subunit vaccine are Hepatitis B , Influenza [5] and tuberculosis [12]. Subunit vaccine can be differentiated on the basis of protein or a polysaccharide. This gives different immunological strengths [5]. Discussing immunological memory provided by subunit vaccine with the help of influenza make it easy to understand the development of long term immunity. Influenza viruses are from *Orthomyxoviridae*. The major instinct o this family is to evolve at a fast rate [13]. Influenza viruses are of 4 different types. These 4 types are A, B, C and D [13]. Type A effects different species including humans , Type B effects only *Homo sapiens*, Type C effects humans and pigs whereas, Type D has not shown any case of infection in humans [14].

Type A is further differentiated on glycoproteins present on the surface. These glycoproteins are hemagglutinin and neuraminidase. Many HA and NA subtypes

have been discovered. Almost 18 subtypes for HA and 11 for NA have been found. These subtypes are discovered in different birds and mammals [15]. Haemagglutinin on the surface of influenza virus help enter the cell. HA causes minor antigenic drift. Major antigenic drift occur due to reassortment of hemagglutinin gene in various influenza virus. Hence, causing diseases such as, Spanish pandemic influenza [1].

Vaccine for pandemic influenza is being developed. Whereas, vaccine for seasonal influenza is being provide to people for protection against infection. The need of both vaccines varies. The people already demonstrate immunity against previous infection and vaccine. Hence, a single non-adjuvant vaccination can improve immunity in an adult individual. Adjuvant vaccination is used for old age individuals and for severe ill patients for protection. New pandemics are caused by a mismatch with vaccine and circulating virus [1].

H5N1 is the main reason behind pandemic infection. It was discovered in Honk Kong in 1997. But it has now spread in different ancestors of birds. Non-adjuvant or weak adjuvant vaccines cannot provide protection against H5 [16]. Adjuvant vaccines consisting of MF59 provide protection after getting vaccinated twice. The dose containing 7.5 µg of HA provides a long lasting memory [17], [18]. This may reduce the pandemic influenza. As it prepares the individual after pre-pandemic vaccination. Providing protection against H5 clade in future after one booster. Interestingly, it is not important to find a similar stain that matches because MF59 adjuvanted vaccine provides protection against all H5 strains [18].

Immunological mechanisms provided by MF59 adjuvant pandemic vaccines was first studies on animal models. It showed that MF59 generated local pro inflammatory signals and release activated CD11c⁺ cells at

injected area [21]. The antigens injected make T-cells more efficient [19]. One MF59 adjuvant H5 vaccine can generate high concentration of antigen specific CD4⁺T cells in healthy adults [19]. CD4⁺T-cell may provide long term memory [1]. Having a look at the advantages and disadvantages of the vaccine the advantages are more than the disadvantages. The advantages and disadvantages are similar to that of toxoid vaccine. One disadvantage is the use of adjuvant in vaccine [5].

Glyco-conjugated vaccines role in immunological memory:

Vaccine that show covalent bonding between proteins and microbes polysaccharides are known as conjugated vaccines [20]. Hence, Glyco-conjugate is obtained when covalent bond is formed between carrier protein and capsular polysaccharides [21]. Many successful conjugated vaccines have been developed since the last four decades. Some of these vaccines used to infection of different microorganisms are *Haemophilus influenza*, different serogroups of meningococcus (A, C, and ACWY) and of pneumococcus [20].

Glyco-conjugated vaccines provide immunity by activating T-cells to assist B-cells. B-cells release IgG antibodies for components of polysaccharides. This allows the glycol-conjugate to generate switch of polysaccharides specific IgM-to-IgG, B-cell are produced and T-cell with long term memory are generated [22, 23]. A few drawbacks of the vaccine are that the immunogenicity i.e. the immune response, may vary according to the makeup of polysaccharides [24, 25]. Moreover, immunosuppressive adults and old age people are more likely to develop a disease in some areas [21][22]. Immune response of conjugated vaccines depends on age factors. In new born babies the antibodies are hard to find but antibodies increase by repeated dose. By time the

antibodies may decrease but they are still more than a child that is not immunized. If the dose is given at the age of three to five the antibody concentration increases to about 3-10 times and generates B-cells. Children of 12-36 months the effects resemble to a new born. Hence, a booster is necessary in both. In adolescent the concentration of antibodies decreases by time after the first vaccine. The concentration will increase on a booster if given after 3 or more years. The booster increases the antibody concentration upto 5-10 times. Thus, by this it can be concluded B-cells are produced on the first dose which respond on the booster [20].

Long term memory of B-cells is due to the assistance of CD4+ T-cells [1]. Carrier proteins help in analyzing the quantity and quality of immunity produced by vaccine. This helps determine the time span of protection [26]. Meningococcal polysaccharides covalently bond to protein-carrier. Synthetic protein-carrier carry T-cell epitopes. They bind to alleles of MHC class II. This gives faster immunity [26]. The lack of interaction with anti-carrier antibodies activated by vaccination [26]. Supporting the exploitation of chimeric carriers enhancing the effect of glycol-conjugated vaccines in kids [1]. The effect of glycol-conjugated vaccine with innate immunity may help maintain immunological memory [27].

Killed/Inactivated Vaccine in Immune memory:

Inactivated and killed vaccines are consisting of an inactive antigen [28]. The first killed vaccine developed was of typhoid [5]. Few examples of inactivated vaccines are polio, hepatitis A, cell pertussis vaccine [5, 28]. The immunological memory of killed/inactivated vaccine is same as that of Toxoid vaccine as discussed above. The only difference observed in them is that of antibody

response is made against a wide range of antigens. When the vaccine is given to the individual immature dendritic cells quickly perform phagocytosis. The antigenic fragments produced bind to MHC II. Hence, activating T_H2 carrying TCR. Whereas, B cells carrying BCR attach with antigens. Antigens will be incorporated forming MHC II + antigenic fragment. Thus, allowing attachment with T_H2 . In return Interleukin 2,4,5 and 6 are released. They help in B-cell activation. Furthermore, IgM will convert to IgG and memory cell are formed [5].

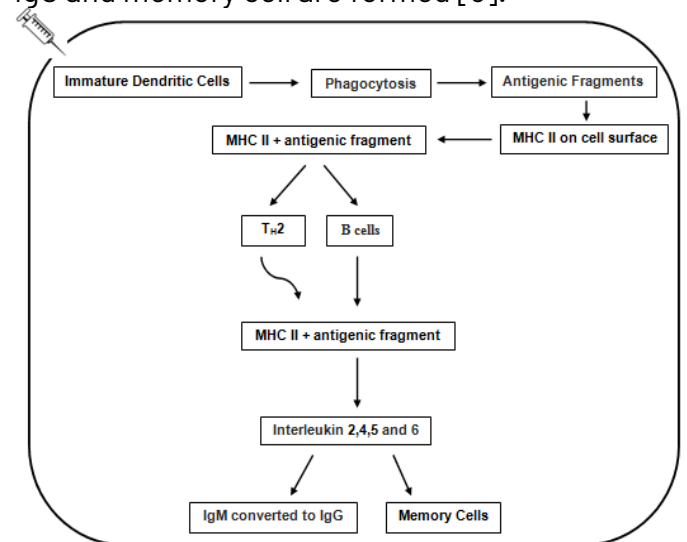


Figure 4: Flowchart showing immunological memory of killed/inactivated vaccine [5]

The benefits of the vaccine are similar to that of Toxoid vaccine [5]. The negative impact of the vaccine is that multiple shots are required to be given to an individual. This is necessary for developing long-term immunological memory [29].

Conclusions:

Different types of vaccine are used to develop immunological memory. Different doses are required for various vaccines to provide immunological memory. Live attenuated vaccines (LAV) are made up of pathogen with weakened pathogenicity. Live attenuated vaccines are considered to be one of the best with fewer disadvantages. They provide good long term protection but can revert. Toxoid

vaccines consist of inactivated toxin. These toxins are released by pathogens. They do not revert and are stable. Toxoid vaccines contain adjuvants and multiple shots are needed for the vaccine to show long term immunological memory, which are drawback of this vaccine. Subunit vaccines consist of specific elements such as, proteins or polysaccharides of pathogen. They have similar advantages and disadvantages to toxoid vaccines. Glyco-conjugate vaccines are developed by the linkage of antigen with proteins. They provide long term immunity but many boosters are required. Killed/inactivated vaccines are manufactures from killed antigens. They also share similar advantages to toxoid vaccines. Few drawbacks are that multiple boosters are needed and it consists of adjuvant. Comparing the advantages and disadvantages of the vaccines and also the strength of long term immunological memory live attenuated vaccines are considered to be one of the best types of vaccines.

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