S. S. College, Jehanabad

Department: Biotechnology

Class: B.Sc. Part 2

Subject: Immunology

Topic: Introduction to Immunology with historical perspective

Mode of teaching: Google classroom & Zoom

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Teacher: Praveen Deepak, Assistant Professor, Department of Zoology, S. S. College, Jehanabad

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INTRODUCTION TO IMMUNOLOGY: HISTORICAL APPROACH

Immunology is the branch of animal physiology that deals with the mechanism of protection against foreign and non-self. It focuses on the functioning of body's defense against infections and tumor cells. In a healthy person, the immune system helps the body fight infection by rejecting viruses, bacteria, and tumor cells but, when the immune system is defective, malfunctioning, it fails to protect the body from that invading microorganisms and growing tumors in the body, and even sometimes causes damage to self in the case of autoimmunity. Other disorders of immune system include hypersensitivity, in which the system responds inappropriately or too intensely as in the case of allergy and asthma. Thus, it is the study of all aspects of the immune system in all organisms dealing with physiological functioning of the immune system in health and disease, malfunctioning of the immune system in immunological disorders, the physical, chemical, and physiological characteristics of the components of the immune system in vitro, in situ, and in vivo.

It is based on different components of immune system that are coordinately functioning to confer immunity (protection) to the individual. Thus immunity may be defined as the body's ability to fight or resist foreign particles like bacteria, viruses, toxins, etc. Foreign particles, such as bacteria, viruses, and other antigens are able to stimulate the immune system and stimulated/activated immune system generates optimal effective response to eliminate the foreign particles, termed as immune response. Hence, it can be understood that immunology has been fundamentally connected with microbiology from beginning or before coming it into general standing. However, scriptures suggest that society of early days of the Common Era (CE) were aware of the immunity of survivors of certain plagues (perhaps smallpox) for recurrent infection (*A group is also an opinion that evidence of immunological practices is even dates back to ~ 430 BC when Thucydides during Peloponesian War describes plague as – the ones who had recovered from the disease could nurse the sick without getting the disease a second time*). By the end of first millennium of Common Era, Chinese and Hindu (and even Turk) healers were well aware of the efficacy of the homeopathic practice of insufflation (blowing on), in which powdered scabs of the afflicted were blown through straws into the lungs of healthy individuals[1]. This observation drew these ancient doctors of the region to a fundamental insight on acquired immunity that some property of the diseased could induce long-lasting and specific protection in naïve individuals. Centuries of observation and reconceptualization about the specificity of this protection led to Fracastoro's fourteenth century germ theory of infectious disease, which held that infectious diseases were caused by disease-specific agents. This concept resulted a mino blow in the late 1700s, when Jenner found that vaccination with cowpox protected against the different though closely related disease smallpox. However, the successes of both variolation and vaccination spurred the deliberate experiments of Pasteur in the following century to develop attenuated vaccines and a modern version of Specific Germ Theory of infectious disease.

The immunology term was coined by Russian biologist Ilya Ilyich Mechnikov by combining two words 'Immune' and '-ology' in 1906. Ilya Ilyich Mechnikov and Paul Ehrlich were jointly awarded with Nobel Prize in 1908 in Physiology or Medicine' in recognition of their work on

[1] J. R. Rodgers. Immunity. In: Encyclopedia of Microbiology (Third Edition), 2009, Elsevier Inc., Philadelphia, USA.

immunity.

The term 'immunity' was derived from the Latin 'immunitas',which was actually a legal status of Romancity-states granted immunity from paying tributes to Rome or to individuals freed from municipal duties; the root 'munis' refers to change and (ex)changeable goods. This is the direct origin of the legal meaning of 'immunity from prosecuation', but in the first century, Lucan (De Bello Civile) had already used the word metaphorically to describe the Psylli of North Africa as immune to the bites of venomous snakes.

The immunity can be characterized into two types; innate immunity and adaptive immunity.

Innate Immunity

Immune immunity is early line of defense against nonself or pathogens. It is also called as native immunity or natural immunity because innate immunity is provided to the organism by birth from the nature (instinct; encoded; by birth).

Basic features of innate immunity:

- First Line of defense – show immediate reaction against the pathogens (1 to 12 hrs).
- Phylogenetically oldest – co-evolved along with microbes to protect all multicellular organisms.
- Does not require antigen presentation.
- Non-specific and/or less specific - innate immunity can recognize a large molecular pattern and therefore less specific.
- Less diverse or limited diversity – innate immune system recognize only limited number of molecular patterns present on pathogens.

Pathogen associated molecular patterns (PAMPs) are those component of microbial cell wall which are vital for the pathogens. The receptors recognizing PAMPs i.e. PRRs (pattern recognition receptors) are encoded in the genome, and there is no somatic recombination which results in limited diversity of PRRs.

Adaptive Immunity

It is also called specific immunity or acquired immunity. Unlike to innate immunity, the reaction of adaptive immunity is specific to the antigen challenging the host .The mode of action of the adaptive immune system is to increase the state of immune reactivity by recognition of molecules and developing an immunological memory. As a result of this immunological memory, the immune system gets adopted to the response to an antigen, when encountered for a second time. It means, acquired immunity can occur from exposure to an infection, wherein a person gets a disease and develops immunity as a result. Acquired immunity also occurs from vaccination wherein the vaccine mimics a particular disease, causing an immune response in the vaccinated individual without getting them ill.

Passive immunity

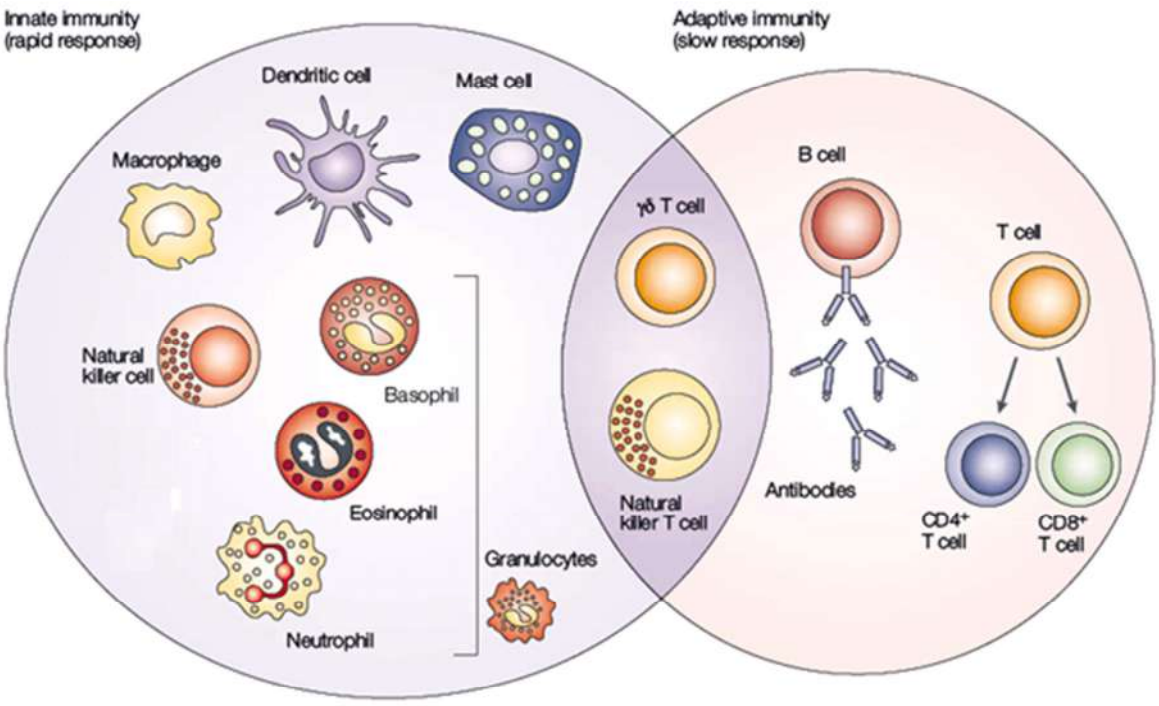
It is the body's capacity to resist pathogens by "borrowing" antibodies. For example, antibodies can be transferred to a baby from a mother's breast milk, or through blood products containing

antibodies such as immunoglobulin that can be transfused from one person to another. The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last one to two months of pregnancy (maternal IgG; can cross placental barrier). As a result, a full-term infant will have the same antibodies as its mother. These antibodies protect the infant from certain diseases for up to a year, and act to defend against specific antigens. Although beneficial, passive immunity is temporary until the antibodies are gone (wane), since the body has not produced the antibodies.

Component of Immune System

Immune response is generated by a specialized system of the body known as immune system. The immune system is composed of different cells (known as immune cells), and organs related to immunity, such as skin, bone marrow, thymus, lymph node, etc. The cells of the immune system are phagocytic cells, such as macrophages, neutrophil, etc., lymphocytes, and other leukocytes. These are all types of white blood cells. However, some cells can impart their role mostly in innate immune system, such effector cells are neutrophils, macrophages, and mast cells, reacting within minutes to hours with the help of complement activation and cytokines, while lymphocytes are part of adaptive immune system, which precisely recognize unique antigens (Ag) through cell-surface receptors and take long time to generate immune response against the antigen.

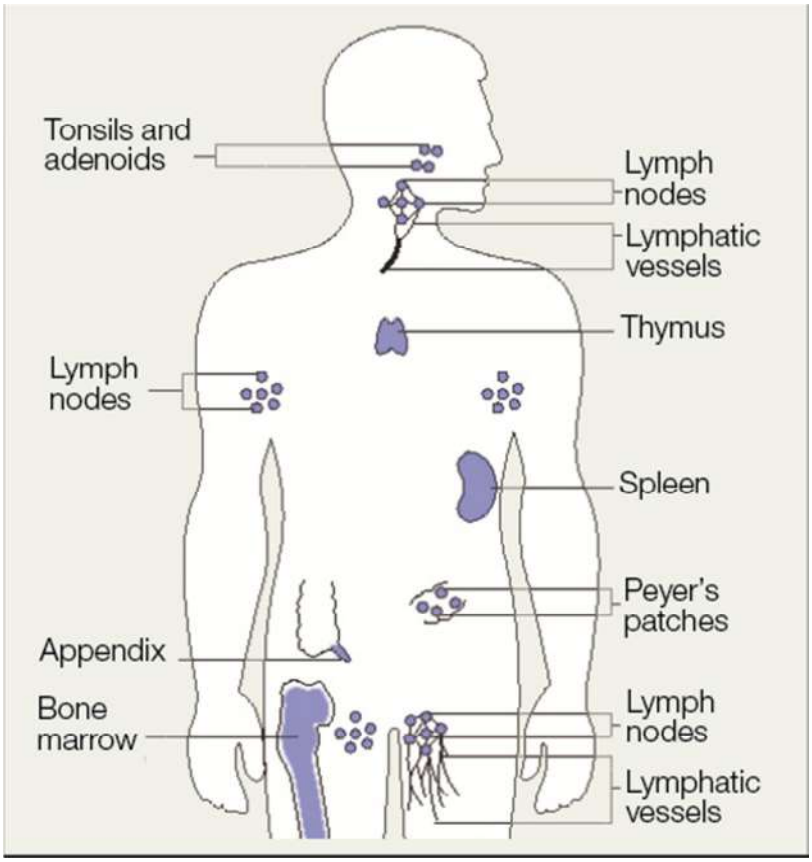
Cells of the immune system: Cells of the innate immune system are mostly originated form myeloid progenitor cells (MPCs), while that of adaptive immune system are originated from lymphoid progenitor cells (LPCs). The cells of the innate immune system or myeloid cells are as follows:



Cells of the immune system

***Monocytes**:* A type of phagocytic cell located in the bloodstream that, when moving to tissues, transforms into a macrophage. They are largest white blood cells that produce macrophages and dendritic cells. *Macrophages* are phagocytic cells having a large number of membranous extensions or pseudopodia. They engulf and process cell debris, pathogens, and cancer cells, and involved in wound healing, tissue regeneration, and pro-inflammatory activities. They take various forms (with various names) throughout the body (e.g., histiocytes, Kupffer cells, alveolar macrophages, microglia, and others). On the other hand, *dendritic cells* are present in tissues like skin, lungs, and intestines and have large dendritic processes. They present antigens to B and T cells and also secrete cytokines.

Neutrophils: They are the granulocytic leukocytes, which have multi-lobed nuclei. They are also a phagocytic cells that act at the site of tissue damage to eliminate pathogens especially bacteria by phagocytosis. They rise in number in the bloodstream through illness and are primarily responsible for the elevated amount of white blood cells associated with some infections.



Eosinophils: They are also granulocytic leukocytes with a kidney-shaped, lobed nucleus. They release the contents of their granules to kill pathogens. They produce a variety of growth factors and cytokines and help other immune cells.

Basophils: They are the largest granulocytic leukocytes with a bilobed nucleus. They have histamine-rich granules and involve in inflammatory responses. They help in the secretion of cytokines involved in the maturation of T-helper cells.

Mast cells: They are granulocytes that secrete heparin, histamine, and other factors. They help in wound healing, angiogenesis, and elimination of parasites.

Natural killer (NK) cells (May develop from both Myeloid and Lymphoid progenitor): They are produced from the bone marrow and are found in the bloodstream and tissues in reasonably low quantities. They are cytotoxic cells that have small granules with perforins and granzymes and destroy infected cells and cancer cells rapidly.

Lymphocytes: Lymphocytes are white blood cells and one of the body's main types of immune cells. They are made in the bone marrow and found in the blood and lymph tissue. They are of two types; B cells that produce antibodies, and T cells. T cells are further categorized into two types; helper T cells (Th) cells and cytotoxic T (Tc) cells. Helper T cells are further sub-classified as T helper 1 (Th1) cells and T helper 2 (Th2) cells. However, it appears that both innate and adaptive have distinct immune cell populations, but this is not the case. Both immune responses function as a highly interactive and cooperative system, providing complete protection against infectious disease. They achieve effector function either by releasing effector mediator molecules or by direct cell-to-cell contact.

Organs of the immune system: The organs of the immune system are involved in the production of immune cells and their maturation. They can be classified into two types; primary lymphoid organs and secondary lymphoid organs. The primary lymphoid organs are red bone marrow and thymus. In red bone marrow, immune cells are produced, whereas in the thymus, T lymphocytes are matured. The secondary lymphoid organs filter out pathogens and maintain the population of mature lymphocytes. The major lymphoid organs are as follows:

Thymus: The thymus is an organ located in the upper chest. Immature lymphocytes leave the bone marrow and find their way to the thymus where they are "educated" to become mature T-lymphocytes.

Liver: The liver is the major organ responsible for synthesizing proteins of the complement system. In addition, it contains large numbers of phagocytic cells which ingest bacteria in the blood as it passes through the liver.

Bone marrow: The bone marrow is the location where all cells of the immune system begin their development from primitive stem cells.

Tonsils: Tonsils are collections of lymphocytes in the throat.

Lymph nodes: Lymph nodes are collections of B-lymphocytes and T-lymphocytes throughout the body. Cells congregate in lymph nodes to communicate with each other.

Spleen: The spleen is a collection of T-lymphocytes, B-lymphocytes and monocytes. It serves to filter the blood and provides a site for organisms and cells of the immune system to interact.

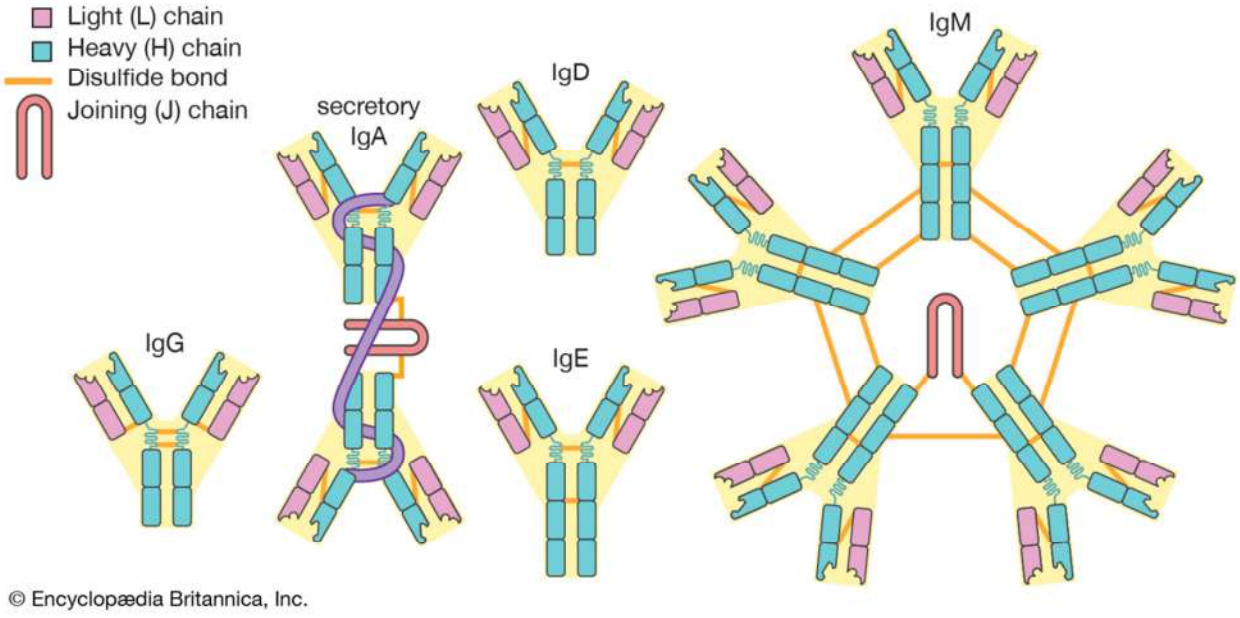
Effector molecules of the immune system: There are several types of effector molecules present in the immune system that play crucial role in the generation of immune response. Such molecules are cytokines, chemokines, antibodies, etc.

Cytokines: They are small protein molecules that carry messages from one cell to another for different functions, such as gene expression of certain effector molecules, induction for cell-specific effector function, etc., through autocrine as well as paracrine signaling. Some type of cytokines is secreted by lymphocytes to act upon lymphocytes that are called as interleukin, e.g. IL-1, IL-2, IL-4, IL-6, etc.

Chemokines: These are a large family of small, secreted a protein that signal through cell surface G protein-coupled heptahelical chemokine receptors, and stimulates the migration of cells, most notably white blood cells (leukocytes).

Complement: It is a large number of distinct plasma proteins produced by liver that react with one another to opsonize pathogens and induce a series of inflammatory responses that help to fight infection**.** A complement system is composed of at least 30 plasma proteins. Some of the proteins of the complement system coat germs to make them more easily taken up by neutrophils. Other complement components act to send out chemical signals to attract neutrophils to sites of infection.

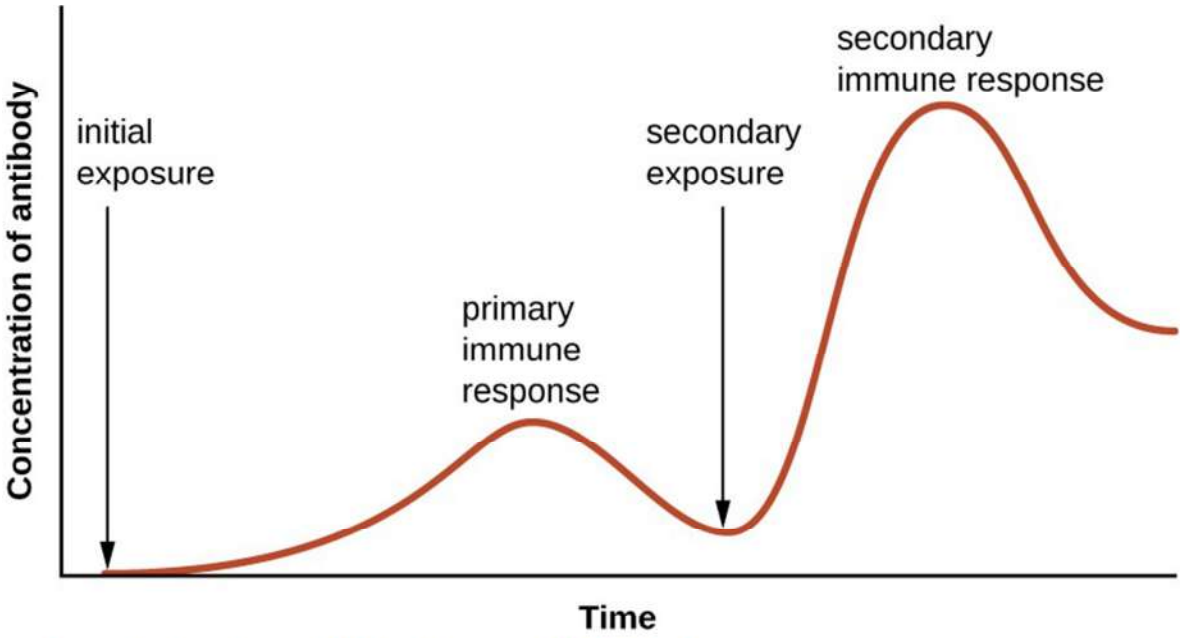
Immunoglobulins: They are plasma proteins produced by B cells. They have antigen binding site called paratope and binds to antigens to neutralize them. They are 5 classes of immunoglobulins are IgG, IgM, IgA, IgD and IgE. These are secreted upon activation of B cells



due to antigen stimulation. Every antibody is composed of light (L) chain and heavy (H) chain and seen as divisible into two regions; antigen binding region or Fab (Fragment antigen-binding) and the tail region called as Fc (Fragment crystallizable) that interacts with cell surface receptors called Fc receptors and some complement proteins.

IgA: Immunoglobulin A is an antibody that plays a crucial role in the immune function of mucous membranes, where it acts as first line of defense. It has 320 kD (secretary, which is dimer joined by J chain and attached to a secretary piece) with heavy chain of 50 kD. The modifications in IgA allow it to be secreted into mucus, intestinal juices and tears where it protects those areas from infection. Non-secretary IgA is found as monomer. Its serum concentration is 1 to 4 mg/ml. Percent of total immunoglobulin is 15% and glycosylation by weight is 10%. Its main function is to protect mucus membrane.

IgG: It is the major immunoglobulin class in the body and is found in the blood stream as well as in tissues. Its molecular weight is 150 kD with heavy chain of 53 kD. Its serum



Graph showing effect of immunologicl memory on immune response

concentration is 10 to 16 mg/ml. Percent of total immunoglobulin is 75% and glycosylation by weight is 3%. Its main function is secondary response.

IgD: It is a monomeric antibody that is expressed in the plasma membrane of immature B cells. It is said to be ancestral antibody. Its molecular weight is 180 kD with heavy chain of 70 kD. Its serum concentration is 0 to 4 mg/ml. Percent of total immunoglobulin is 0.2% and glycosylation by weight is 13%. It is distributed all over the lymphocyte surface. Secreted IgD enhances mucosal homeostasis and immune surveillance by "arming" myeloid effector cells such as basophils and mast cells with IgD antibodies reactive against mucosal antigens, including commensal and pathogenic microbes.

IgE: It is found only in mammal. It is well known for its role in mediating allergic reactions. Its molecular weight is 200 kD with heavy chain of 73 kD. Its serum concentration is 10 to 400 ng/ml. Percent of total immunoglobulin is 0.002% and glycosylation by weight is 12%. It is distributed on basophils and mast cells in saliva and nasal secretions.

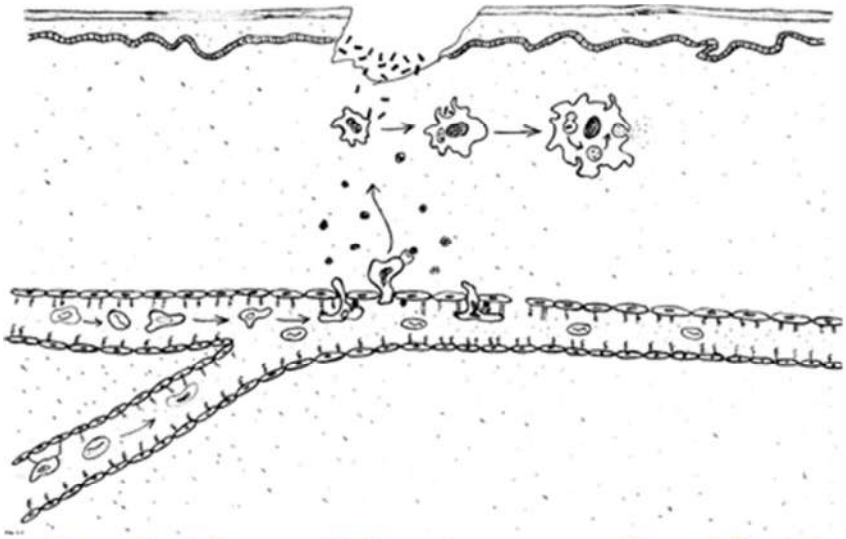
IgM: It is composed of five immunoglobulin molecules attached to each other (pentamer). It is formed very early in infection and activates complement very easily. Its molecular weight is 900 kD (pentamer) with heavy chain of 65 kD. Its serum concentration is 0.5 to 2.0 mg/ml. Percent of total immunoglobulin is 10% and glycosylation by weight is 12%. Its distribution is mostly intravascular and has its role in primary response.

Inflammatory response

When a tissue is damaged either by a wound or by an invading pathogen, inflammatory reaction ensues, which is a complex sequence of events. The inflammation is characterized by any of

these symptoms – redness *(rubor)*, swelling *(tumor)*, heat *(calor)*, pain *(dolor)* and loss of function (*functio laesa*) – as reported in the first century and second century AD.

The following major events are seen in inflammatotory process upon infection to bacteria:



Generalized diagram of inflammatory response (Deepak P, et al. Immunology 2nd Edition)

(1) Blood vessels dilate and nearby capillaries engorged with blood, resulting in redness (erythema) of tissue and rise in the temperature of tissues.

(2) Tissue swelling (edema) occurs as a result of accumulation of exudates. The accumulation is caused by the increased capillary permeability letting an influx of fluid and cells into the tissues.

(3) The increased capillary permeability also facilitates the flowing in of phagocytes into the tissues. The influx of phagocytes into the tissues develops into a complex series of events – adherence of the cells to the endothelial wall of the blood vessels, emigration into the tissue and finally migration to the site of inflammation (inflammatory response). This inflammatory response is called chemotaxis. Pus formation at the site of inflammation is caused by accumulation of dead cells, digested material and fluid.

This sequential event is facilitated by several soluble molecules, such as acute phase proteins, histamine, fibrin, etc. The acute phase protein, like C-reactive protein (CRP) is annular pentameric protein, produced by liver in response to inflammatory stimuli, such as IL-6. Level of CRP is directly proportional to the degree of inflammation, thus the CRP is regarded as the marker of inflammation. Histamine is mainly produced by basophils and mast cells that vasodilates and increases capillary permeability for lymphocyte trafficking. Kinins, scuh as bradykinin and kallidin) present in inactive form in blood plasma are activated by tissue injury and cause pain sensation, arteriolar dilation, increase vascular permeability and cause contractions in smooth muscle through G-protein-cpoupled receptors, being a part of kinin-kallikrein system. Fibrin (clotting factor) enters into the inflammatory response system as insoluble strands, to prevent the spread of infection. As a result of the above chemical mediation the tissue repair process is increased and regeneration of new tissues set in.

Immunological memory

Immunological memory is the ability of the immune system to quickly and specifically recognize an antigen that the body has previously encountered and initiate a corresponding immune

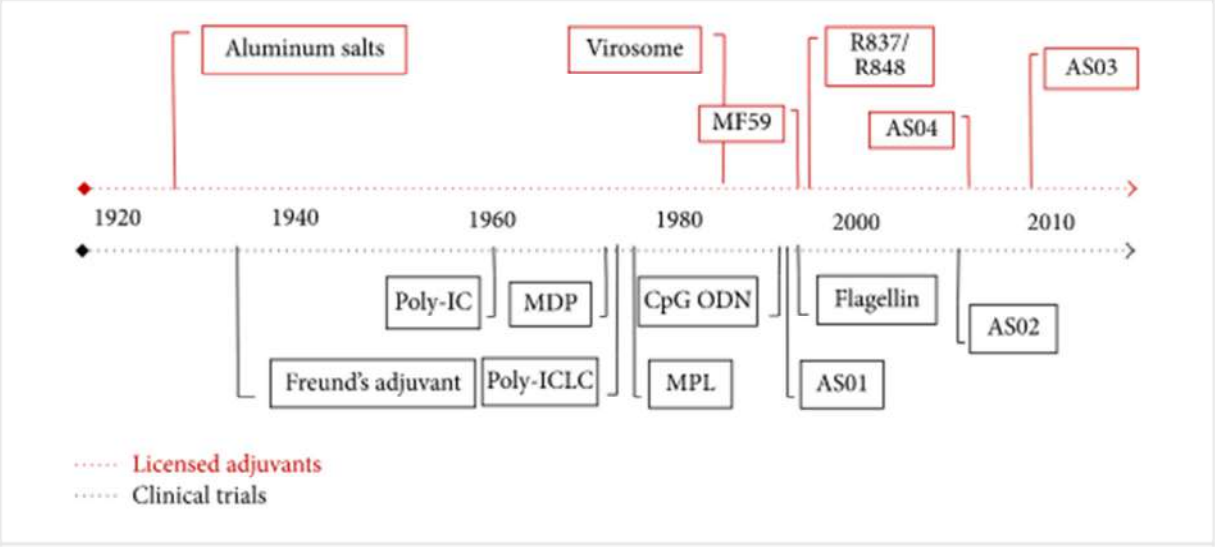
response. A faster and heightened state of response is generated on a subsequent exposure of antigen. Immunological memory is generated, when the antigen (Ag) reach the lymph node carried by macrophages and/or dendritic cells or lymphocytes, where Ag is processed within the macrophages and/or dendritic cells and present them to lymphocytes in association with major histocompatibility complex (MHC) I or II molecules.

Immune dysfunction and clinical immunology

The immune system is a highly regulated and balanced system and when the balance is disturbed, disease can result. There may be either hyperactive immune system or hypoactive (immunocompromised state) immune system. In some cases, there is a immunodeficient state where immunity is not functioning in the individual either due to mutation (e.g. X-linked agammaglobulinemia, Wiskott-Aldrich Syndrome, Severe Combined Immune Deficiency or SCID – *mutation I gamma chain*, Hyper IgM syndrome – *mutation in CD40 ligand*, etc.) or due to infection (e.g. HIV). The disorders of immune system are follows:

Immunodeficiency: It involves problems with the immune system that impair its ability to mount an appropriate defense. As a result, these are almost always associated with severe infections that persist, recur and/or lead to complications, making these disorders severely debilitating and even fatal. There are two types of immunodeficiency disorders: primary immunodeficiency and secondary immunodeficiency. Primary immunodeficiencies (typically present from birth) are generally hereditary and are relatively rare, e.g. common variable immunodeficiency (CVID). Secondary immunodeficiencies generally develop later in life and may result following an infection, as is the case with AIDS following HIV infection.

Autoimmune disorders: It occurs when the immune system attacks own body instead of protecting it. In this case, immune system becomes unable to distinguish 'self' from 'non-self' or 'foreign' molecules. *Autoimmune diseases* may be described as 'primary' autoimmune diseases, like type-1 diabetes, which may be manifested from birth or during early life; or as *'secondary' autoimmune diseases*, which manifest later in life due to various factors. Rheumatoid arthritis and multiple sclerosis are thought to belong to this type of autoimmunity. Also, autoimmune



diseases can be localised, such as Crohn's Disease affecting the GI tract, or systemic, such as systemic lupus erythematosus (SLE).

Allergies: These are hypersensitivity disorders that occur when the body's immune system reacts against harmless foreign substances known as allergen, resulting in damage to the body's own tissues. Almost any substance can cause allergies, but most commonly, allergies arise after eating certain types of food, such as peanuts, or from inhaling airborne substances, such as pollen, or dust. In allergic reactions, the body believes allergens are dangerous and immediately produces substances to attack them. This causes cells of the immune system to release potent chemicals like histamine, which causes inflammation and many of the symptoms associated with allergies.

Asthma: It is a debilitating and sometimes fatal disease of the airways. It generally occurs when the immune system responds to inhaled particles from the air, and can lead to thickening of the airways in patients over time.

Cancer: It is a disease of abnormal and uncontrolled cell growth and proliferation. It evades immune system by breaching anti-cancer immune response generated in the host.

Means of innate or non-specific host defense in vertebrates

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3-5) retards growth of microbes.
Mucous membrane	Normal flora competes with microbes for attachment sites and nutrient. Mucous entraps foreign microorganisms. Cilia propel microorganisms out.
Physiological barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested pathogens.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis.
Phagocytic/endocytic barriers	various cells internalize (endocytosis) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophil, tissue macrophages) internalize (pahgocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

Timeline of Immunology

1549	The earliest account of inoculation of smallpox (variolation) occurs in Wan Quan's (1499–1582) *Douzhen Xinfa*
1718	Smallpox inoculation in Ottoman Empire realized by West, and Lady Mary Wortley Montagu, recorded the positive effects of variolation.
1796	First demonstration of smallpox vaccination (Edward Jenner)
1808–1813	First experimental demonstration of the germ theory of disease by Agostino Bassi though he does not formally propose the theory until 1844
1837	Description of the role of microbes in putrefaction and fermentation (Theodore Schwann)
1838	Confirmation of the role of yeast in fermentation of sugar to alcohol (Charles Cagniard-Latour)
1850	Demonstration of the contagious nature of puerperal fever (childbed fever) (Ignaz Semmelweis)
1857–1870	Confirmation of the role of microbes in fermentation (Louis Pasteur)
1862	Phagocytosis (Ernst Haeckel)
1867	Aseptic practice in surgery using carbolic acid (Joseph Lister)
1876	Demonstration that microbes can cause disease-anthrax (Robert Koch)
1877	Mast cells (Paul Ehrlich)
1878	Confirmation and popularization of the germ theory of disease (Louis Pasteur)
1880–1881	Theory that bacterial virulence could be attenuated by culture in vitro and used as vaccines. Used to make chicken cholera and anthrax "vaccines" (Louis Pasteur)
1883–1905	Cellular theory of immunity via phagocytosis by macrophages and microphages (polymorhonuclear leukocytes) (Elie Metchnikoff)
1885	Introduction of concept of a "therapeutic vaccination". Report of a live "attenuated" vaccine for rabies (Louis Pasteur and Pierre Paul Émile Roux).
1888	Identification of bacterial toxins (diphtheria bacillus) (Pierre Roux and Alexander Yersin)
1888	Bactericidal action of blood (George Nuttall)
1890	Demonstration of antibody activity against diphtheria and tetanus toxins. Beginning of humoral theory of immunity. (Emil von Behring) and (Kitasato Shibasaburo)
1891	Demonstration of cutaneous (delayed type) hypersensitivity (Robert Koch)
1893	Use of live bacteria and bacterial lysates to treat tumors-"Coley's Toxins" (William B. Coley)

1894	Bacteriolysis (Richard Pfeiffer)
1896	An antibacterial, heat-labile serum component (complement) is described (Jules Bordet)
1900	Antibody formation theory (Paul Ehrlich)
1901	Blood groups (Karl Landsteiner)
1902	Immediate hypersensitivity anaphylaxis (Paul Portier) and (Charles Richet)
1903	Intermediate hypersensitivity, the "Arthus reaction" (Maurice Arthus)
1903	Opsonization
1905	"Serum sickness" allergy (Clemens von Pirquet and (Bela Schick)
1909	Paul Ehrlich proposes "immune surveillance" hypothesis of tumor recognition and eradication
1911	2nd demonstration of filterable agent that caused tumors (Peyton Rous)
1917	Hapten (Karl Landsteiner)
1921	Cutaneous allergic reactions (Otto Prausnitz and Heinz Küstner)
1924	Reticuloendothelial system
1938	Antigen-Antibody binding hypothesis (John Marrack)
1940	Identification of the Rh antigens (Karl Landsteiner and Alexander Weiner
1942	Anaphylaxis (Karl Landsteiner and Merill Chase)
1942	Adjuvants (Jules Freund and Katherine McDermott)
1944	Hypothesis of allograft rejection
1945	Coombs test a.k.a. antiglobulin test (AGT)
1946	Identification of mouse MHC (H2) by George Snell and Peter A. Gorer
1948	Antibody production in plasma B cells (Astrid Fagraeus)
1949	Growth of polio virus in tissue culture, neutralization, and demonstration of attenuation of neurovirulence (John Enders) and (Thomas Weller) and (Frederick Robbins)
1951	A vaccine against yellow fever
1953	Graft-versus-host disease
1953	Validation of immunological tolerance hypothesis
1957	Clonal selection theory (Frank Macfarlane Burnet)
1957	Discovery of interferon by Alick Isaacs and Jean Lindenmann
1958–1962	Discovery of human leukocyte antigens (Jean Dausset and others)
1959–1962	Discovery of antibody structure (independently elucidated by Gerald

	Edelman and Rodney Porter)
1959	Discovery of lymphocyte circulation (James Gowans)
1960	Discovery of lymphocyte "blastogenic transformation" and proliferation in response to mitogenic lectins-phytohemagglutinin (PHA) (Peter Nowell)
1960	Radioimmunoassay – (Rosalyn Sussman Yalow)
1961–1962	Discovery of thymus involvement in cellular immunity (Jacques Miller)
1961	Demonstration that glucocorticoids inhibit PHA-induced lymphocyte proliferation (Peter Nowell)
1963	Development of the plaque assay for the enumeration of antibody-forming cells in vitro by Niels Jerne and Albert Nordin
1963	Gell and Coombs classification of hypersensitivity
1964–1968	T and B cell cooperation in immune response
1965	Discovery of lymphocyte mitogenic activity, "blastogenic factor" (Shinpei Kamakura) and (Louis Lowenstein) (J. Gordon) and (L.D. MacLean)
1965	Discovery of "immune interferon" (gamma interferon) (E.F. Wheelock)
1965	Secretory immunoglobulins
1967	Identification of IgE as the reaginic antibody (Kimishige Ishizaka)
1968	Passenger leukocytes identified as significant immunogens in allograft rejection (William L. Elkins and Ronald D. Guttmann)
1969	The lymphocyte cytolysis Cr51 release assay (Theodore Brunner) and (Jean-Charles Cerottini)
1971	Peter Perlmann and Eva Engvall at Stockholm University invented ELISA
1972	Structure of the antibody molecule
1973	Dendritic Cells first described by Ralph M. Steinman
1974	Immune Network Hypothesis (Niels Jerne)
1974	T-cell restriction to MHC (Rolf Zinkernagel and (Peter C. Doherty)
1975	Generation of monoclonal antibodies (Georges Köhler) and (César Milstein)
1975	Discovery of Natural Killer cells (Rolf Kiessling, Eva Klein, Hans Wigzell)
1976	Identification of somatic recombination of immunoglobulin genes (Susumu Tonegawa)
1980–1983	Discovery and characterization of interleukins, 1 and 2 IL-1 IL-2 (Robert Gallo, Kendall A. Smith, Tadatsugu Taniguchi)
1983	Discovery of the T cell antigen receptor TCR (Ellis Reinherz) (Philipa Marrack) and (John Kappler) (James Allison)
1983	Discovery of HIV (Luc Montagnier) (Françoise Barré-Sinoussi) (Robert Gallo)

1985–1987	Identification of genes for the T cell receptor
1986	Hepatitis B vaccine produced by genetic engineering
1986	Th1 vs Th2 model of T helper cell function (Timothy Mosmann)
1988	Discovery of biochemical initiators of T-cell activation: CD4- and CD8-p56lck complexes (Christopher E. Rudd)
1990	Gene therapy for SCID
1991	Role of peptide for MHC Class II structure (Scheherazade Sadegh-Nasseri & Ronald N. Germain) (http://doi.org/10.1038/353167a0)
1992	Discovery of transitional B cells (David Allman & Michael Cancro)
1994	'Danger' model of immunological tolerance (Polly Matzinger)
1995	James P. Allison describes the function of CTLA-4
1995	Regulatory T cells (Shimon Sakaguchi)
1995	First Dendritic cell vaccine trial reported by Mukherji et al.
1996–1998	Identification of Toll-like receptors
1997	Discovery of the autoimmune regulator and the AIRE gene.
2000	Characterization of M1 and M2 macrophage subsets by Charles Mills
2001	Discovery of FOXP3 – the gene directing regulatory T cell development
2005	Development of human papillomavirus vaccine (Ian Frazer)
2006	Antigen-specific NK cell memory first reported by Ulrich von Andrian's group after discovery by Mahmoud Goodarzi
2010	The first autologous cell-based cancer vaccine, provenge, is approved by the FDA for the treatment of metastatic, asymptomatic stage IV prostate cancer.
2010	First immune checkpoint inhibitor, ipilimumab (anti-CTLA-4), is approved by the FDA for treatment of stage IV melanoma
2011	Carl H. June reports first successful use of CAR T-cells expressing the 4-1BB costimulatory signaling domain for the treatment of CD19+ malignancies
2014	A second class of immune checkpoint inhibitor (anti-PD-1) is approved by the FDA for the treatment of melanoma. Pembrolizumab and nivolumab are approved within months of each other.
2016	Halpert and Konduri first characterize the role of dendritic cell CTLA-4 in Th immune polarization
2016	A third class of immune checkpoint inhibitor, anti-PD-L1 (atezolizumab), is approved for the treatment of bladder cancer
2017	First autologous CAR T-cell therapy tisagenlecleucel approved for the treatment of pediatric B-ALL; second autologous CAR T-cell therapy

	axicabtagene (Yescarta) is approved.
2020	The first mRNA vaccines (BNT162b2, mRNA-1273), are developed for SARS-CoV-2 infection; this new technology completed design, testing, and emergency approval in under one year.

Vaccines

A preparation that is used to stimulate the body's immune system against diseases. Vaccines are usually administered through needle injections, but some can be administered by mouth or sprayed into the nose. There are different types of vaccines, which are:

Inactivated vaccines: Inactivated vaccines use the killed version of the germ that causes a disease. Inactivated vaccines usually don't provide immunity (protection) that's as strong as live vaccines. Therefore, several doses (booster shots) are needed over time in order to get ongoing immunity against diseases, e.g. Hepatitis A, Flu (shot only), Polio (shot only), Rabies, etc.

Live-attenuated vaccines: Live vaccines use a weakened (or attenuated) form of the germ that causes a disease. Because these vaccines are so similar to the natural infection that they help prevent, they create a strong and long-lasting immune response. Just 1 or 2 doses of most live vaccines can give a lifetime of protection against a germ and the disease it causes, e.g. Measles,

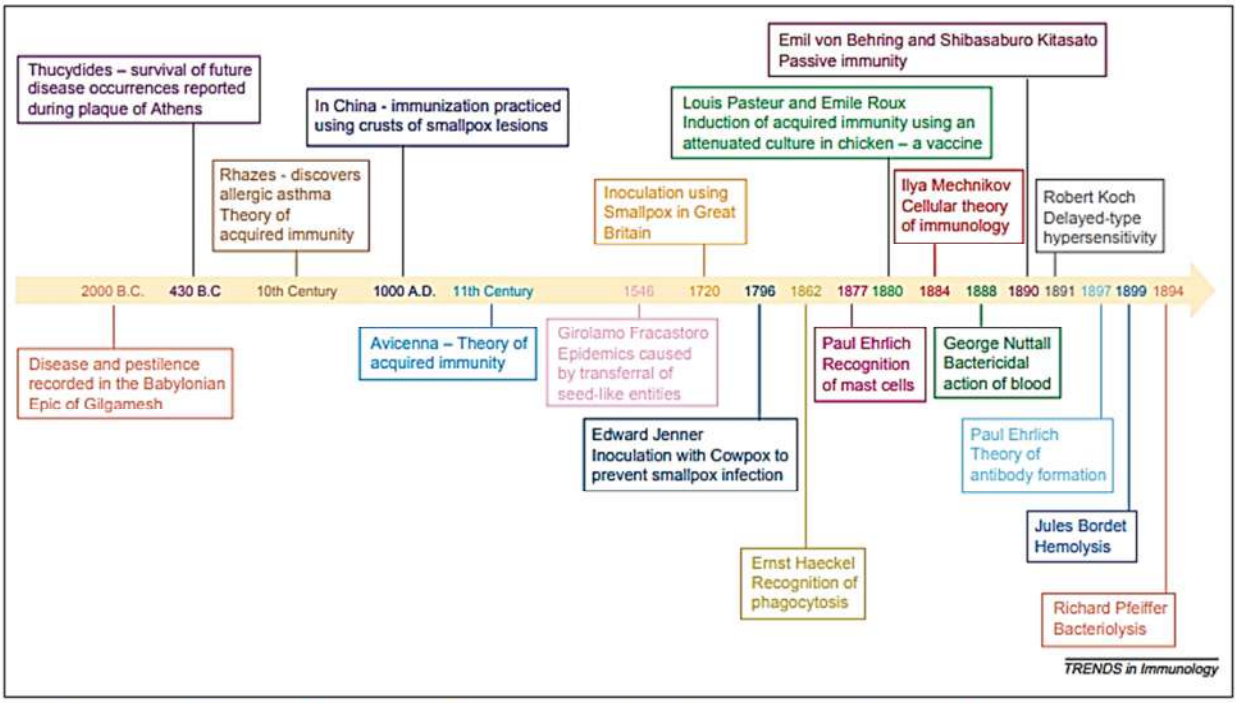


Figure 1. Timeline through the early development of immunology. Discoveries impacting on the immune system found prior to the 20th century.

mumps, rubella (MMR combined vaccine), Rotavirus, Smallpox, Chickenpox, Yellow fever, etc

Messenger RNA vaccines (mRNA vaccines): Some of the COVID-19 vaccines are produced using this approach. mRNA vaccines make proteins in order to trigger an immune response. mRNA vaccines have several benefits compared to other types of vaccines, including shorter

manufacturing times and, because they do not contain a live virus, no risk of causing disease in the person getting vaccinated.

Subunit, recombinant, polysaccharide, and conjugate vaccines: Subunit, recombinant, polysaccharide, and conjugate vaccines use specific pieces of the germ, like its protein, sugar, or capsid, and therefore they give a very strong immune response that's targeted to key parts of the germ. They can also be used on almost everyone who needs them, including people with weakened immune systems and long-term health problems, e.g. Hib (*Haemophilus influenza* type B) disease, Hepatitis B, HPV (Human Papillomavirus),Whooping cough (part of DTaP; diphtheria, tetanus, pertussis)**,** Pneumococcal disease, Meningococcal disease, and Shingles.

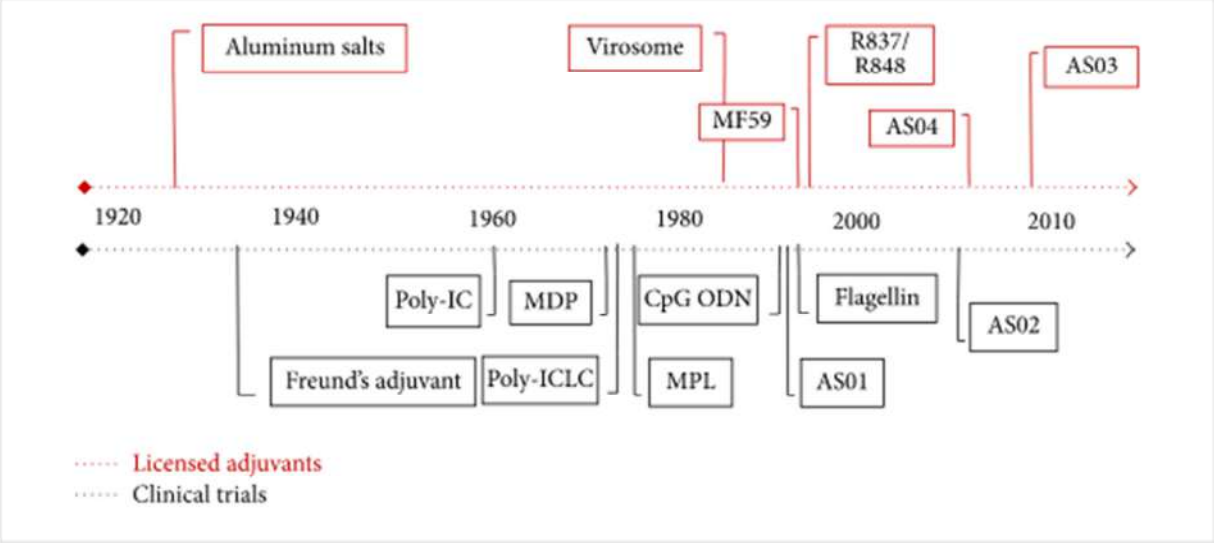
Toxoid vaccines: Toxoid vaccines use a toxin (harmful product) made by the germ that causes a disease. They create immunity to the toxin instead of the whole germ. However, booster shots are needed to get ongoing protection against diseases, e.g. Diptheria, Tetanus, etc.

DNA vaccines: Easy and inexpensive to make, and able to produce strong, long-lstng immunity. However, it is still under study.

Recombinant vector vaccine (platform-based vaccines): It acts like a natural infection.

Adjuvant

It is an ingredient used in some vaccines that helps create a stronger immune response in people receiving the vaccine**.** In other words, adjuvants help vaccines work better.



Adjuvants are many types, which are as follows:

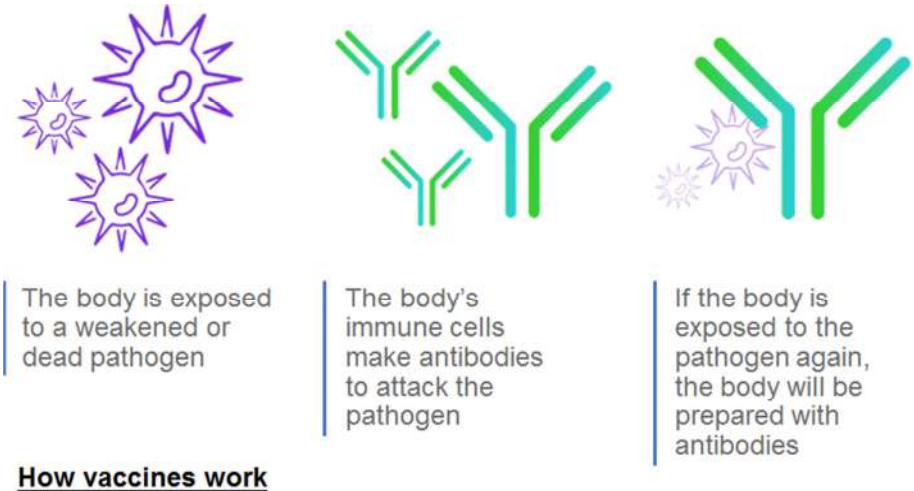
Freund's adjuvants: It is of two types; Freund's complete adjuvants and Freund's incomplete adjuvants.

Freund's complete adjuvants: It is water-in-oil emulsion contains mineral oil, the surfactant mannide monoleate and heat-killed *Mycobacterium tuberculosis*, *M. butyricum* or their extracts, used for aggregation of macrophages at the inoculation site. It stimulates both innate immunity and cell-mediated immunity. However, the FCA also has disadvantages. For instance, it can produce some immunologically toxic effects, due to the non-metabolizable mineral oil.

Freund's incomplete adjuvants: It is water-in-oil emulsion that contains oil, the surfactant mannide monoleate and no Mycobacterium. Therefore, it is less effective than the FCA (Freund's complete adjuvants).

Ribi Adjuvant system: It is oil-in-water emulsion. The antigen is mixed with squalene, which is a metabolizable oil. It is then emulsified in a saline solution containing Tween 80. It also contains refined mycobacterial product and a gram negative bacterial product monophosphoryl lipid A.

Titermax: It does not contain any biological materials and has lower level of toxicity compared to other. It is based on mixtures of surfactant acting, linear, blocks or chains of non-ionic copolymers polyoxypropylene (POP) and polyoxyethylene (POE). The properties of Titermax induce chemotaxis, along with complementing activation and antibody production. The Titermax adjuvant also has the ability to form a microparticulate water-in-oil emulsion with a copolymer and metabolizable squalene oil.



How vaccines work

Other Adjuvants

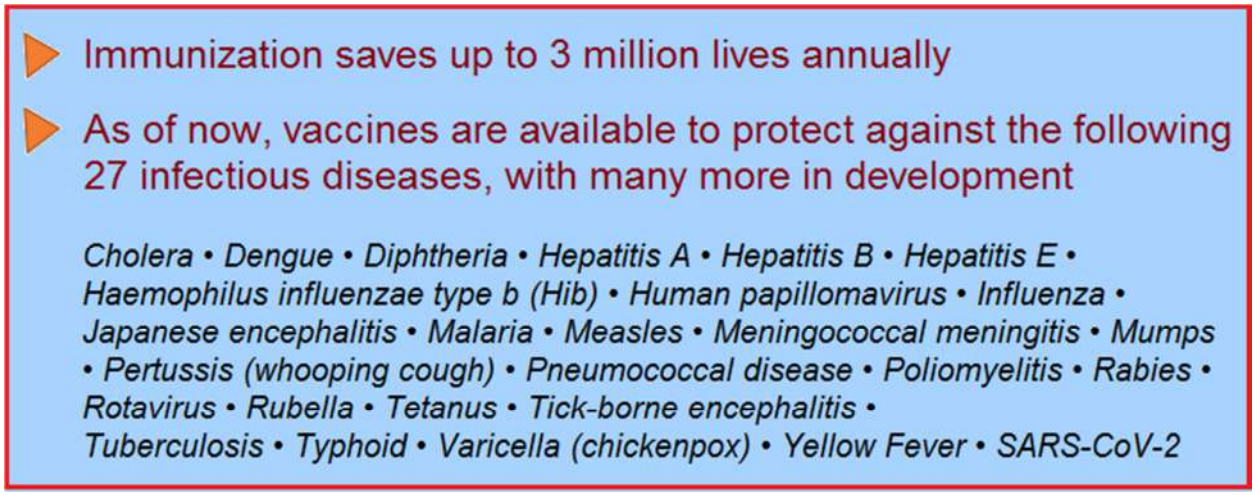
Specol: It is water in purified mineral oil. The number of toxic effects it produces is lower and it also induces an immune response comparable to Freund's adjuvant.

Aluminum salts: Aluminum salt adjuvants are used with antigens: As aluminum-precipitated vaccines or aluminum-adsorbed vaccines. Al (OH) can be used to adsorb proteins in a ratio of 50 to 200 g protein per mg aluminum hydroxide. They are generally weaker adjuvants than emulsion adjuvants. However, they induce a mild inflammatory response. Due to their efficacy of generating memory cells and for safety reasons, the Al (OH) adjuvants are mainly used as primary adjuvants in human vaccinations.

Immunization

Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine, which have clearly defined target group. It is a proven tool for controlling and eliminating life-threatening infectious diseases. It may be of two types; active immunization and passive immunization

Active immunization: It is the process of stimulating the specific immune response in individual through administration of a vaccine or toxoid. It stimulates the immune system to produce antibodies against a particular infectious agent. It may be artificial active immunization, where the microbe is injected into the person before they are able to take it in naturally. The microbe is treated, so that it will not harm the infected person. Depending on the type of disease, it can be taken with dead microbes, parts of the microbe, or treated toxins from the microbe, such as vaccinations.



Passive immunization: It is the process of conferring of specific immunity to a person by administration of preformed antibodies derived from humans or animals. It is used when there is a high risk of infection and insufficient time for the body to develop its own immune response. It may be natural and artificial. Natural passive immunization or immunity is the resistance passively transferred from mother to foetus through placenta or to infants through first milk (colostrum). It is maternal IgG that confers initial immunity to new born. Artificial passive immunization is achieved by transfer of antibodies made by someone else. These antibodies neutralize the infectious agents in the usual way, but the protection lasts only a few weeks because the antibodies gradually break down and are not replaced. One of the popular example of artificial passive immunization is convalescent plasma therapy (plasma taken from recovered individual through plasmapheresis and administer to sick individual).

Nobel Prizes for Immunologic Research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxin
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff	Russia	Role of phagocytosis (Metchnikoff)
	Paul Ehrlich	Germany	Antitoxin (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Bordet	Belgium	Complement-mediated bacteriolysis

1930	Karl Landsteiner	United States	Discovery of human blood group
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. M. Burnet	Australia	Discovery of acquired immunological tolerance
	Peter Medawar	Great Britain	
1972	Rodney R. Porter	Great Britain	Chemical structure of antibody
	Gerald M. Edelman	United States	
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	Baruj Benacerraf	United states	Major Histocompatibility Complex
	George Snell	United States	
	Jean Dausset	United States	
1984	Cesar Milstein	Great Britain	Monoclonal antibody
	Georges F. Köhler	Germany	
	Niels K. Jerne	Denmark	
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas	United States	Transplantation immunity
	Joseph Murray	United States	
1996	Peter C. Doherty	Australia	The specificity of the cell-mediated immune response
	Rolf M. Zinkernagel	Switzerland	

Different branches of immunology

- **Classical immunology:** deals with the fields of epidemiology and medicine.
- **Clinical immunology:** study of diseases caused by disorders of the immune system (failure, aberrant action, and malignant
- **Computational immunology:** deals with the organization of massive, raw immunological data with the help of computational approaches into an understandable form, enabling the researcher to generate meaningful interpretations.
- **Diagnostic immunology:** study of diagnostic method that relies on antigen-antibody reaction for detection of the disease. It is also called as immunological diagnostics.
- **Evolutionary immunology:** study of the evolution of immunity and the immune system over ages.

- **Systems immunology:** study of immunology with the approach of system biology involving various mathematical approaches and computational methods to examine the interactions within cellular and molecular networks of the immune system.

- **Immunomics:** study of immune system regulation and response to pathogens using genome-wide approaches.

- **Immunoproteomics:** study of large sets of proteins (proteomics) involved in the immune response.

- **Immunophysics:** interdisciplinary research field using immunological, biological, physical and chemical approaches to elucidate and modify immune-mediated mechanisms and to expand our knowledge on the pathomechanisms of chronic immune-mediated diseases

- **Immunoengineering:** new discipline that creates and applies engineering tools and principles to investigate and modulate the immune system.

- **Immunochemistry:** A branch of biochemistry concerned with immune responses and systems.

- **Ecoimmunology:** tudy of the causes and consequences of variation in immunity. It is an interdisciplinary field combining aspects of immunology with ecology, biology, physiology, and evolution. It is also called as Wild immunology.

- **Immunopathology:** branch of medicine that deals with immune responses associated with disease.

- **Nutritional immunology:** field of **immunology** that focuses on studying the influence of **nutrition** on the immune system and its protective functions.

- **Psychoneuroimmunology:** study of the effect of the mind on health and resistance to disease.

- **Reproductive immunology:** field of medicine that studies interactions between the immune system and components related to the reproductive system.

- **Circadian immunology:** study on the effect of circadian rhythm on the immunity.

- **Immunotoxicology:** study of toxic effects of chemicals (or in some cases physical agents such as radiation) on the immune system.

- **Palaeoimmunology:** study of matrix proteins in historic and pre-historic materials. Using histpochemical analysis.

- **Tissue-based immunology**

    - ***Testicular immunology****:* study of the immune system within the testis.

- ***Immunodermatology:*** study of immunologic phenomena as they affect skin disorders and their treatment or prophylaxis.
- ***Intravascular immunology***: study of immune response in the bloodstream, and its role in fighting the spread of pathogens.
- ***Osteoimmunology:*** study of how the immune and skeletal systems interact.
- ***Mucosal immunology:*** study of the immune system associated with mucosal sites such as the gut mucosa that comprises Peyer's patches (PPs), intestinal lamina, etc.
  - ***Respiratory tract antimicrobial defense system***: Respiratory tract
- ***Neuroimmunology:*** study of neurological conditions caused by the immune system becoming mis-programmed and attacking itself rather than protecting the body from foreign invaders such as viruses and bacteria.
- ***Ocularimmunology:*** deals with highly specialized diagnostic and therapeutic skills in caring for patients with destructive inflammatory diseases of the eye mediated by abnormal immunoregulatory processes.
- ***Cancer immunology/Immunooncology:*** the study and development of treatments that take advantage of the body's immune system to fight cancer

Beneficiary	Age	Vaccine
Infants	Birth	BCG* and OPV**
	6 weeks	DPT&OPV
	10 weeks	DPT&OPV
	14 weeks	DPT&OPV
	9 months	Measles vaccine
	18 months	DPT& OPV(Booster dose)
Children	5 years	DT vaccine
	10 years	Tetanus Toxoid
	16 years	Tetanus Toxoid

National immunization schedule-India

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