Human have three basic protection mechanisms against infectious agents, which are follows;

1. Natural barriers,
2. Innate, antigen-nonspecific immune defenses,

**Natural barriers**

Anatomical barriers are the physical barriers that prevent the entry and colonization of many microbes. The skin is dry, acidic, and has a lower temperature than body temperature. These conditions are not suitable for bacterial growth. Mucous membranes secrete mucus. The mucus traps microbes. Mucus also contains lysozyme to degrade bacterial structure. There are two other molecules lactoferrin and lactoperoxidase. Lactoferrin binds iron and keep it from microbes, and lactoperoxidase generates toxic superoxide radicals that kill microbes. A cilium (plural *cilia*) is an organelle found in epithelial cells. They propel mucus and trapped microbes upwards towards the throat. Then the microbes are swallowed and are killed in the stomach. Also the epithelial cells of nose and sinuses contain cilia.

Coughing and sneezing remove mucus and trapped microbes. Also vomiting, diarrhea, urine, tear, saliva and sweat remove pathogens and toxins from the body.

The normal body flora keep away harmful microbes by producing metabolic products such as fatty acids, bacteriocins, by covering host cells, by using nutrients and by stimulating the immune system.

There are many antigen-nonspecific antimicrobial chemicals produced by the body. The hydrochloric acid and enzymes found in gastric secretions and they destroy microbes that are swallowed. Lysozyme is found in tears, mucus, saliva, plasma, tissue fluid, etc. Lysozyme breaks down of peptidoglycan in bacteria and cause osmotic lysis. Defensins form pores in the cytoplasmic membrane of a variety of microorganisms. Defensins are produced by leukocytes, epithelial cells, and other cells. They are also found in blood plasma and mucus. Cathelicidins are proteins produced by skin and mucosal epithelial cells. The cathelicidins are also directly toxic to a variety of microorganisms. Lactic and fatty acids, found in sweat and sebaceous secretions, inhibit microbes on the skin. Lactoferrin and transferrin trap iron and prevent its use by microorganisms.

**Innate immune system**

Innate immune system are formed by cells and molecules. It has different types of cells. They are phagocytes and lymphocytes. Most important cells are phagocytes. There are two types of phagocytes. The mononuclear phagocytes are circulating monocytes and tissue macrophages. The
other family of phagocytes is polymorphonuclear granulocytes. In addition to the tissue macrophages, splenic macrophages are important for clearing bacteria, especially encapsulated bacteria, from blood. Asplenic (congenitally or surgically) individuals are highly susceptible to pneumonia, meningitis, and other manifestations of *Streptococcus pneumoniae, Neisseria meningitidis*, and other encapsulated bacteria.

There are three types of polymorphonuclear granulocytes. They are neutrophil, eosinophil and basophil. Neutrophils are the first cell type to respond to the most infections, particularly bacterial and fungal infections. They can ingest microbes in the circulation, and they can rapidly enter extravascular tissues at sites of infection. They release the enzyme kallikrein and other enzymes. They catalyze the synthesis of prostaglandins and bradykinins. Prostaglandins and bradykinins promote inflammation by causing vasodilation, increasing vascular permeability, and increasing mucous production. In addition, during phagocytosis the granules may leak their contents to cause tissue damage. Their life span is a few hours to a few days. They do not multiply. They circulate in the blood for around 6 hours and they undergo apoptosis. In tissue, they function for several hours and die. The dead neutrophils produce pus. The eosinophils are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes extracellularly. They play specialized role in immunity to fungi, protozoa, and parasitic worms (helminths). Basophils and mast cells release histamine, leukotrienes, and prostaglandins, that promotes inflammation.

There are four populations of lymphocytes play important roles in innate immunity. They are NK cells, NKT cells, Intraepithelial T-lymphocytes (γδ T cells), and B-1 lymphocytes. NK cells are able to recognize and kill infected cells, cancer cells, and stressed cells. They also secrete inflammatory cytokines to promote an inflammatory response. Cytokines such as interleukin-2 (IL-2) and interleukin-12 (IL-12) produced by respectively Th1 lymphocytes and macrophages activate NK cells. Once activated, NK cells themselves produce large amounts of IFN-gamma to activate macrophages so they can kill ingested microbes. NK cells also play a role in adaptive immune responses. NK cells have roles in antibody-dependent cellular cytotoxicity (ADCC). They can kill antibody bounded cells. NKT cells cells are a subset of lymphocytes. They recognize glycolipid antigen presented by CD1 by using TCR receptors. Intraepithelial T-lymphocytes (γδ T cells) may protect mucosal surface the body. They are found in the epidermis of the skin and the mucosal epithelia. They can recognize pathogen-associated molecular patterns (PAMPs) by using restricted TCRs. B-1 lymphocytes are found mostly in the peritoneal and pleural cavities. They respond to T-independent antigens, such as polysaccaride and lipid antigens of microbes, by producing antibodies. These antibodies are called natural antibodies.

Some molecules involved in innate immune response. They are complement proteins and acute phase proteins. The complement system is a series of proteins circulating in the blood and found in the
fluids surrounding tissues. In normal conditions, the complement proteins are in inactivae form. In response to the recognition, they are activated. There are three activation pathways that form the complement system. These are the classical complement pathway, the lectin pathway, and the alternative complement pathway. The pathways produce a key enzyme called C3 convertase. The classical complement pathway is activated by antigen-antibody complexes. The lectin pathway is activated by the interaction of microbial carbohydrates with mannose-binding lectin (MBL). The alternative complement pathway is activated by microbe. The result of complement activation is the promoting of immunity responses by triggering inflammation, by enhancing of phagocytosis and by lysis of gram-negative bacteria. On activation, some components of complement system play role in activation of naive B-lymphocytes and in the removing of immune complexes from the body.

Many plasma proteins increase rapidly after infection. This protective response is called the acute phase response to infection. The proteins, that are produced at acute phase of infection, are called acute phase proteins or acute phase reactants. Plasma MBL is a protein that recognizes microbial carbohydrates and can bind microbes for phagocytosis or activate the complement cascade by the lectin pathway. Surfactant proteins in the lung protect the airways from infection. C-reactive protein (CRP) binds to phosphorylcholine on microbes and coats the microbes for phagocytosis by macrophages, which express a receptor for CRP.

Innate immunity recognize molecules are not found in mammalian cells. These microbial molecules are called pathogen-associated molecular patterns or PAMPS. Some PAMPs are listed below.

- Lipopolysaccharide
- Bacterial lipoproteins and lipopeptides
- Porins
- Peptidoglycan
- Lipoteichoic acids
- Lipoarabinomannan
- Mannose-rich glycans
- Flagellin
- Bacterial and viral nucleic acid
- N-formylmethionine
- Double-stranded viral RNA
- Single-stranded viral RNA
- Lipoteichoic acids, glycolipids, and zymosan
- Phosphorylcholine and other lipids
In order to recognize PAMPs, various body cells have a variety of receptors called pattern-recognition receptors or PRRs. Cells that typically have pattern recognition receptors include macrophages, dendritic cells, endothelial cells, mucosal epithelial cells, and lymphocytes.

Endocytic pattern-recognition receptors are found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes. They are mannose, scavenger, opsonin, and N-formly methionine receptors.

A series of signaling pattern-recognition receptors known as toll-like receptors (TLRs) are found on the surface of a variety of defense cells and other cells. The binding of a microbial antigens to signalling TLRs, transmits a signal to the host cell's nucleus. This signal induces the expression of genes coding for the synthesis of cytokines.

Many of the TLRs after binding to PAMPs stimulate to produce the inflammatory cytokines. The cytokines that produced in innate immun responses are IL-1, IL-6, IL-8, IL-12, IL-15, IL-18, type-I interferon, interferon gamma and TNF-alpha. TNF-alpha is the main cytokine that mediates acute inflammation. In excessive amounts it causes systemic complications such as the shock cascade.

The other signaling PRRs found in the membranes of the endosomes are TLR-3, TLR-7, TLR-8 and TLR-9. Most of the TLRs that bind to viral components trigger the synthesis of cytokines called interferons that block viral replication within infected host cells.

NOD proteins including NOD-1 and NOD-2, are cytostolic proteins that play role in the recognition of intracellular peptidoglycan components. RIG-1 and MDA-5 are cytoplasmic sensors for viral RNA. After activation, they stimulate the production of interferon.

When effectors cells of innate immun system recognize microbial antigens, they respond by phagocytosis, by producing cytokines, by activating complement system, by extracellular killing, by synthetizing acute phase proteins and by homing of effector cells to infection side. All this responses of immune systems form the inflammation. Acute inflammation is an early defense mechanism to an infection for preventing its spread from the initial focus and signaling subsequent specific immune responses. The three major events in acute inflammation are (1) expansion of capillaries to increase blood flow (causing redness or a rash and releasing heat); (2) increase in permeability of the microvasculature structure to allow escape of fluid, plasma proteins, and leukocytes from the circulation (swelling or edema); and (3) recruitment of macrophages their accumulation and response to infection at the site of injury.

In order to perform effector functions, the cells have to pass out the blood vessels. This process is called diapedesis. The resident macrophages recognize the microbe and produce soluble proteins called cytokines. Two of these cytokines, called tumor necrosis factor (TNF) and interleukin-1 (IL-1) stimulate the endothelial cells for the expression the adhesion molecules and the production of chemokines. The endothelial adhesion molecules are called E-selectin, P-selectin and ligands for
integrins. Circulating neutrophils and monocytes express ligands for selectins. These ligands bind weakly to the selectins. The neutrophils become tethered to the endothelium. Following the leucocytes begins to roll on the endothelial surface. The other molecules named integrins are present in a low-affinity state on unactivated leukocytes. The endothelial cells produce chemokines. These chemokines stimulate to increase the affinity of the leukocyte integrins for their ligands on the endothelium. The integrins leukocytes bind firmly to their ligands. The cells pass out the blood vessels and club at the infection site. Chemokines also stimulate the motility of leukocytes. As a result, the leukocytes migrate along the chemokine concentration gradient to the site of infection.

The recognition of microbes by neutrophils or macrophages induces the phagocytosis of the microbes and to kill the ingested microbes. In phagocytosis process, the phagocyte membrane zip up around the recognized microbe. And the membrane closes up and corners the particle. At the end the target particle is ingested in a membrane-bound vesicle, called a phagosome. The phagosome fuses with lysosome to form phagolysosomes. At the same time several enzymes in the phagolysosomes are activated. One of these enzymes, called phagocyte oxidase, converts molecular oxygen into superoxide anion and free radicals. These substances are called reactive oxygen intermediates (ROIs). They are toxic to the ingested microbes. A second enzyme, called inducible nitric oxide synthase, catalyzes the conversion of arginine to nitric oxide (NO), also a microbicidal substance. The third set of enzymes are lysosomal proteases, which break down microbial proteins.

All these microbicidal substances are produced mainly within lysosomes. They act on the ingested microbes but do not damage the phagocytes. In strong reactions, the same enzymes may be liberated into the extracellular space and may injure host tissues.

**Antigen-specific response**

Microbes enter the body mainly through the skin (by contact), the gastrointestinal tract (by ingestion), the respiratory tract (by inhalation), the genitourinary system (by sexual contact) and the blood (by injection of insects bites). The epithelial tissue contains a population of professional APCs.

If a microbe enter the body by different way it may be captured by immature dendritic cells that live in these tissues. And these antigens, inside the APC, are transported to lymph nodes. Soluble antigens in the lymph are picked up by dendritic cells that reside in the lymph nodes, and blood-borne antigens are handled by dendritic cells in the spleen. In regional lymph nodes is the only meeting place for the antigens and T lymphocytes. When microbial antigens are introduced at any site in the body the T cell response begins within 12 to 18 hours.

In a lymphoid organ, the three main types of APC are; DCs, macrophages and B cells. Extracellular proteins are internalized by professional APCs into vesicles. These proteins are processed and displayed by class II MHC molecules. But proteins in the cytosol of nucleated cells are processed and displayed by class I MHC molecules. Extracellular microbes are captured by APCs, including B
lymphocytes and macrophages, and are presented by class II molecules. Class II MHC molecules are expressed mainly by APCs. Because of the specificity of CD4 for class II, class II-associated peptides are recognized by CD4⁺ T lymphocytes. The main function CD4⁺ T lymphocytes to help. These helper T cells help B lymphocytes to produce antibodies, and they help phagocytes to ingest and destroy microbes.

Neither of these mechanisms is effective against viruses that live in the cytoplasm of host cells. Cytosolic antigens are processed and displayed by class I MHC molecules, which are expressed on all nucleated cells—again, as expected, because all nucleated cells can be infected with some viruses. Class I-associated peptides are recognized by CD8⁺ T lymphocytes, which differentiate into CTLs. The CTLs kill the infected cells.

The main function of T lymphocytes in adaptive immunity is elimination of microbes that are able to live in phagocytic vesicles or in the cytoplasm of infected cells. CD4⁺ helper T lymphocytes also help B cells to produce antibodies.

CD4⁺ helper T cells may differentiate into subsets of effector cells. These cells produce the cytokines to perform their functions. These subsets are called T_H1 cells and T_H2 cells (for type 1 helper T cells and type 2 helper T cells). The most important cytokine produced by T_H1 cells is interferon-γ (IFN-γ). IFN-γ is a potent activator of macrophages. It also stimulates the production of antibody isotypes. These antibodies promote the phagocytosis of microbes and activate complement. Some product of complement bind phagocyte complement receptors. Therefore, T_H1 cells stimulate phagocyte-mediated ingestion and killing of microbes, the key component of cell-mediated immunity. IFN-γ also stimulates the expression of class II MHC molecules and B7 costimulators on APCs, especially macrophages. And this action of IFN-γ amplify the T cell responses.

T_H2 cells, produce IL-4 which stimulates the production of IgE antibodies, and IL-5, which activates eosinophils. Therefore, T_H2 cells stimulate phagocyte-independent, eosinophil-mediated immunity. This response is especially effective against helminthic parasites. Some of the cytokines produced by T_H2 cells, such as IL-4, IL-10, and IL-13, inhibit macrophage activation and suppress T_H1 cell-mediated immunity.

Therefore, the benefit of cell-mediated immune responses may be determined by a balance between the activation of T_H1 and T_H2 cells in response that microbe.

Macrophages and dendritic cells respond to many bacteria and viruses by producing a cytokine called IL-12. The same APCs present antigens to naive T cells and produce IL-12. IL-12 promotes the differentiation of the T cells into the T_H1 subset. If the infectious microbe does not elicit IL-12 production by APCs, the T cells themselves produce IL-4. IL4 induces the differentiation of naive T cells towards the T_H2 subset.
CD8$^+$ T lymphocytes activated by antigen and costimulators differentiate into CTLs that are able to kill infected cells expressing the antigen. Effector CTLs kill infected cells by secreting proteins that create pores in the membranes of the infected cells and induce DNA fragmentation and apoptotic death of these cells.

A fraction of antigen-activated T lymphocytes differentiates into memory T cells. The memory T cells are long lived and functionally inactive. These memory T cells can be found in lymphoid tissues, in mucosal barriers, and in the circulation. Memory T cells do not continue to produce cytokines or kill infected cells. Memory T cells may answer so rapidly when they encounter the same antigen.

Antibodies are the primary protection against extracellular bacteria and reinfection. Antibody is important for promoting complement activation, opsonizing the bacteria for phagocytosis, blocking bacterial adhesion, and neutralizing (inactivating) exotoxins (e.g., tetanospasmin, botulinum toxin) and other cytotoxic proteins produced by bacteria (e.g., degradative enzymes). Vaccine immunization with inactivated exotoxins (toxoids) is the primary means of protection against the potentially lethal effects of exotoxins.

IgM antibodies are produced early in the antibacterial response. IgM bound to bacteria activates the classical complement cascade, promoting both the direct killing of gram-negative bacteria and the inflammatory responses. The large size of IgM limits its ability to spread into the tissue. Later in the immune response, T-cell help promotes differentiation of the B cell and immunoglobulin class switching to produce IgG. IgG antibodies are the predominant antibody, especially on rechallenge. IgG antibodies, except IgG4, fix complement and promote phagocytic uptake of the bacteria through Fc receptors on macrophages. The production of IgA requires TH2 cytokines and other factors. IgA is the primary secretory antibody and is important for protecting mucosal membranes. Secretory IgA acquires the secretory component that promotes interaction and passage of IgA through mucosal epithelial cells. IgA neutralizes the binding of bacteria and their toxins at epithelial cell surfaces.

Some bacteria are able to resist microbicidal mechanisms. They use different ways for this aim. These mechanisms are listed below.

- The escaping from phagocytosis by covering of the microbial antigens and by forming coagulase mediated fibrin.
- The inhibition of the fusing of endosome to phagosome.
- The escaping into cytoplasm before the fusing of endosome to phagosome.
- The resistance to and destroying of microbicidal enzyme in phagolysosome.
- The inhibition of complement activation.
- The production of enzyme for killing of the phagocytes.
The stimulation of apoptosis of macrophages.
The removing of MAC complex by elongating of LPS
Clevage of IgA
Binding to Fc portion of antibody
Changing of bacterial antigenic apperance

**Specific Immune Responses to Fungi**

The primary protective responses to fungal infection are promoted by TH1-mediated inflammatory reactions. Patients deficient in these responses (e.g., patients with AIDS) are most susceptible to fungal (opportunistic) infections. Macrophages activated by IFN-γ are important for killing the fungi. Neutrophil production of cationic proteins may be important for some fungal infections (e.g., mucormycosis), and nitric oxide may be important against *Cryptococcus* and other fungi. Antibody, as an opsonin, may facilitate clearance of the fungi.

**Specific Immune Responses to Parasites**

Extracellular parasites, such as *Trypanosoma cruzi*, *Toxoplasma gondii*, and *Leishmania* species, are phagocytosed by macrophage. Antibody may facilitate the uptake of (opsonize) the parasites. Killing of the parasites follows activation of the macrophage by IFN-γ (produced by NK, γ/δ T, or CD4 TH1 cells) or TNF-α (produced by other macrophages) and induction of oxygen-dependent killing mechanisms (peroxide, superoxide, nitric oxide). TH1 production of IFN-γ and activation of macrophages are also essential for defense against intracellular protozoa and for the development of granulomas around *Schistosoma mansoni* eggs and worms in the liver. The granuloma, formed by layers of inflammatory cells, protects the liver from toxins produced by the eggs.

Neutrophils phagocytose and kill extracellular parasites through both oxygen-dependent and oxygen-independent mechanisms.

For parasitic worm infections, cytokines produced by CD4 TH2 T cells are very important for stimulating the production of IgE and the activation of mast cells. IgE bound to Fc receptors on mast cells targets the cells to antigens of the infecting parasite. Eosinophils localize near parasites, bind to IgG or IgE on the surface of larvae or worms, degranulate by fusing their intracellular granules with the plasma membrane, and release the major basic protein into the intercellular space. The major basic protein is toxic to the parasite. In the lumen of the intestine, antigen binding and cross-linking of the IgE on the mast cell surface stimulate the release of histamine and substances toxic to the parasite and promote mucus secretion to coat and promote expulsion of the worm. IgG antibody also plays an important role in antiparasitic immunity, as an opsonin and by activating complement on the surface of the parasite.
Animal parasites have developed remarkable mechanisms for establishing chronic infections in the vertebrate host. These mechanisms include intracellular growth, inactivation of phagocytic killing, release of blocking antigen, and development of cysts. The African trypanosomes can reengineer the genes for their surface antigen (variable surface glycoprotein) and therefore change their antigenic appearance. Schistosomes can coat themselves with host antigens, including MHC molecules.

Antiviral Responses

The humoral and cellular immune responses are important for antiviral immunity. Unlike for a bacterial infection, the ultimate goal of the immune response in a viral infection is to eliminate both the virus and the host cells harboring or replicating the virus. Interferons, NK cells, CD4 TH1 responses, and CD8 cytotoxic killer T cells are more important for viral infections than for bacterial infections.

Body temperature, fever, interferons, other cytokines, the mononuclear phagocyte system, and NK cells provide a local rapid response to viral infection and also activate the specific immune defenses. Often the nonspecific defenses are sufficient to control a viral infection, thus preventing the occurrence of symptoms. Viral infection can induce the release of cytokines (e.g., TNF, IL-1) and interferon from infected cells, immature dendritic cells, and macrophages. Body temperature and fever can limit the replication of or destabilize some viruses. Many viruses are less stable (e.g., herpes simplex virus) or cannot replicate (rhinoviruses) at 37°C or higher.

The dendritic cells and the macrophages phagocytose the viral and cell debris from virally infected cells. Macrophages in the liver (Kupffer cells) and spleen rapidly filter many viruses from the blood. Antibody and complement bound to a virus facilitate its uptake by macrophages (opsonization). Dendritic cells and macrophages also present antigen to T cells and release IL-1, IL-12, and IFN-α to expand the innate and initiate the antigen-specific immune responses. Activated macrophages can also distinguish and kill infected target cells.

NK cells are activated by interferon and IL-12 to kill virally infected cells. Viral infection may reduce the expression of MHC antigens or may alter the carbohydrates on cell surface proteins to provide cytolytic signals to the NK cell.

Interferon is a very important defense against infection, but it is also a cause of the systemic symptoms associated with many viral infections, such as malaise, myalgia, chills, and fever (nonspecific flulike symptoms), especially during viremia. IFN-α and IFN-β are type 1 interferons. B cells, epithelial cells, monocytes, macrophages, and immature dendritic cells make IFN-α. Fibroblasts and other cells make IFN-β in response to viral infection and other stimuli. IFN-γ is a type 2 interferon, a cytokine produced by activated T and NK cells later in the infection. Although IFN-γ inhibits viral replication, its structure and mode of action differ from those of the other interferons. IFN-γ is also known as macrophage activation factor and is the defining component of the TH1 response.
IFN-α and IFN-β can be induced and released within hours of infection. The interferon binds to specific receptors on the neighboring cells and induces the production of antiviral proteins – the antiviral state. Interferons stimulate cell-mediated immunity by activating effector cells and enhancing recognition of the virally infected target cell. Interferons stimulate pre-NK cells to differentiate to NK cells to activate an early, local, natural defense against infection. Activation of macrophages by IFN-γ promotes production of more IFN-α and IFN-β, secretion of other biologic response modifiers, phagocytosis, recruitment, and inflammatory responses. IFN-γ increases the expression of class II MHC antigens on the macrophage to help promote antigen presentation to T cells. IFN-α and IFN-β increase the expression of class I MHC antigens, enhancing the cell's ability to present antigen and making the cell a better target for cytotoxic T cells (CTLs).

Antibody blocks the progression of disease through the neutralization and opsonization of cell-free virus. Protective antibodies are generated toward the viral capsid proteins of naked viruses and the glycoproteins of enveloped viruses. These antibodies interact with cell surface receptors (viral attachment proteins). Binding of antibody to viral proteins also opsonizes the virus, promoting its uptake and clearance by macrophages. Antibody recognition of infected cells can also promote antibody-dependent cellular cytotoxicity (ADCC) by NK cells. Antibodies to other viral antigens may be useful for serologic analysis of the viral infection. The major antiviral role of antibody is to prevent the spread of extracellular virus to other cells. Antibody is especially important in limiting the spread of the virus by viremia, preventing the virus from reaching the target tissue for disease production. Antibody is most effective at resolving cytolytic infections. Resolution occurs because the virus kills the cell factory and the antibody eliminates the extracellular virus. Antibody is the primary defense initiated by vaccination.

The CD4 TH1 response is generally more important than TH2 responses for controlling a viral infection, especially noncytolytic and enveloped viruses. CTLs induce apoptosis of the target cell. The CD8 CTL response probably evolved as a defense against virus infection. Cell-mediated immunity is especially important for resolving infections by syncytia-forming viruses (e.g., measles, herpes simplex, and varicella-zoster viruses), which can spread from cell to cell without exposure to antibody; by noncytolytic viruses (e.g., hepatitis A and measles viruses); and for controlling latent viruses (herpes viruses and papillomaviruses). CTLs kill infected cells and, as a result, eliminate the source of new virus.

Viral Mechanisms for Escaping the Immune Response

A major factor in the virulence of a virus is its ability to escape immune resolution. Viruses may escape immune resolution by evading detection, preventing activation, or blocking the delivery of the immune response. Some viruses even encode special proteins that suppress the immune response.