Immunity – (Innate and Acquired)

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Learning objectives

By the end of this session student will know

- Define innate immunity, acquired immunity
- To understand cells involved in innate and acquired immunity

IMMUNITY

- The term 'immunity' (Latin word '*immunitas*', means freedom from disease) is defined as the resistance offered by the host against microorganism(s) or any foreign substance(s).
- Immunity can be broadly classified into two types-
  - Innate immunity- present right from the birth
  - Acquired / Adaptive- acquired during the course of the life

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Resistance to infection that an individual possesses from birth	Resistance to infection that an individual acquires during his lifetime
Immune response occurs in minutes	Immune response occurs in days
Prior exposure to the antigen is not required	Develops following the antigenic exposure
Diversity is limited, acts through a restricted set of reactions	More varied and specialized responses

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Immunological memory responses are absent	Immunological memory responses are present
Respond to microbial antigens that are not specific to some microbe, rather shared by many microbes (called as microbes-associated molecular patterns)	Respond to specific microbial antigens
Host cell receptors (pattern recognition receptors) are non- specific – e.g. Toll-like receptor	Host cell receptors are specific- e.g. T cell receptors and B cell immunoglobulin receptors

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Components of innate immunity Anatomical barriers such as skin and mucosa Physiological barriers (e.g. body temperature) Phagocytes (neutrophils, macrophages & monocytes) Natural killer (NK) cells Other Classes of lymphocytes –γδ T cells , NK–T cells, B–1 cells and marginal–zone B cells Mast cells Dendritic cells	Components of acquired immunity T cell B cell Classical complement pathway Antigen presenting cells Cytokines (IL–2, IL–4, IL–5, IFN–γ)
Complement pathways– alternate & mannose binding pathways Fever and inflammatory responses Normal resident flora Cytokines– TNF–α, certain interleukin (IL–1, IL–6, IL–8, IL–12, IL–16, IL–18), IFN–α, β and TGF– β Acute phase reactant proteins (APRs)	Types of acquired immunity– It can be classified in two ways: • Active and passive immunity • Artificial and natural immunity

INNATE IMMUNITY

- Innate immunity is the inborn resistance against infections that an individual possesses right from the birth, due to his genetic or constitutional makeup.

Features of innate immunity

- Acts in minutes
- Prior microbial exposure is not required
- Diversity is limited
- Non-specific
- No memory

Innate immunity

Type of innate immunity	Explanation	Examples
Species immunity	Innate immunity towards a microbe exhibited by all members of a given species	frogs are resistant to *Bacillus anthracis*; while toads are susceptible.
Racial immunity	innate immunity confined to a particular race; may be absent in other communities	Negroes of America are more susceptible to tuberculosis than the whites.
Individual immunity	Antimicrobial defense mechanisms that are confined to a particular individual; may not be exhibited by others.	One exception is identical twins who exhibit similar degrees of susceptibility to infections

Factors influencing innate immunity

- Age
- Hormone
- Nutrition

MECHANISMS OF INNATE IMMUNITY

- **Receptor interaction**
  - Following the exposure of microorganisms, several mediators of innate immunity are recruited to the site of infection.
  - The first step that takes place is *attachment*, which involves binding of the surface molecules of microorganisms to the receptors of cells of innate immunity.

MECHANISMS OF INNATE IMMUNITY

- ***Microbial surface molecules***-
  - Repeating patterns of conserved molecules which are common to most microbial surfaces; called as *Microbes-associated molecular patterns (MAMPs)*.
  - Examples - peptidoglycan, lipopolysaccharides (LPS), teichoic acid and lipoproteins present on bacterial surface.

MECHANISMS OF INNATE IMMUNITY

- ***Pattern recognition receptors (PRRs)-***
  - Molecules present on the surface of host cells (e.g. phagocytes) that recognize *MAMPs.*
  - Conserved regions, encoded by germ line genes.
  - *Toll like receptors(*TLRs) – classical examples of pattern recognition receptors.

MECHANISMS OF INNATE IMMUNITY

- ***Pattern recognition receptors (PRRs)-***
  - TLRs binds to MAMPs → signals are generated → activate transcription factors → stimulate expression of genes encoding cytokines & enzymes →antimicrobial activity.
  - Most important transcription factors activated by TLR signals are:
    - *Nuclear factor κβ (NF-κβ)* – promotes production of cytokines.
    - *Interferon regulatory factors* (IRFs) – stimulate expression of the antiviral interferons α & β.

Toll like receptors

- So named because they are similar to Toll receptors present in the fruit fly- *Drosophila,* where it is the main receptor for induction of innate immunity.
- There are **13 types** of Toll like receptors (TLR 1 to 13). Important ones are-
  - TLR-2 binds to bacterial peptidoglycan
  - TLR-3 binds to dsRNA of viruses
  - TLR-4 binds to LPS of Gram negative bacteria
  - TLR-5 binds to flagella of bacteria
  - TLR-7 & 8 bind to ssRNA of viruses
  - TLR-9 binds to bacterial DNA

Components of innate immunity

1. Anatomical and physiological barriers
2. Phagocytes
3. Natural killer (NK) cells and other classes of lymphocytes
4. Mast cells
5. Dendritic cells
6. Complement pathways
7. Inflammatory response
8. Normal resident flora
9. Cytokines
10. Acute phase reactant proteins (APRs)

Anatomical and physiological barriers

Anatomical Barrier	Function
Skin Barrier	
	• Mechanically prevents entry of microbes • Produces sebum containing antimicrobial peptides and fatty acids • Killing of microbes by intraepithelial lymphocytes
Mucosal Barrier	
1. Mucous membrane	Prevents entry of microbes mechanically and by producing mucous which entraps microbes
2.Cilia	Cilia present in the lower respiratory tract propel the microbes outside
3.Normal flora	Intestinal & respiratory mucosa are lined by normal flora.

Anatomical and physiological barriers

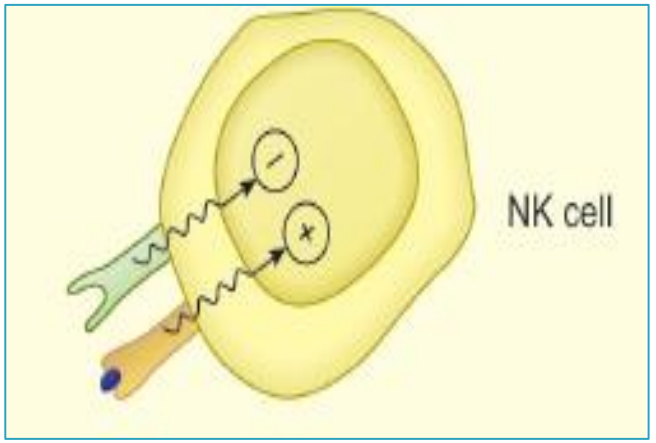
Physiological Barrier		Function
1.Temperature		Normal body temperature inhibits the growth of some microbes
2.Low pH		Gastric acidity inhibits most of the microbes
3.Secretory products of mucosa		
	Saliva	Enzymes in saliva damage the cell wall and cell membrane of bacteria
	Tears	Contains lysozyme, that destroys the peptidoglycan layer in bacterial cell wall
	Gastric juice	HCl kills microbes by its low pH
	Trypsin	Hydrolyse bacterial protein
	Bile salts	Interfere with bacterial cell membrane
	Fatty acids	Denature the bacterial proteins
	Spermine	Present in semen, inhibits growth of Gram positive bacteria
	Lactoferrin	Binds to iron, thus interferes with acquisition of iron by bacteria

Phagocytes

- Phagocytes – *neutrophils*, *macrophages* including *monocytes* are the main component of innate immunity.
- Rapidly recruited to the infection site. Phagocytosis involves three sequential steps:
  - Engulfment of microbes and subsequent hosting in phagosome.
  - Fusion of lysosome with phagosome to form phagolysosome
  - Microbial killing

Natural killer (NK) cells and o*ther classes of lymphocytes*

- NK cells:
  - Class of lymphocytes that kill virus infected cells and tumor cells.

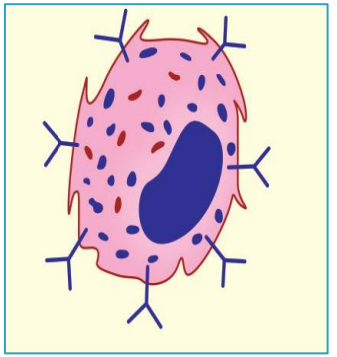


Natural killer (NK) cells and other classes of lymphocytes

- *γδ T cells* (also called as intraepithelial lymphocytes) –present in epithelial lining of skin and mucosa
- *NK–T cells* – present in epithelium and lymphoid organs
- *B–1 cells* – found mostly in the peritoneal cavity and mucosal tissues.
- *Marginal–zone B cells* – present at the edges of lymphoid follicles of spleen

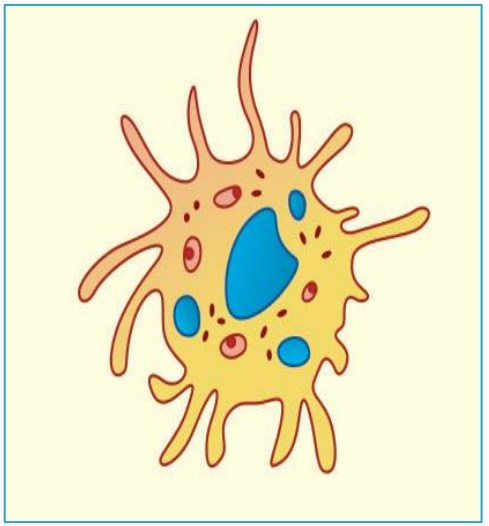
Mast cells

- Present lining the respiratory and other mucosa.
- Activated by microbial products binding to toll like receptors or by IgE antibody dependent mechanism.
- They release abundant cytoplasmic granules rich in histamine, prostaglandins & cytokines that initiate inflammation and proteolytic enzymes that can kill bacteria.



Dendritic cells

- Respond to microbes by producing numerous cytokines that initiate inflammation.
- Serve as vehicle in transporting the antigen(s) from the skin and mucosal site to lymph nodes where they present the antigen(s) to T cells – bridge between innate and acquired immunity.



Complement pathways

- Alternate and mannose binding pathways are the chief mediators of innate immunity.
- *Alternate complement pathway* is activated in response to bacterial endotoxin.
- *Mannose binding pathway* is stimulated by mannose carbohydrate residues on bacterial surface.

Complement pathways – Biological function

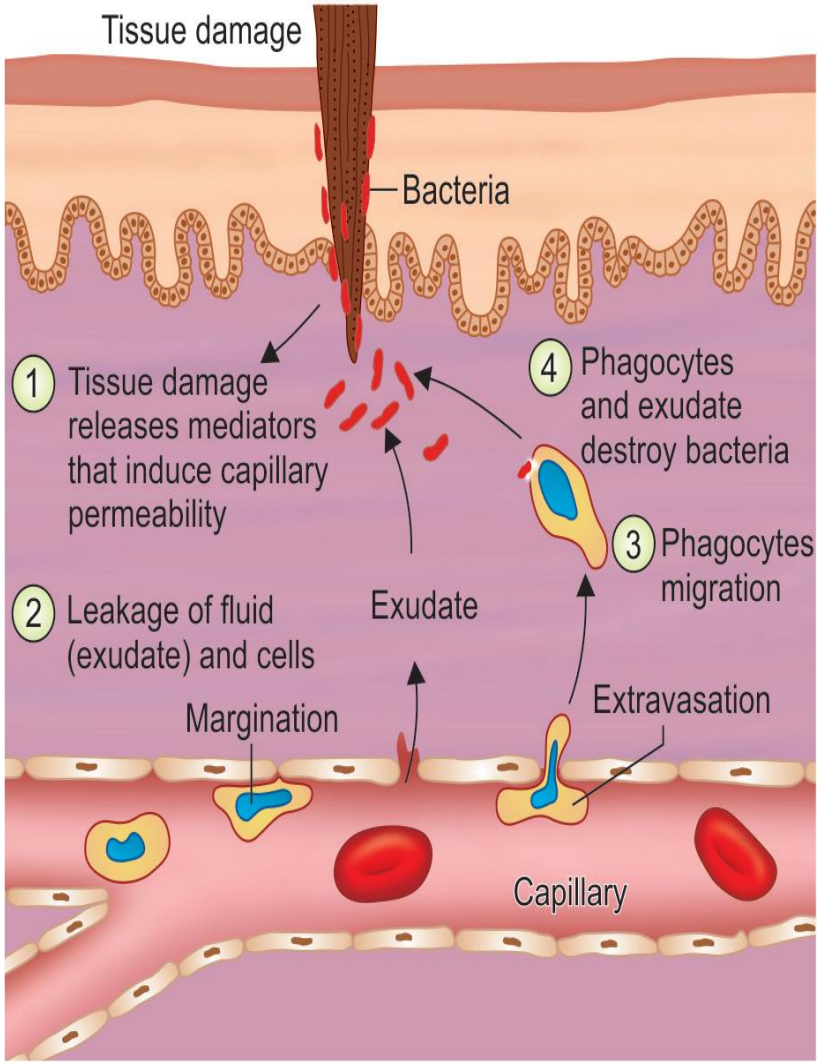
- Lysis of the target microbes (by forming pores on the microbial surfaces)
- Stimulate inflammation (by secreting inflammatory mediators)
- Stimulate acquired immunity– Complements are another bridge between innate and acquired immunity.

Inflammatory response

Inflammation is defined as the biological response of vascular tissues to harmful stimuli, such as microorganisms or other foreign substances.

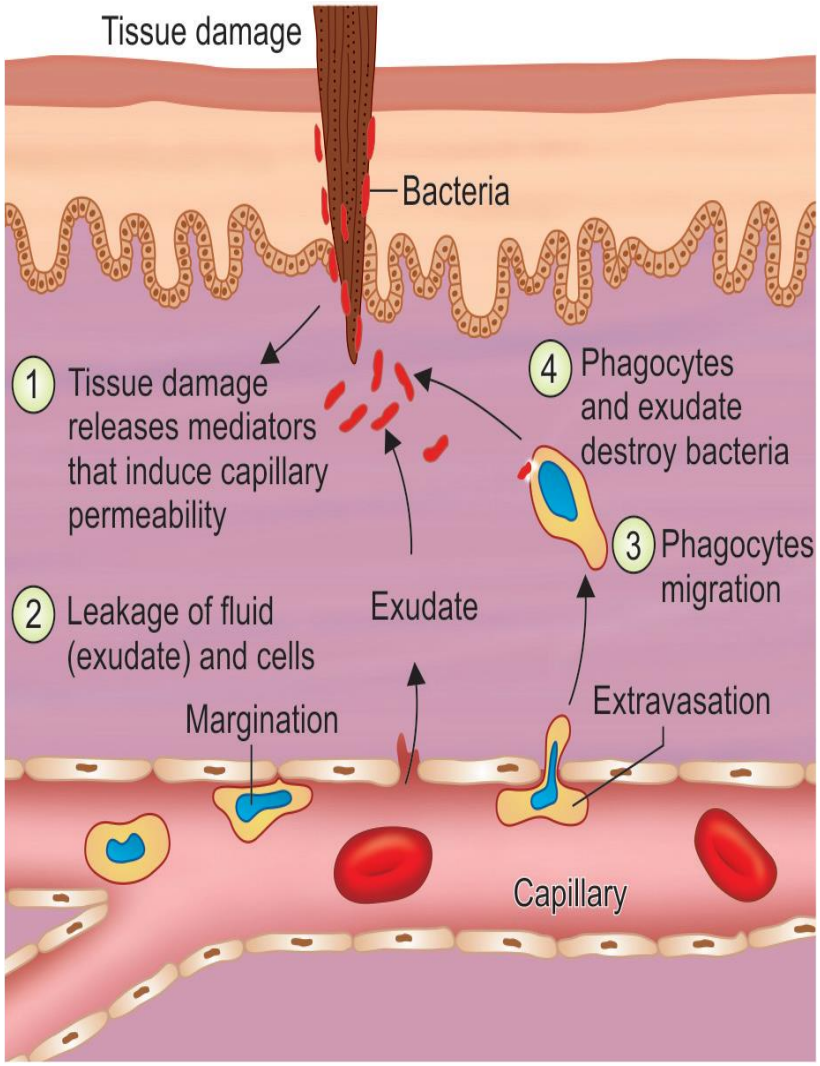
Inflammatory response

- *Vasodilation* due to release of vasoactive substances from the damaged tissues
- *Leakage* of plasma proteins through blood vessels



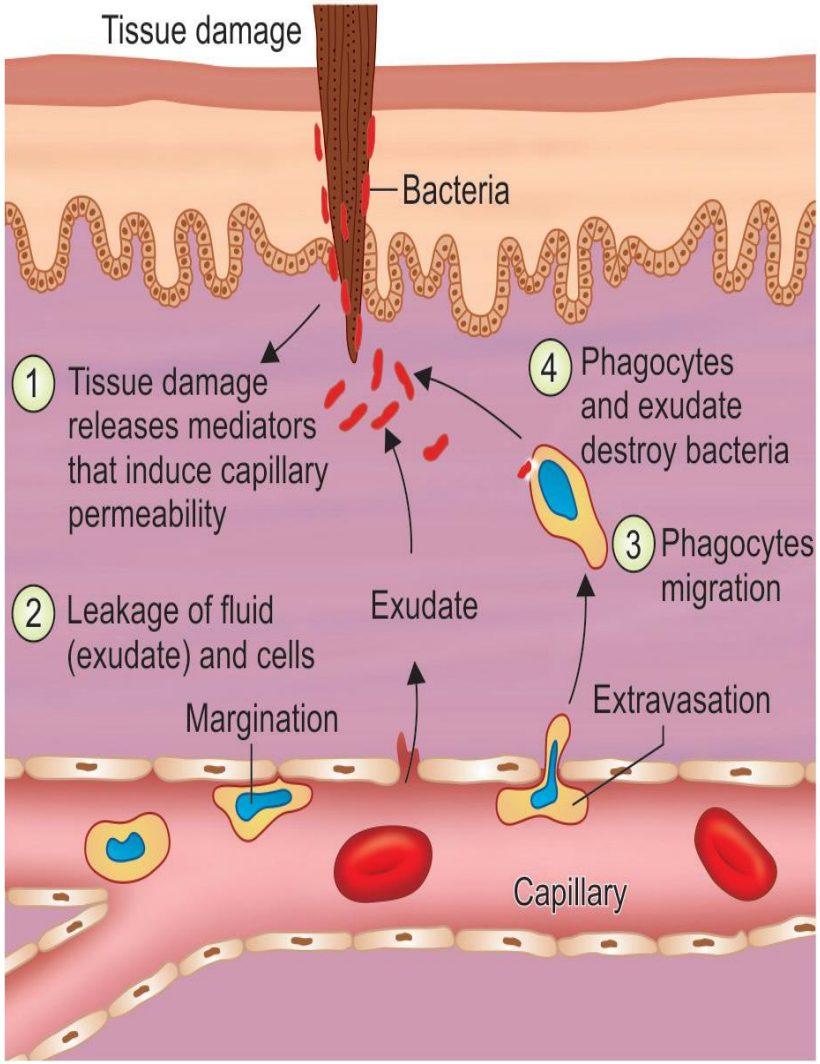
Inflammatory response

- Recruitment of phagocytes (e.g. neutrophils) to the site of inflammation.
- Phagocytes undergo the following steps
  - Margination (adherence to the endothelium).
  - Rolling on endothelium
  - Extravasation (moves out of the blood vessels)
  - Chemotactic migration to the inflammation site



Inflammatory response

- Engulfment of microbes and dead material by the phagocytes
- Destruction of the microbes
- Inflammation is not always protective in nature – hypersensitivity reactions (injurious consequence).



Normal resident flora

- Normal resident flora lining intestinal, respiratory and genital tract exert several antimicrobial activities.
- Compete with the pathogens for nutrition .
- Produce antibacterial substances.

Cytokines

- In response to the microbial antigens, dendritic cells, macrophages, and other cells secrete several cytokines that mediate many of the cellular reactions of innate immunity such as:
  - Tumor necrosis factor (TNF),
  - Interleukin-1 (IL-1), IL-6, IL-8, IL-10 & IL-16
  - Interferons (IFN-α, β) and
  - Transforming growth factor (TGF-β)

Acute phase reactant proteins (APRs)

- Proteins synthesized by liver at steady concentration, but their synthesis either increases or decreases exponentially during acute inflammatory conditions.
- APRs can also be synthesized by various other cells such as endothelial cells, fibroblasts, monocytes and adipocytes.

Positive APRs

- Proteins whose levels increase during acute inflammation. Examples include-
  - Serum Amyloid A
  - C- Reactive protein
  - Complement proteins – Complement factors (C1-C9), factor B,D, and properdin
  - Coagulation protein- e.g. fibrinogen, von Willebrand factor
  - Proteinase inhibitors- e.g. α1 antitrypsin
  - α1 acid glycoprotein
  - Mannose binding protein
  - Haptoglobin
  - Metal binding proteins- e.g. ceruloplasmin

Negative APRs

- Proteins whose levels are decreased during acute inflammation thus creating a negative feedback that stimulates the liver to produce positive APRs.
- Examples of negative APRs include:
  - Albumin
  - Transferrin
  - Antithrombin.

Role of APRs

- APRs have various antimicrobial and anti-inflammatory activities (e.g. complement factors)
- Metal binding proteins can chelate various metals such as iron, copper, etc making them unavailable for the bacteria.

C- Reacting protein (CRP)

- CRP belongs to beta globulin family.
- CRP is so named because it precipitates with C-carbohydrate (polysaccharide) antigen of *Pneumococcus*.
- CRP not an antibody against the C- carbohydrate antigen of *Pneumococcus*; it is non-specific, can be raised in any inflammatory conditions.
- Commonest markers of acute inflammation, used in most diagnostic laboratories.

C- Reacting protein (CRP)

- Normal level - <0.2mg/dl.
- Increases by several folds in acute inflammatory conditions:
  - *Insignificant increase* (<1 mg/dl) -heavy exercise, common cold, and pregnancy
  - *Moderate increase* (1-10 mg/dl)- bronchitis, cystitis, malignancies, pancreatitis, myocardial infarction
  - *Marked increase* (>10 mg/dl)- acute bacterial infections, major trauma and systemic vasculitis

Detection of CRP

- Precipitation method using C carbohydrate antigen (obsolete, not in use now)
- Latex (passive) agglutination test using latex particles coated with anti-CRP antibodies -most widely used.
- Detection limit of CRP by latex agglutination test – 0.6mg/dl

Highly sensitive CRP (hs-CRP)test

- Minute quantities of CRP can be detected by various methods (e.g. nephelometry, enzyme immunoassays).
- Useful in assessing the risk to cardiovascular diseases.

PROPERTIES OF ACQUIRED IMMUNITY

- **Mediators-** *T cells* & *B cells* are the chief mediators of acquired immunity. Others include-
  - Classical complement pathway
  - Antigen presenting cells
  - Cytokines (IL-2, IL-4, IL-5)
- **Response occurs in days** - It requires the activation of T and B cells against the microbial antigens.
- **Requires prior microbial exposure**- Acquired immunity develops only after the exposure to the microbes.

PROPERTIES OF ACQUIRED IMMUNITY

- **Specific**-Acquired immunity is highly specific; directed against specific antigens that are unique to the microbes.
- **Memory present**- A proportion of T and B cells become memory cells following primary contact of the microbe, which play an important role when the microbe is encountered subsequently.
- **Diversity is wide**- Acquired immunity though takes time to develop is active against a wide range of repertoire of antigens.

PROPERTIES OF ACQUIRED IMMUNITY

- **Host cell receptors** of acquired immunity are specific for particular microbial antigen–
  - Examples include–T cell receptors and B cell immunoglobulin receptors
  - Encoded by genes produced by somatic recombination of gene segments

Types of Acquired immunity

- Active and passive immunity
- Artificial and natural immunity

ACTIVE IMMUNITY

- Active immunity is the resistance developed by an individual towards an antigenic stimulus.
- Active immunity may be induced naturally or artificially:
  - *Natural active immunity* occurs following an exposure to a microbial infection (e.g. measles virus infection)
  - *Artificial active immunity* develops following an exposure to an immunogen by vaccination (e.g. measles vaccine).

ACTIVE IMMUNITY

- **Long-lasting**- Active immunity usually lasts for longer periods but the duration varies depending on the type of pathogen.
  - Last life long- e.g. following certain viral infections such as chicken pox, measles, small pox, mumps and rubella.
  - Last short- e.g. following influenza infection.
  - Premunition or concomitant immunity – Immunity may last as long as the microbe is present. Once the disease is cured, the patient becomes susceptible to the microbe again (Spirochaetes and *Plasmodium).*

ACTIVE IMMUNITY

- Premunition or concomitant immunity – Immunity may last as long as the microbe is present. Once the disease is cured, the patient becomes susceptible to the microbe again (Spirochaetes and *Plasmodium).*
- Active immunity may not be protective at all– e.g. for *Haemophilus ducreyi*, the patient may develop genital lesions following reinfection even while the original infection is active.

Immune response

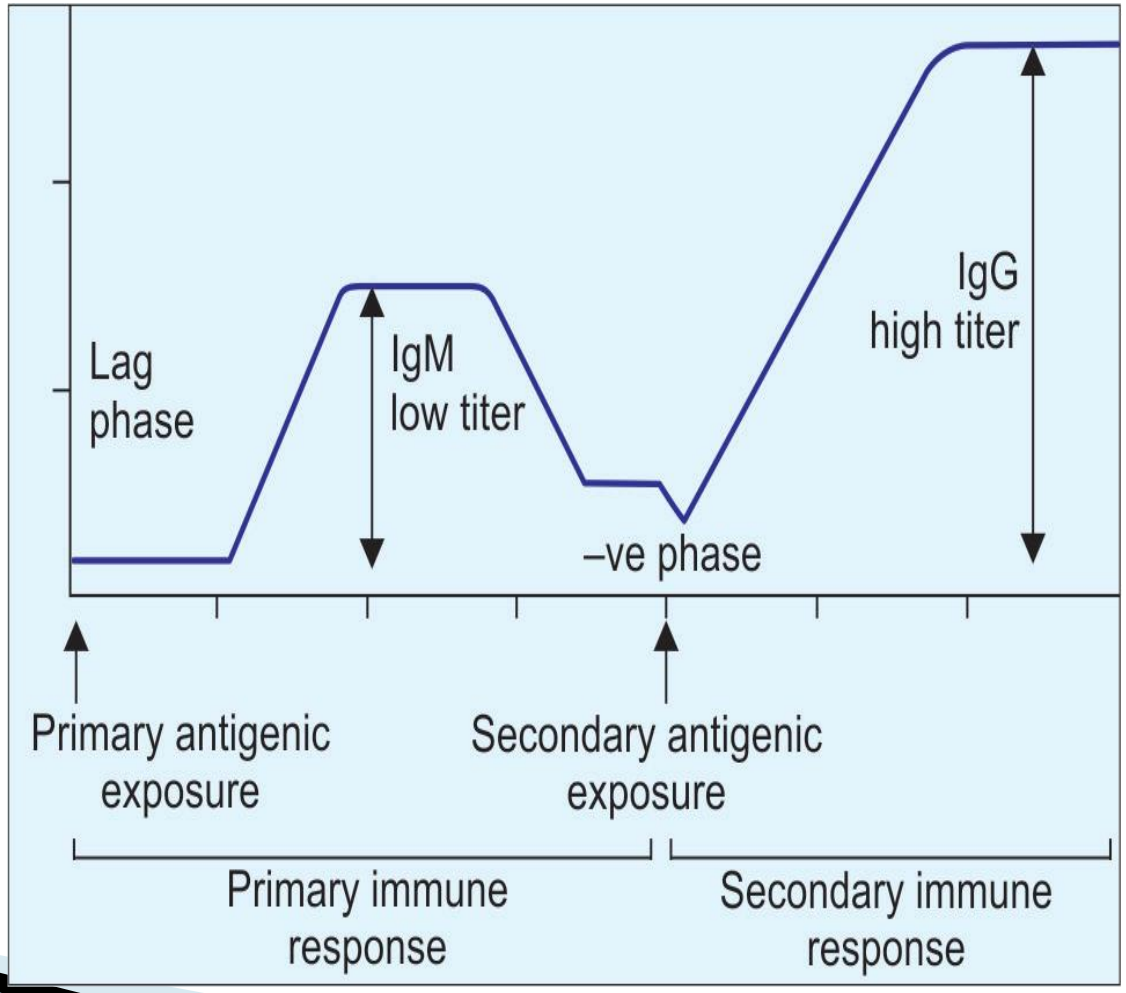
- Immune responses in active immunity are different for the microbial exposure that occurs for the first time (called primary immune response) and subsequent time (called secondary immune response).

Primary immune response

- When the antigenic exposure occurs for the first time, the following events take place-
  - *Latent or lag period* – Active immunity develops which corresponds to the time required for the host's immune apparatus to become active.
  - *Effector cells*-Majority of activated T and B cells against the antigenic stimulus become effector T and B cells
    - Effector T cells such as helper T cells and cytotoxic T cells
    - Effector B cells include plasma cells

Primary immune response

- *Memory cells*- A minor proportion of stimulated T and B cells become memory cells, which are the key cells for secondary immune response.
- *Antibody surge*
  - Activated B cells produce antibodies (mainly IgM type).
  - Antibodies appear in the serum in slow & sluggish manner; reach peak, maintain the level for a while and then fall down.
  - Finally, a low titer of baseline antibodies may be maintained in the serum.


Lag
phase
IgM
low titer
–ve phase
IgG
high titer
Primary antigenic
exposure
Secondary antigenic
exposure
Primary immune
response
Secondary immune
response

Secondary immune response

- When the same antigenic exposure occurs subsequently, the events which take place are as follows:
  - *Latent period*
  - *Negative phase*
  - *Antibody surge*

PASSIVE IMMUNITY

- Passive immunity is defined as the resistance that is transferred passively to a host in a 'readymade' form without active participation of the host's immune system.
- Passive immunity can also be induced naturally or artificially.
  - *Natural passive immunity* involves the IgG antibody transfer from mother to fetus across the placenta.
  - *Artificial passive immunity* develops following readymade transfer of commercially prepared immunoglobulin (e.g. Rabies immunoglobulin)

Role of passive immunity

- Immunodeficient individuals (as host's immune apparatus is not effective)
- Post exposure prophylaxis; when an immediate effect is warranted.
- Passive immunity *develops faster*; there is no lag phase or negative phase.
- There is *no immunological memory* as the memory cells are not involved.
- *Booster doses are not effective*

Differences between active and passive immunity

Active immunity	Passive immunity
Produced actively by host immune system	Immunoglobulins received passively
Induced by • Infection (natural) • Vaccination (artificial)	Acquired by- • Mother to fetus IgG transfer (natural) • Readymade antibody transfer (artificial)
Long lasting	Lasts for short time
Lag period present	No Lag period
Memory present	No Memory
Booster doses-useful	Subsequent doses-Less effective
Negative phase may occur	No Negative phase
In immunodeficiency individuals not useful	Useful in immunodeficient individuals

Differences between Primary and Secondary immune response

Primary immune response	Secondary immune response
Immune response against primary antigenic challenge	Immune response against subsequent antigenic challenge
Slow, sluggish (appear late) and short lived	Prompt, powerful & prolonged (long lasting)
Lag period is longer (4-7 days)	Lag period is absent or short (1-3 days)
No negative phase	Negative phase may occur
Antibody produced in low titer & is of IgM type. Antibodies are more specific but less avid	Antibody produced in high titer & is of IgG type Antibodies are less specific but more avid
Antibody producing cells- Naive B cells	Antibody producing cells- Memory B cells
Both T dependent and T independent antigens are processed.	Only T dependent antigens are processed.

BRIDGES BETWEEN INNATE AND ACQUIRED IMMUNITY

- **Macrophages** and dendritic cells:
  - Belong to innate immune system but as antigen presenting cells, they present the antigenic peptides to T cells.
  - Cytokines secreted from macrophages (interleukin-1) are also involved in T cell activation.
- **ADCC** (antibody dependent cell mediated cytotoxicity):
  - Type of cell mediated immune response (CMI), which involves both innate and adaptive components.
  - Cells of innate immunity such as NK cell, eosinophils, and neutrophils destroy (by cytotoxic effect) the target cells coated with specific antibodies.

BRIDGES BETWEEN INNATE AND ACQUIRED IMMUNITY

- **Complements** (classical pathway)
  - Part of both innate and adaptive immunity.
  - Destroy the target cells which are coated with specific antibodies.
  - Alternate and mannose binding pathways do not take help of antibodies.
- **Cytokines**
  - Secreted from cells of innate immunity can activate cells of adaptive immunity and vice versa.
  - E.g. IL-1 secreted from macrophage activates helper T cells and interferon-γ secreted by helper T cell can activate macrophage.

BRIDGES BETWEEN INNATE AND ACQUIRED IMMUNITY

- **Rare classes of lymphocytes** such as γδ T cells , NK-T cells, B-1 cells and Marginal-zone B cells.
  - These cells have many characteristics that place them in the border of innate & acquired immunity.
  - Function in the early defense against microbes as part of innate immunity.
  - Although their receptors are encoded by somatic recombination of genes (similar to that of classical T and B cells), but these receptors have limited diversity.
  - Develop a memory phenotype in contrast to the property of innate immunity.

Local (or mucosal) immunity

- Immune response that is active at the mucosal surfaces such as intestinal or respiratory or genitourinary mucosa.
- Mediated by a type of IgA antibody called secretory IgA.
- Local immunity can only be induced by natural infection or by live vaccination (but not by killed vaccines).

Herd immunity

- Herd immunity is defined as the overall immunity of a community (or herd) towards a pathogen.
- Elements that contribute to create a strong herd immunity are-
  - Occurrence of clinical and subclinical cases in the herd
  - On-going immunization programme
  - Herd structure i.e. type of population involved
  - Type of pathogen-Herd immunity may not be strong in a community against all the pathogens.

Herd immunity

- Herd immunity develops following effective vaccination against some diseases like:
  - Diphtheria and Pertussis vaccine
  - Measles, Mumps and Rubella (MMR) vaccine
  - Polio (Oral polio vaccine)
  - Smallpox vaccine

Adoptive immunity

- Special type of cell mediated immune response (CMI) which develops following injection of immunologically competent T-lymphocytes known as Transfer factor.
- Useful for treatment when the CMI is low- e.g. in lepromatous leprosy.

Thank You