Immunity

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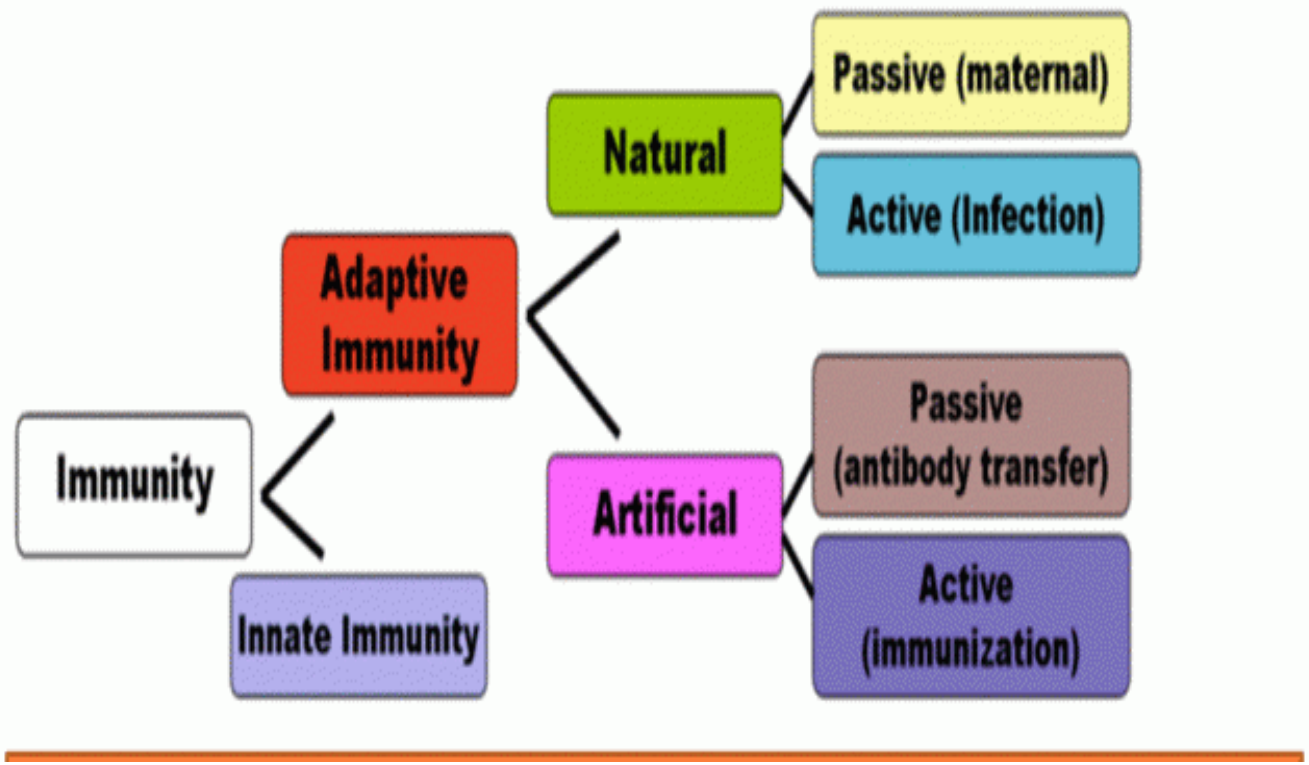
Introduction

- 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
- Two types of immunity

1)Innate or non specific

2)Acquired or adaptive

Immunity and its types



Innate 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.

- **Acts in minutes:** Innate immunity is the **first line of host defense** against infections; occurs immediately after the microbial entry.
- **Microbial exposure is not required:** Innate immunity is independent of prior exposure to the microbes; present even before the first entry of the microorganism.
- **Diversity is limited:** Innate immunity is active only against a limited repertoire of antigens; in contrast to acquired immunity which is more varied and involves specialized immune responses.
- **Non-specific:** Cells of innate immunity are non-specific in their action; can be directed against any microbial antigen(s).

- **No memory:** Innate immunity does not have a memory component. Response to a repeat infection is identical to the primary response.

Innate immunity may be confined to a particular species, race or individual.

- **Species immunity** is the innate immunity towards a microbe exhibited by all members of a given species. For example, frogs are resistant to *Bacillus anthracis*; while toads are susceptible.
- **Racial immunity:** Sometimes, innate immunity is confined to a particular race; may be absent in other communities. For example, Negroes of America are more susceptible to tuberculosis than the Whites.
- **Individual immunity** refers to the antimicrobial defense mechanisms that are confined to a particular individual; may not be exhibited by others.

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Several factors determine the degree of innate immunity exhibited by the host, such as:

- **Age:** Certain infections are common in a particular age. For example, congenital infections like rubella is common in fetal life, chickenpox and measles occur in children, whereas urinary tract infection is common in adults.
- **Hormone:** Certain hormonal disorders (e.g. diabetes mellitus) or patients on hormone therapy (e.g. corticosteroids) are at increased risk of developing various infections.
- **Nutrition:** Malnutrition suppresses the host immunity, thereby predisposes to various infections.

Microbial Surface Molecules

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

Pattern Recognition Receptors (PRRs)

These are the molecules present on the surface of host cells (e.g. phagocytes) that recognize MAMPs. They are generally conserved regions, encoded by germ line genes. **Toll-like receptors (TLRs)** are classical examples of pattern recognition receptors (see box below).

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- Other PRRs include C type lectin receptor(CLR), Retinoic acid-inducible gene-I-like receptors (RLRs)

- 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 and 8 bind to ssRNA of viruses
- TLR-9 binds to bacterial DNA

Mechanism of innate immunity

- Following exposure to microbes, several mediators of innate immunity are recruited at site of infections
- The first step is attachment which involves binding of MAMPS to PRRs

Signals generated following binding of TLRs to MAMPs activate transcription factors that stimulate expression of genes encoding cytokines and enzymes, which are involved in several antimicrobial activities of cells of innate immunity.

The most important transcription factors activated by TLR signals are:

- **Nuclear factor κβ (NF-κβ),** which promotes production of various cytokines and
- **Interferon regulatory factors (IRFs),** which stimulate expression of the antiviral interferons α and β.

Components of innate immunity

1)Anatomical and physiological barriers
2)Phagocytes
3)Natural killer cells
4)Complement system
5)Normal flora
6)Acute phase proteins
7)Cytokines
8)Mast cells
9)Inflammation and fever

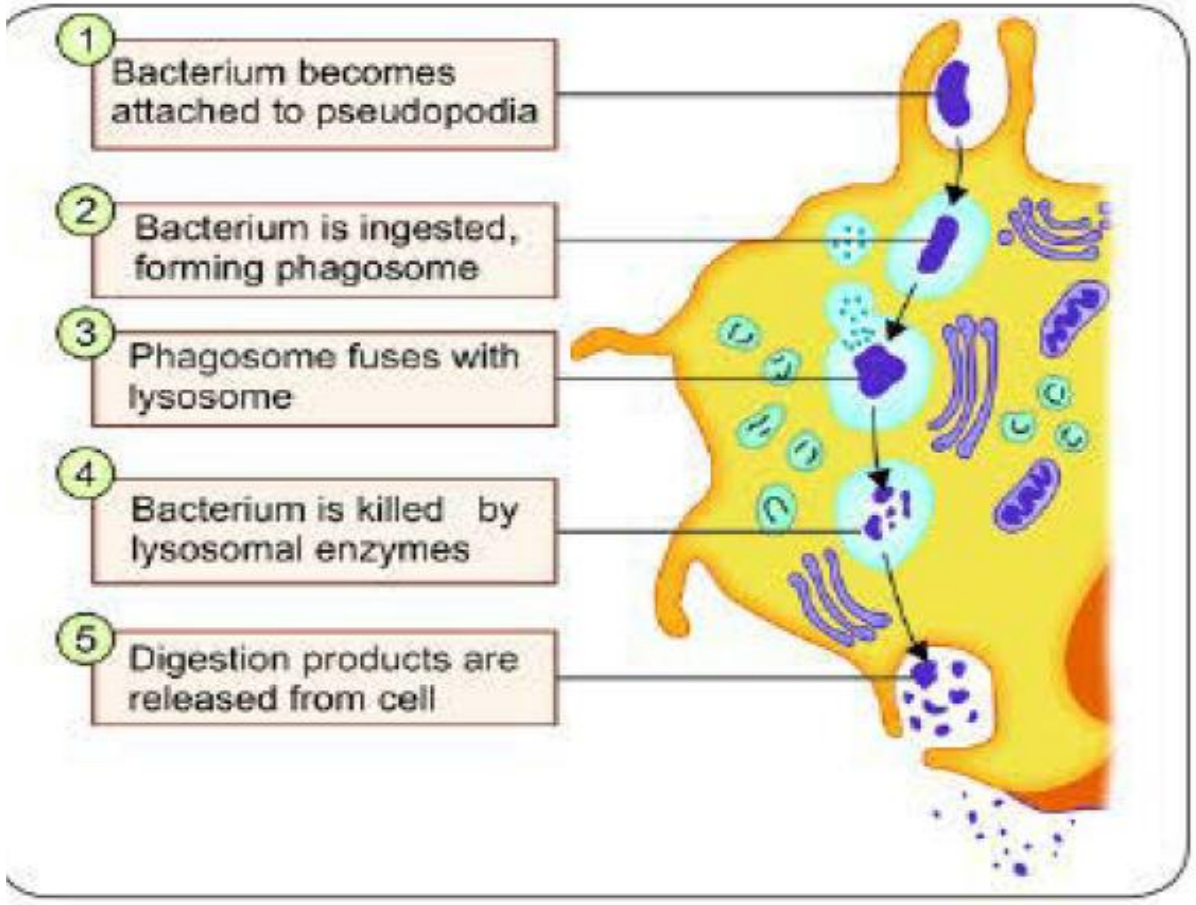
TABLE 9.2: Role of barriers in innate immunity

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	
Mucous membrane	Prevents entry of microbes mechanically and by producing **mucous** which entraps microbes
Cilia	Cilia present in the lower respiratory tract propel the microbes outside
Normal flora	Intestinal and respiratory mucosa are lined by normal flora

Physiological barrier	Function
Temperature	Normal body temperature inhibits the growth of some microbes
Low pH	Gastric acidity inhibits most of the microbes
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	Hydrolyses bacterial protein
Bile salts	Interfere with bacterial cell membrane

Phagocytes

Phagocytes such as **neutrophils, macrophages** including **monocytes** are the main component of innate immunity.



Complement system

Alternate and mannose binding pathways are the chief mediators of innate immunity.

- Alternate complement pathway is activated in response to bacterial endotoxin whereas the mannose binding pathway is stimulated by mannose carbohydrate residues on bacterial surface.

Complement acts by:

- 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.

Acute-Phase Proteins: Produced in liver and secreted into the blood

Proteins	Functions
C-reactive protein	opsonization
Serum amyloid A	
Ferritin	Bind and sequester iron, thereby inhibiting the growth of pathogens
Transferrin	
Fibrinogen	Formation of blood clots that trap bacterial pathogens
Mannose-binding lectin	Activates complement cascade

Natural killer cells

- They are class of lymphocytes that target virus infected cells and tumor cells
- Kills cells by secretions of perforins and granenzymes
- Perforins forms pores through which granzymes enter the cell and lyse target cells
- These enzymes are present constitutively in NK cells cytoplasm

Cytokines

Cytokines	Functions
Interleukins	Stimulate and modulate immune system
Chemokines	Recruit white blood cells to infected area
Interferons	Induce apoptosis of virus-infected cells, induce antiviral defenses in infected and nearby uninfected cells, stimulate immune cells to attack virus-infected cells

Mast cells

Mast Cells

They are present lining the respiratory and other mucosa.

- They are activated by microbial products binding to toll-like receptors or by IgE antibody dependent mechanism, following which;
- They release abundant cytoplasmic granules rich in histamine, prostaglandins and cytokines that initiate inflammation and proteolytic enzymes that results in killing of bacteria.

Inflammation

- Inflammation is defined as biological response of vascular tissues to harmful stimuli. Steps in inflammation

- **Vasodilation** due to release of vasoactive substances from the damaged tissues
- **Leakage** of plasma proteins through blood vessels
- **Recruitment** of phagocytes (e.g. neutrophils) to the site of inflammation—phagocytes undergo the following steps—(1) margination (adherence to the endothelium), (2) rolling on endothelium, (3) extravasation (moves out of the blood vessels), (4) chemotactic migration to the inflammation site
- **Engulfment** of microbes and dead material by the phagocytes
- **Destruction** of the microbes

- **Fever**

Exogenous pyrogens

↓

Leukocytes activated

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IL-1, IL-6, IFN-γ and TNF released

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Prostaglandin E2 (PGE2) released

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Alters “thermostat setting” of hypothalamus

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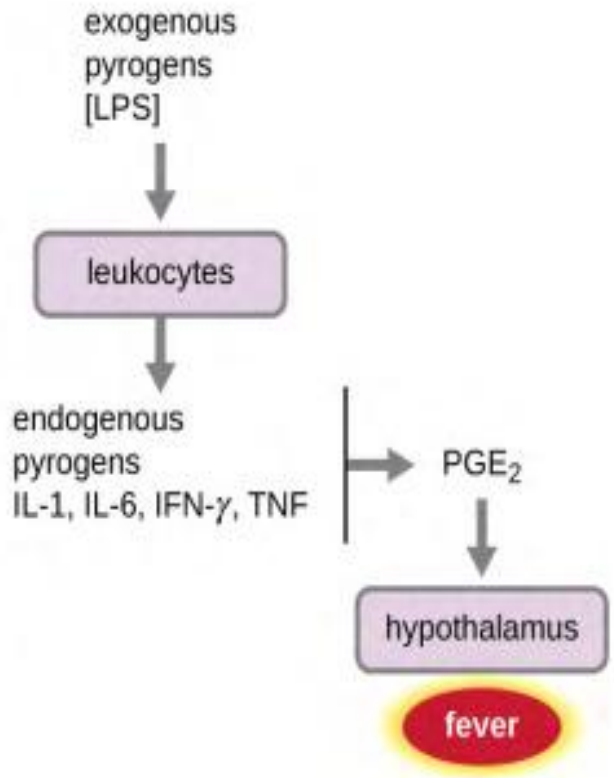
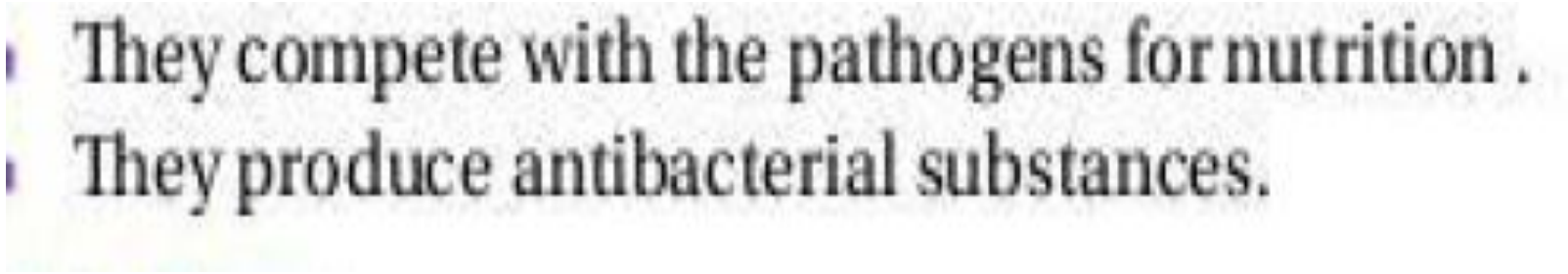
Fever



Normal microbial flora

- Normal flora lining intestinal,respiratory tract, genital tract exert antimicrobial properties by:



Acquired immunity

Acquired immunity

Acquired immunity is defined as the resistance against the infecting foreign substance that an individual acquires or adapts during the course of his life.

❖Properties

- **Mediators: T cells and B cells** are the chief mediators of acquired immunity. Other mediators include:
  - Classical complement pathway
  - Antigen presenting cells
  - Cytokines (IL-2, IL-4, IL-5)
- **Response occurs in days:** Acquired immunity involves activation of T and B cells against the microbial antigens; which takes several days to weeks to develop, following the microbial entry.

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- Requires prior microbial exposure
- Specific: highly specific; directed against specific antigens that are unique to microbes
- **Memory present:** A proportion of T and B cells become memory cells following primary contact of microbe, which play an important role when the microbe is encountered subsequently
- **Diversity is wide:** active against a wide range of antigens.
- **Host cell receptors:** specific for particular microbial antigen. Examples include T cell receptors and B cell immunoglobulin receptors

Types of acquired immunity

1)Active immunity

2)Passive immunity

Active immunity

- resistance developed by an individual toward an antigenic stimulus
- host's immune system is actively involved in response to antigenic stimulus
- production of immunologically active T cells, B cell and production of specific antibodies
- maybe induced naturally or artificially

a) Natural active immunity occurs following an exposure to a microbial infection. Eg measles infection

b)Artificial active immunity develops following an exposure to immunogen by vaccination. Eg. Measles vaccine

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- Active immunity often fails to develop when the host is immunocompromised

Long-lasting: Active immunity usually lasts for longer periods, but the duration varies depending on the type of pathogen.

- It may last life long, e.g. following certain viral infections such as chickenpox, measles, smallpox, mumps and rubella.
- It may last short, e.g. following influenza virus infection.
- It may last for as long as the microbe is present. Once the disease is cured, the patient becomes susceptible to the microbe again. This is called

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premunition or concomitant immunity. It is seen following some microbial infections like spirochetes 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.

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).

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- Very important in following cases

➢When host is immunocompromised

➢Postexposure prophylaxis: when immediate effect is needed

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:

TABLE 9.4: 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
Not useful in immunodeficiency individuals	Useful in immunodeficient individuals

Types of immune response in active immunity vary depending on 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 only after a latent period following the antigenic exposure, 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
- **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:** Effector B cells produce antibodies (mainly IgM type). Antibodies appear in the serum in slow and 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 (Fig. 9.2).

Secondary Immune Response

When the same antigenic exposure occurs subsequently, the events which take place are as follows (Fig. 9.2).

- **Latent period** is either absent or of short duration. This is because memory cells become active soon after the antigenic exposure.
- **Negative phase:** At the onset of secondary immune response, there may be a negative phase during which the antibody level may become lower than it was before the antigenic stimulus. This is because the exposed antigen combines with the pre-existing antibody and thus the antibody level in serum falls down.
- **Antibody surge:** Secondary antibody response is prompt, powerful, long-lasting and mainly of IgG type. Hence it is said that, the booster doses of vaccines are more effective than the first dose.

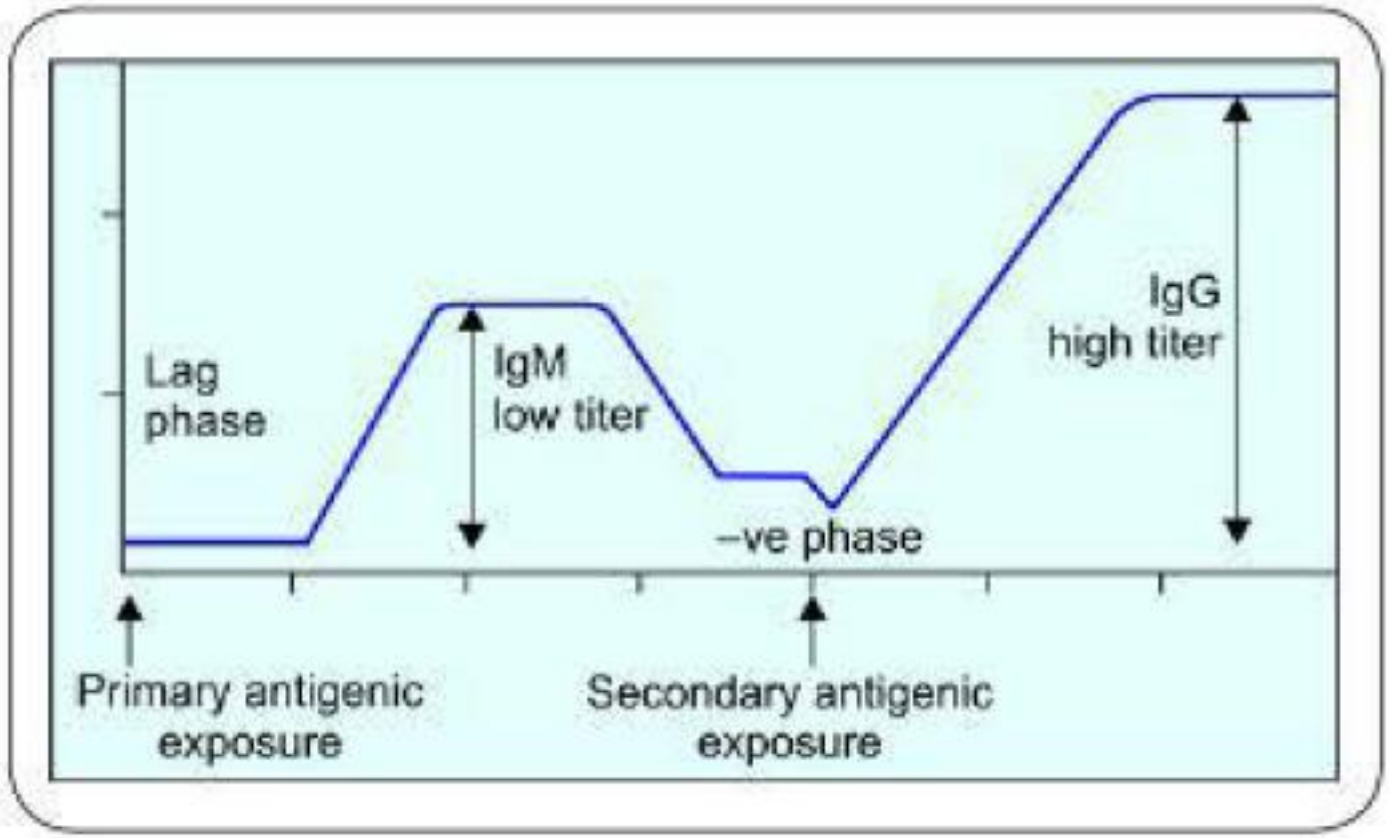

Fig. 9.2: Primary and secondary immune responses

TABLE 9.3: 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 and 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 and is of IgM type. ▪ Antibodies are more specific but less avid	Antibody produced in high titer and 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