CHAPTER (10)

GENERAL VIROLOGY

- Viruses are **one of the smallest infectious agents**
- They are **obligatory intracellular parasites** → because **they have no metabolic activity**

- **Viruses can infect all organisms in nature:**
  - **① Bacteriophages:** are **bacterial viruses**
  - **② Plant viruses:** include **complete viruses** & **viroids**
  - **③ Animal viruses:** infect **insects** or **vertebrates including man**

- **Viruses differ from bacteria in the following:**
  - ❶ Viruses are **very small in size**, ranging from **20-300 nm** → therefore:
    - ① They can **only be seen under the electron microscope** (**except pox-viruses**)
    - ② They can **pass through bacterial filters**
    - ③ They need **ultracentrifugation for sedimentation**
  - ❷ Viruses contain **only one type of nucleic acid** (DNA or RNA), **never both**
  - ❸ They are **obligatory intracellular parasites** (can **only replicate inside living cells**) and do **not divide by binary fission**
  - ❹ They **cannot be cultivated in the laboratory** on **artificial culture media** → however, they **can be grown on tissue culture**
  - ❺ They are **not susceptible to antibacterial antibiotics**

Structure & Composition of Viruses:

Typical complete virus particle, called virion → consists of:

- ❶ **Genome** → of either **DNA or RNA**
- ❷ Surrounded by **capsid** (**protein coat**)

→ **Nucleic acid** & **protein coat** are called **nucleo-capsid** → **non-enveloped** (**naked**) **viruses**

- ❸ Some viruses, called **enveloped viruses**, have **outer lipid-containing envelope**

① Viral nucleic acid (genome)

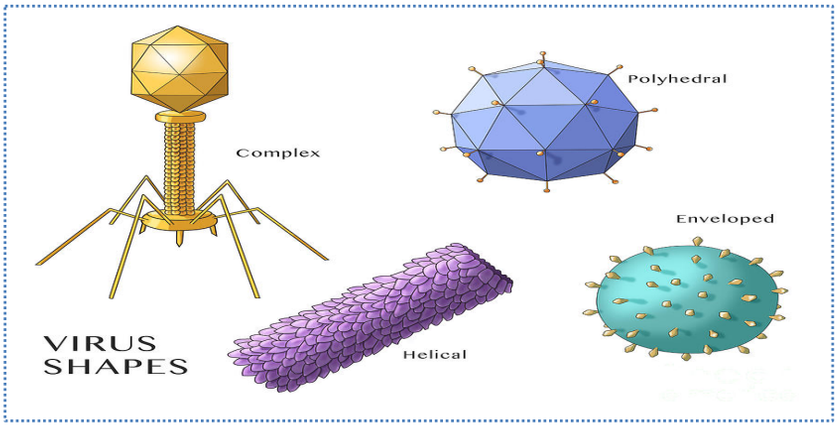
- It is the **genetic material of a virus** → which may be **either RNA or DNA**
- Most **DNA viruses** are **double-stranded (ds)** while most **RNA viruses** are **single-stranded (ss)**
  → The **viral ssRNA** may be **positive sense strand (+sense)** or **negative sense strand (-sense)**
- It is **responsible for virulence** → i.e. it is the **infectious part of the virus**

② Viral capsid

- Viral capsid is composed of **many small protein subunits called capsomers**

- **It has the following functions:**
  - ❶ It **protects the nucleic acid (genome)** against **harmful environmental factors**
  - ❷ It **mediates attachment to host cell** (in **non-enveloped viruses**)
  - ❸ It is **responsible for the viral symmetry** (or **morphology**) which may be:

① Icosahedral (many sided) symmetry	② Helical (colied tubes) symmetry	③ Complex symmetry
∗ **Icosahedral** or **isomeric** or **cubic viruses** → resemble **crystal with 20 triangular facets** & **12 corners**	∗ Viral **nucleic acid is closely associated** with **protein capsid** forming **coil-shaped helical nucleocapsid**	
∗ This includes ❶ **All DNA viruses**, except **poxviruses** (**brick shaped**) ❷ **Some RNA viruses**	∗ This includes **many of RNA viruses**, e.g. **rabies virus**	∗ Examples include ❶ The brick-shaped **poxviruses** ❷ **Bacteriophages**



③ Viral envelope

- It is **lipoprotein membrane** composed of:
  - ❶ **Lipids** → derived from **host cell membrane** during **release by budding**
  - ❷ **Protein** → that is **virus-specific**

- Frequently, the **envelope may have glycoprotein spikes** → which are the **organ of attachment of the enveloped virus** to **host cell receptors**
  → Therefore, **dissolving the envelope inhibits attachment** & the **virus loses its infectivity**

- **Enveloped viruses are less stable** → i.e. more **easily inactivated than naked viruses**
  → They are **more sensitive to** heat, drying, detergents & lipid solvents
  → Therefore **enveloped viruses**, being **unable to survive in the environment** → **transmitted** essentially by **direct contact** via **blood** & **body fluids**

N.B. **Surface proteins** of virus, whether they are **capsid proteins** (in **naked viruses**) or **glycoproteins** (in **enveloped viruses**) are:
❶ Responsible for **attachment to host cell receptors**
❷ The **principal antigens** against which the **host elicits its immune response to viruses**

Pathogenesis of Viral Diseases:

① Entry of viruses

- **Viruses enter the body either by:**
  - ❶ Inhalation (respiratory tract)
  - ❷ Ingestion (gastrointestinal tract)
  - ❸ Contact (urogenital system)
  - ❹ Through skin (injections, blood transfusion, insect & animal bites)

- **Viral infection may be:**
  - ❶ **Local infection:** where the virus **produces disease at the portal of entry**
  - ❷ **Systemic or deep viral infections:**
    Virus **spreads to distant organs** either via **blood (viraemia)**, or by other means (along **nerves)**

- **Differences between local & systemic viral infections:**

	① Local viral infections	② Systemic viral infections
Example	Common cold (e.g. rhinovirus infection)	Measles
Site of pathology	Portal of entry	At distant sites
Incubation period	Relatively short	Relatively long
Viraemia	Absent	Present
Duration of immunity	Usually short	Usually life-long
Involved immunoglobulin	Secretory IgA	IgM & IgG

② Fate of viral infections

① Inapparent or subclinical viral infections: Viral infection **without overt signs and symptoms**

② Apparent infections (disease):
Local or systemic viral infections with **appearance of clinical signs and symptoms**

③ Persistent viral infections (chronic):
Virus is continuously detected with **mild or no clinical symptoms** → e.g. chronic **hepatitis B**

④ Latent viral infections:
Virus persists in **dormant form** & may **flare up intermittently** to **produce disease** → e.g. **herpes viruses**

⑤ Slow virus infections:
Virus infections with **long incubation periods** (**months or years**) → they are caused by **two types of infectious agents:**
- ❶ **Conventional viruses** → e.g. **variant of measles** virus which causes **subacute sclerosing panencephalitis (SSPE)**
- ❷ **Unconventional agents (prions)**

Classification of Viruses:

① Classification by symptomatology

- Old classification based on **diseases that viruses produce** → i.e. tropism
- e.g. neurotropic viruses, enteroviruses, ... etc

② The hierarchical virus classification

- **Scheme classifying viruses into orders, families & subfamilies is based on:**
  - ❶ Nature of the nucleic acid: RNA or DNA genome
  - ❷ Symmetry of the capsid
  - ❸ Presence or absence of envelope
  - ❹ Virus size
  - ❺ Virus replication strategy

- Further classification is based on **additional properties** → e.g.
  - ❶ Antigenicity
  - ❷ Host range
  - ❸ Nucleic acid sequence

③ The Baltimore classification

- Based on **virus genome replication strategy**
- The central idea is that **all viruses must generate positive strand mRNAs from their genomes**, in order to **produce proteins** & **replicate themselves**
- The precise mechanisms whereby this is achieved differ for each virus family

Laboratory Diagnosis of Viral Infections:

Laboratory diagnosis of viral infection involves 2 main diagnostic methods:

① Direct methods	② Indirect methods
Depend either on: ❶ **Detection of viruses** &/or **their components** in **patient's specimens**, or ❷ **Isolation of viruses**	**Depend either on:** ❶ **Detection of antibodies against suspected virus** in **patient's serum**, or ❷ **Skin tests**

Different techniques used in **diagnosis of viral infections** are discussed in "Practical Microbiology & Immunology"

Treatment of Viral Infections:

- Viruses **cannot be treated with antibiotics** → because they **lack structural targets on which antibiotics can act**
- Viruses are **obligate intracellular parasites** → so antiviral **drugs must selectively inhibit viral replication without causing damage to host cells**
- The **number of antiviral drugs is little** compared to antibacterial drugs

• **Selected antiviral drugs & their mechanism of action and clinical use:**

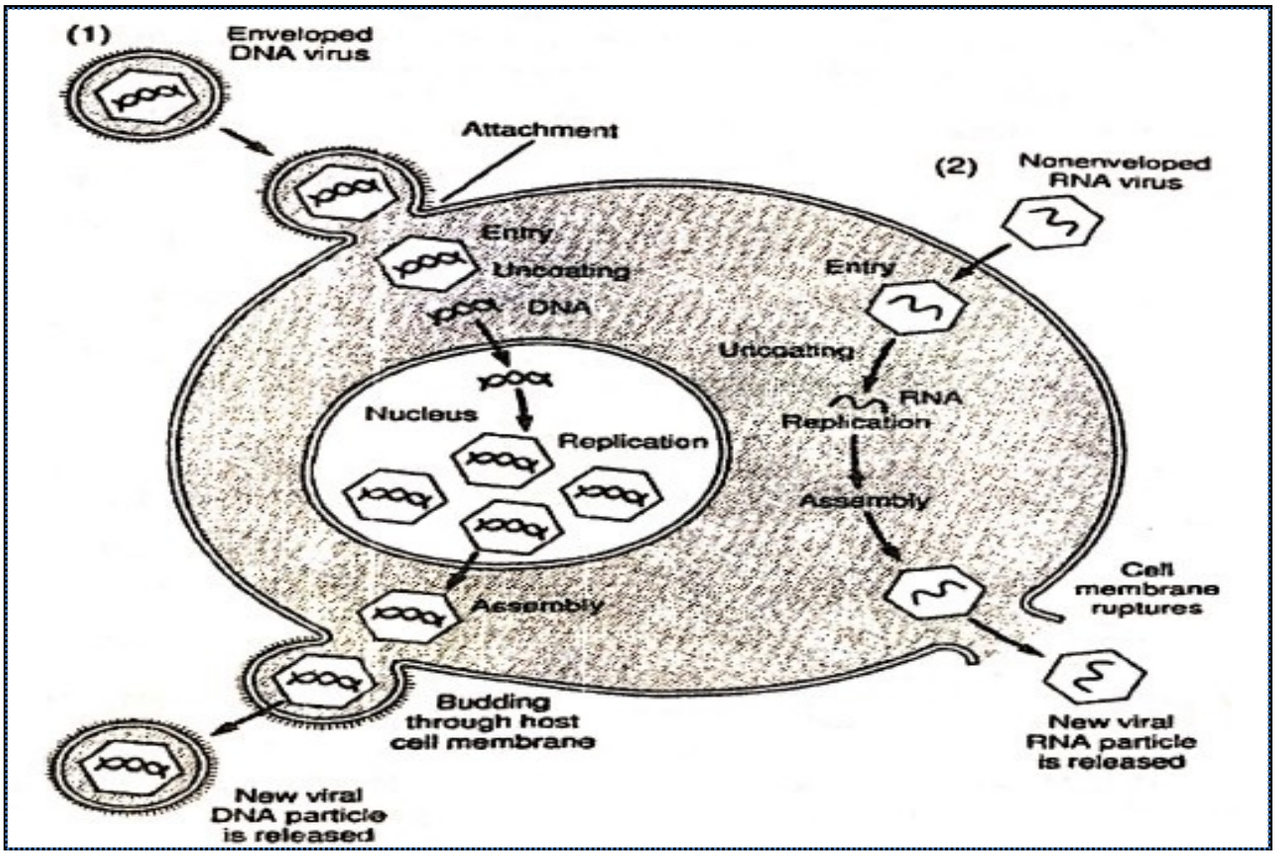
Mechanism of action	Antiviral drugs	Virus infections
❶ **Fusion inhibitors:** (Block virus entry)	Fuzeon (enfuvirtide)	HIV
❷ **Uncoating inhibitors:** (Inhibit virus uncoating)	❶ Amantadine	Influenza A virus
	❷ Rimantadine	Influenza A virus
❸ **Neuraminidase inhibitors:** (Interfere with release of virus from infected cells)	❶ Oseltamivir (Tamiflu)	• Influenza A virus • Influenza B virus
	❷ Zanamivir	• Influenza A virus • Influenza B virus
❹ **Nucleoside analogues that inhibit DNA polymerase** (Inhibit DNA synthesis)	❶ Acyclovir	• **Topical:** herpes simplex virus type 1 & 2 & varicella-zoster virus • **Parenteral:** HBV
	❷ Ganciclovir	Cytomegalovirus
	❸ Vidarabine	Herpes viruses, HBV
	❹ Iododeoxyuridine (IDU)	Herpetic keratoconjunctivitis
❺ **Inhibitors of mRNA synthesis**	Ribavirin (Virazole)	• **Aerosol:** • Respiratory syncytial virus • Influenza B virus • **Parenteral:** • HCV
❻ **Nucleoside analogues that inhibit reverse transcriptase enzyme**	❶ Azidothymidine (AZT) = (Zidovudine)	HIV
	❷ Zalcitabine	HIV
	❸ Lamivudine	HIV & HBV
	❹ Stavudine	HIV
❼ **Protease inhibitors** (They inhibit cleavage of precursors polypeptide)	❶ Indinavir	HIV
	❷ Ritonavir	HIV
	❸ Sanquinavir	HIV
❽ **Inhibitors of viral protein synthesis**	❶ Methisazone	Poxviruses (smallpox)
	❷ Interferons	• HBV & HCV • Human papilloma virus

Virus Replication:

* Viruses are **unable to replicate on their own** → because they **lack genes & enzymes necessary for energy production**

* Therefore, **replication depends on living host cells** & is **directed by viral genome** to **produce the virus components**

* **Viral replication occurs in the following steps:**



① Attachment or adsorption

- Adsorption of virus occurs to **specific receptor sites on surface of susceptible host cell**
- These **interactions determine viral host range** (e.g. **human viruses** & **plant viruses**) & **tissue specificity or tropism** (e.g. hepatotropic viruses & neurotropic viruses)

② Penetration

- The viruses **may enter the host cells by either:**
  - ❶ **Endocytosis** → in case of **non-enveloped viruses**, or
  - ❷ **Fusion of viral envelope with host cell membrane** → in case of **enveloped viruses**

③ Uncoating

Nucleic acid is released from capsid by **action of cellular enzymes** & becomes **available for replication**

④ Eclipse

Time from uncoating until assembly of mature viruses → during **this phase**, **no infectious viruses** can be **detected in the host cell**

⑤ Synthesis of viral components

① Synthesis of viral proteins:

A) Transcription

- Viruses **must first synthesize virus-specific messenger RNA (mRNA)** to **synthesize virus specific proteins**

- **Transcription of mRNA varies according to the type of viral nucleic acid whether DNA or RNA, ds or ss, positive or negative sense strand, as follows:**

DNA viruses:

mRNA is transcribed from **-ve sense strand** using **host's DNA-dependent RNA polymerase (DdRp)**

RNA viruses:

There is **no host cell RNA polymerase** that **can use viral RNA** as **template for synthesis of mRNA**

RNA viruses fall into 4 groups according to the strategy for synthesizing mRNA:

dsRNA viruses:

Negative sense strand is transcribed by viral **RNA-dependent RNA polymerase (RdRp) into mRNA**

ssRNA viruses: → **there are 3 distinct routes to the formation of mRNA:**

❶ The **strand with positive sense** → acts **directly as mRNA**

❷ The **strand with negative sense** → must first be **transcribed**, using **viral RNA-dependent RNA polymerase** (RdRp) → into **positive sense strand** which can **then act as mRNA**

❸ In **retroviruses**, the **positive ssRNA**
→ First **made into a negative sense ssDNA,** using the **viral reverse transcriptase**
→ Then **dsDNA** is formed by **host DNA-dependent DNA polymerase**
→ This **dsDNA enters the nucleus and is either:**
① **Transcribed** by **host's DNA-dependent RNA polymerase** into **mRNA**, or
② **Integrated in host cell genome** causing **transformation**

B) Translation

Once viral **mRNA is transcribed** → it is **translated using host ribosomes** to **synthesize viral proteins**

② Synthesis of viral nucleic acid:

Replication of **viral genome requires** synthesis of **strand with complementary base sequence** → which serves as **template for synthesis of several copies** of the **original viral genome**

⑥ Assembly (Morphogenesis)

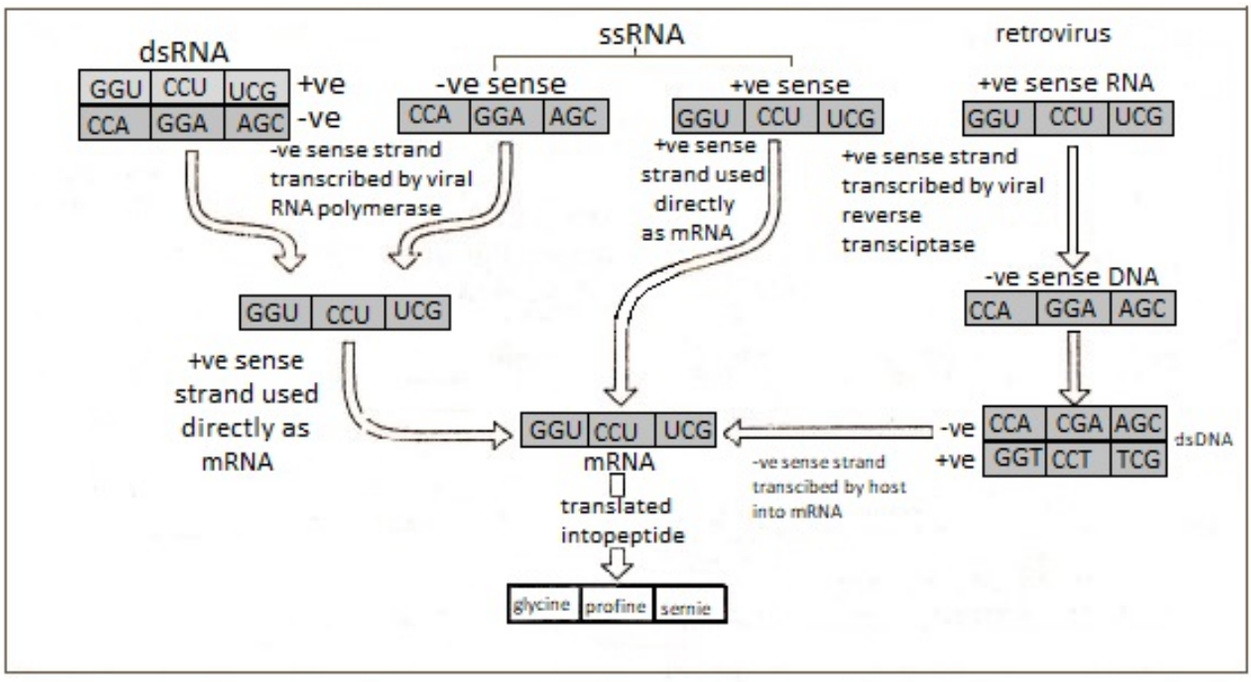
- **Newly synthesized protein coats enclose the replicated nucleic acids** to **form mature viruses** (**virions**)
- This occurs either in:
  ❶ The **nucleus of the host cell** → e.g. **herpes viruses**, or
  ❷ The **cytoplasm** → e.g. **polioviruses**

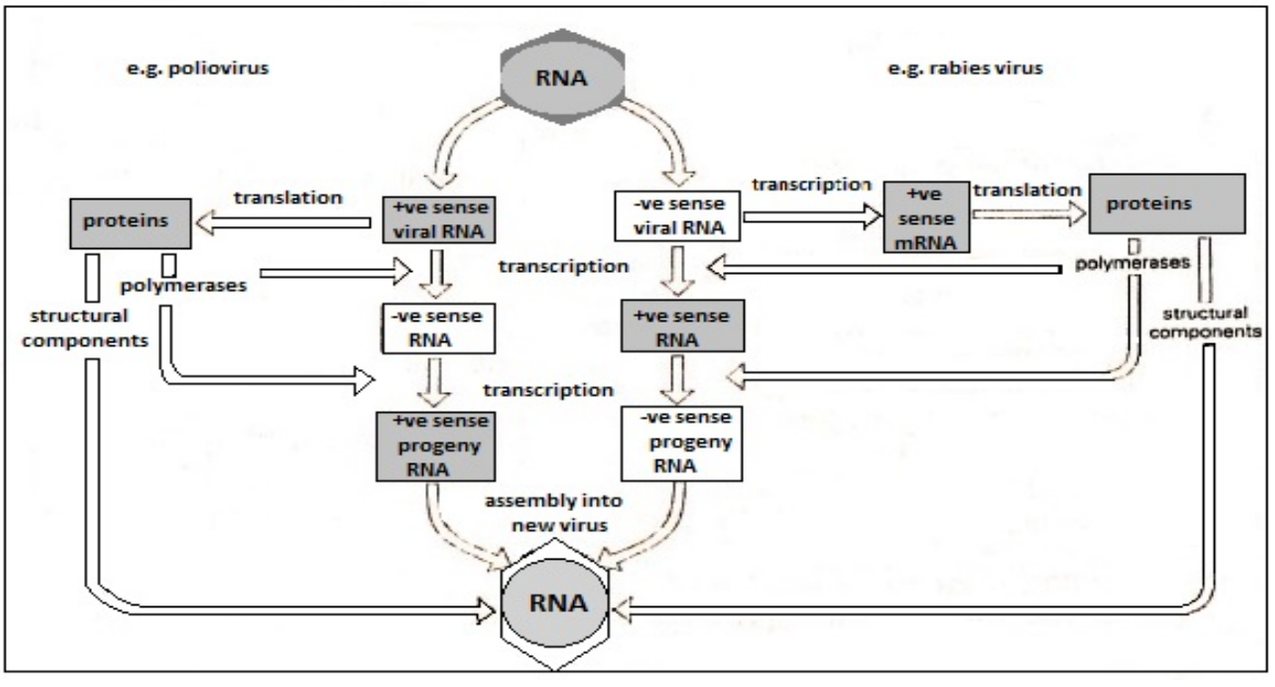
⑦ Release

- The **new viruses are released either by:**
  - ❶ **Lysis of host cell →** in case of **non-enveloped viruses** (e.g. poliovirus), or
  - ❷ **Budding through the cell membrane →** in case of **enveloped viruses**, e.g. HIV

N.B.

Some **viruses do not initiate synthesis** & **remain latent** within host cell for variable periods

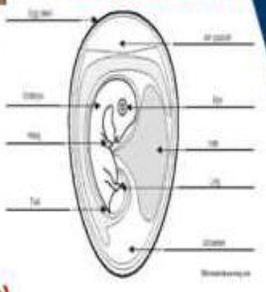


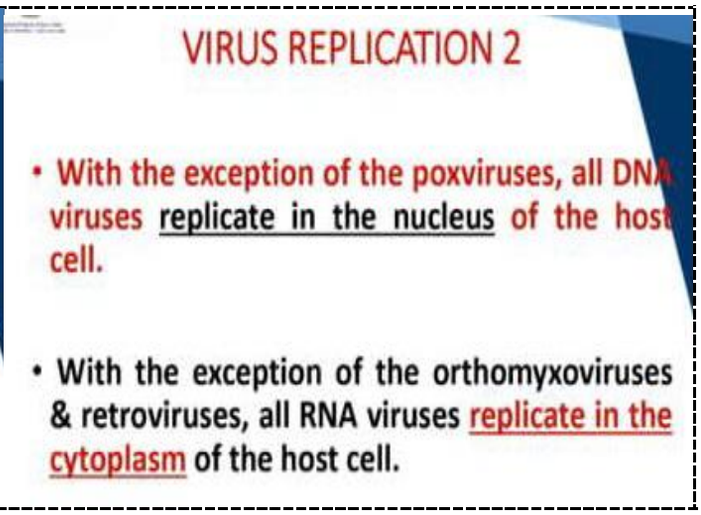


LECTURE EXTRAS

Cell culture (tissue culture)

Laboratory animals (intact animals)





Test Yourself

1) Viruses differ from bacteria in the following EXCEPT:

a- They are very small in size
b- They contain two types of nucleic acid
c- They are obligatory intracellular parasites
d- They need ultra-centrifugation for their sedimentation
e- They can be seen only by the electron microscope

2) All of the following is true concerning viral capsid EXCEPT:

a- It is formed of capsomers
b- It is protein in nature
c- It is responsible for viral symmetry
d- It is the infectious part of the virus
e- It protects the nucleic acid

3) Local viral infections are characterized by:

a- Long incubation period
b- Short duration of immunity
c- Insignificant role of slgA
d- Important role of IgM and lgG
e- A stage of viraemia

Classification of Viruses

RNA Viruses

Enveloped

- Retroviruses: HIV, HTLV
- Orthomyxoviruses: Influenza virus
- Paramyxoviruses: RSV, Measles virus, Mumps virus, Parainfluenza virus, hMPV
- Togaviruses: Rubella virus, Encephalitis viruses
- Coronaviruses: SARS-CoV, MERS-CoV
- Rhabdoviruses: Rabies virus
- Flaviviruses: HCV, Encephalitis viruses,Yellow fever virus, Dengue fever virus, Zika virus
- Bunyaviruses: Encephalitis viruses, Rift Valley fever virus, Hantavirus
- Arenaviruses: Lassa fever virus
- Filoviruses: Ebola virus, Marburg virus

Non-enveloped

- Picomaviruses:
  - Enteroviruses: Poliovirus, Coxsackieviruses A& B, Echovirus, Enteroviruses -68, 69,.....
  - Hepatovirus: HAV
  - Rhinoviruses
  - Aphthovirus
- Reoviruses: Rotavirus*
- Caliciviruses: Norovirus, HEV

DNA Viruses

Enveloped

- Herpes viruses: HSV-1 & 2, VZV, CMV, EBV, HHV-6, 7 & 8
- Hepadnavirus: HBV
- Poxviruses: Smallpox, Cowpox, Vaccinia virus Molluscum contagosum

Non-enveloped

- Adenoviruses
- Parvoviruses: B-19 virus**
- Papillomavirus

N.B:.

- Hepatitis viruses (A-E) belong to different families
- Arboviruses include members in Flavi-, Toga- and Bunyavinudiae families
- Roboviruses include members in Bunyaviridiae and Arenaviridiae families
- Tumour viruses are present among different families

*Rotavirus is the only double-stranded RNA virus

**Parvoviruses are the only single-stranded DNA viruses