# V

## Virus

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### Synonyms

Viral agent; Virion

### Definition

Viruses are smallest infectious agents comprising genetic material (DNA/RNA, never both) surrounded by a protein coat (Brooks 2010).

### Introduction

Viruses are submicroscopic infectious agents which are obligate intracellular parasites. They are metabolically active and can replicate, only inside the host cell (White et al. 1994). The extracellular (transmission) phase alternates with the intracellular (reproductive) phase. Tobacco mosaic virus (TMV) was the first virus to be discovered (Lecoq 2001). Ivanoski (1892) saw that extracts from infected leaves remained infectious after filtration through bacterial filters. Beijerinck (1898) suggested to categorize the causative agent for tobacco mosaic disease as "virus" (Lecoq 2001).

### Structure

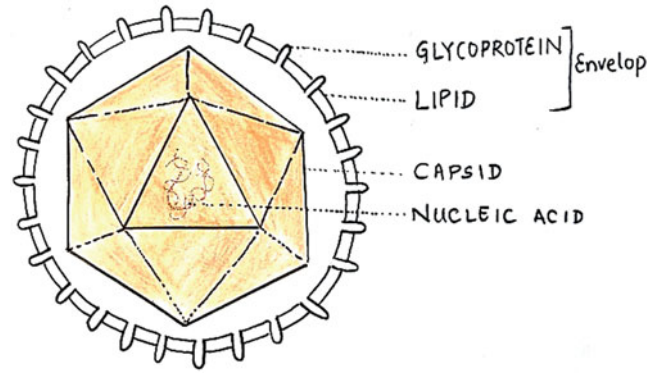
Virion is the infectious virus particle consisting of a nucleocapsid core. Virions may be surrounded by a lipoprotein envelop (Brooks 2010) . The nucleic acid can be single-stranded or double-stranded RNA or DNA. Nucleic acid codes for structural (capsid, envelop proteins, matrix protein) and nonstructural proteins (enzymes like replicases, proteases, and transcriptases) that are important for viral life cycle (White et al. 1994) .

Viral capsid is composed of morphological units called capsomeres. Depending upon the arrangement of these capsomeres around the nucleic acid, a virus can have icosahedral symmetry (Fig. 1), helical symmetry (Fig. 2), or complex symmetry. Lipid part of envelop is acquired from the host cellular membranes and the glycoprotein part is coded by the viral nucleic acid. Capsid and envelop provide protection and stability to the viral nucleic acid and also help viral interaction with the host cell.

### Classification

Viruses can infect plants, animals, and microbes as well. Common plant viruses are TMV, Tomato spotted wilt virus, etc. (Scholthof et al. 2011). Viruses of microbes infect unicellular prokaryotes


T. K. Shackelford, V. A. Weekes-Shackelford (eds.), *Encyclopedia of Evolutionary Psychological Science*,
https://doi.org/10.1007/978-3-319-16999-6_1320-1




**Virus, Fig. 1** Icosahedral symmetry (e.g., Human herpes virus)

(bacteria) and eukaryotes (algae and protozoa) (Debarbieux et al. 2017). Bacteriophages are the commonly studied viruses affecting microbes.

Viruses have been classified (Table 1) depending on factors including virion morphology – type of symmetry, presence or absence of envelop, viral genome – (nucleic acid type and strandedness, sense (positive/ negative), linear or circular, segmented or unsegmented), host range, mode of transmission, etc. (Brooks 2010).

## Replication

The first step in viral replication is **attachment**, where the viral attachment proteins (ligand) bind to specific receptor on the host cell plasma membrane (e.g., gp 120 of HIV binds to CD4 of T-helper cells, EBV binds to CD21 on B-lymphocytes). It is followed by **penetration** of the viral nucleocapsid into the host cell, by different mechanisms. In some enveloped viruses, lipid envelop fuses with host cell membrane by help of viral proteins, e.g., gp41 of HIV, F (fusion) glycoprotein of paramyxovirus. Other viruses (e.g: influenza virus), are taken inside an endosome by clathrin coated pits. Viral envelop and endosome membrane fuse afterwards. **Uncoating** of the viral nucleic acid then occurs, due to dissolution of viral capsid by the host enzymes.

The viral nucleic acid then transcribes mRNA followed by synthesis of early proteins (that shut the host genetic machinery). Viral genomic replication follows and progeny genome causes late mRNA transcription leading to synthesis of viral structural proteins. The structural components of virus assemble to form virions, which are then released from host cell.

Generally viral proteins are synthesized in the host cytoplasm using host ribosomes and viral mRNA, viral genomic RNA replicates in host cytoplasm, and viral genomic DNA is replicated in host nucleus. There are, however, few exceptions (Brooks 2010). Figure 3 shows the strategies adopted by different class of viruses for replication and protein synthesis.

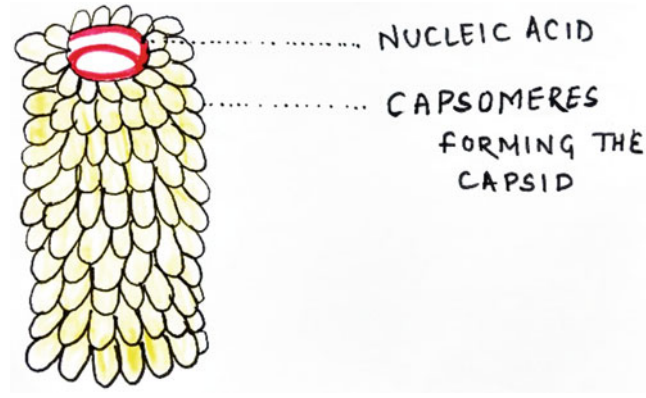
## Immunity Against Virus

Both innate and adaptive immune systems operate against viral infection. The macrophages and dendritic cells engulf the virion and serve as antigen presenting cells (present antigen to T- helper lymphocytes) and also produce variety of cytokines for activation of adaptive immune cells. Viruses downregulate MHC I (Major Histocompatibility Complex – class I) expression by the infected cells. Such cells are targeted by Natural killer cells (NK cells) which produce perforins and granzymes to cause target cell apoptosis. NK cells also produce IFN $\gamma$ and TNF $\alpha$ (tumor necrosis factor $\alpha$) which are essential for combating viral infection. Type 1 Interferons (IFN $\alpha$, IFN $\beta$) are produced by virus infected cells and plasmatoid dendritic cells (even when not infected). Type 1 IFNs upregulates expression of antiviral genes in both infected and uninfected

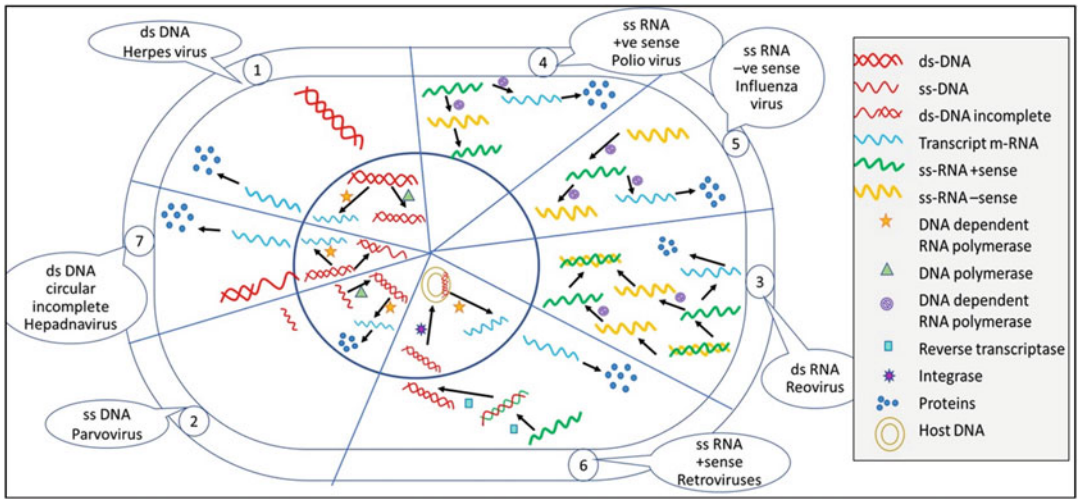
**Virus, Table 1** DNA and RNA viruses with health implications in humans

| Virus families | Symmetry | Genetic material | Envelop | Example of viruses |
|---|---|---|---|---|
| **DNA viruses** | | | | |
| Parvoviridae | Icosahedral | ssDNA linear | Absent | Parvovirus B19 |
| Papillomaviridae | Icosahedral | dsDNA circular | Absent | HPV |
| Polyomaviridae | Icosahedral | dsDNA circular | Absent | JC virus, BK virus |
| Adenoviridae | Icosahedral | dsDNA linear | Absent | Human Adenovirus |
| Herpesviridae | Icosahedral | dsDNA linear | Present | HSV1, HSV-2, VZV, EBV, CMV, HHV-6, -7,-8 |
| Hepadenaviridae | Icosahedral | dsDNA circular incomplete | Present | Hepatitis B virus |
| Poxviridae | Asymmetrical (Complex) | dsDNA linear | Present | Variola, Molluscum contagiosum virus |
| **RNA viruses** | | | | |
| Picornaviridae | Icosahedral | ss +ve sense | Absent | Poliovirus, Echovirus, Enterovirus, Coxsackievirus, HAV |
| Orthomyxoviridae | Helical | ss −ve sense segmented | Present | Influenza virus |
| Paramyxoviridae | Helical | ss −ve sense | Present | Parainfluenza virus, Measles virus, Mumps virus, Nipah virus |
| Rhabdoviridae | Helical | ss −ve sense | Present | Rabies virus, Chandipura virus |
| Togaviridae | Icosahedral | ss +ve sense | Present | Chikungunya virus |
| Flaviviridae | Icosahedral | ss +ve sense | Present | Japanese B Encephalitic virus, Dengue, Yellow fever virus |
| Caliciviridae | Helical | ss +ve sense | Absent | Norwalk virus |
| Arenaviridae | Helical | ss −ve sense segmented | Present | Lassa virus, Lymphocytic choriomeningitic virus |
| Bunyaviridae | Helical | ss −ve sense segmented | Present | Hanta virus, Sandfly fever virus, Ganjam virus |
| Filloviridae | Helical | ss −ve sense | Present | Ebola virus, Marburg virus |
| Reoviridae | Icosahedral | ds segmented | Absent | Reovirus, Rotavirus |
| Retroviridae | Icosahedral | ss +ve sense (2 copies) | Present | HIV, HLV |

Abbreviations: *HPV* Human papilloma virus, *HSV* Herpes simplex virus, *VZV* Varicella zoster virus, *EBV* Epstein barr virus, *CMV* Cytomegalovirus, *HHV* Human herpes virus, *HAV* Hepatitis A virus, *HIV* Human immunodeficiency virus, *HTLV* Human T-cell lymphocytotrophic virus




**Virus, Fig. 2** Helical symmetry (e.g., Tobacco mosaic virus)




**Virus, Fig. 3** shows the strategies of replication and protein synthesis used by different types of viruses: (1)in most dsDNA viruses (e.g., Herpesvirus, Adenovirus), viral DNA transcribes mRNA by the help of enzyme DNA-dependent RNA polymerase (RNA polymerase-II of host), mRNA translates early viral protein in the cytoplasm. DNA replication occurs with the help of host DNA polymerase in the nucleus. In poxvirus, the mRNA transcription and genomic replication occurs in cytoplasm because the virus carries its own DNA and RNA polymerases (2) In Parvovirus ssDNA of virus is first converted to dsDNA by cellular DNA polymerase, then mRNA transcription occurs. (3) In dsRNA containing viruses (e.g., Reovirus), each virion carries RNA-dependent RNA polymerases which use each strand to transcribe mRNA (4) In ssRNA viruses of positive sense, the RNA directly can act as mRNA transcript, genomic RNA is replicated via a negative sense RNA intermediate. (5) Viruses (e.g., influenza virus, rhabdoviruses) with negative sense RNA viruses carry RNA polymerases for mRNA transcription. (6) Retroviruses (e.g., HIV) have reverse transcriptase enzyme which transcribes DNA strand using each of the viral ssRNA strands (RNA-dependent DNA polymerase activity), it then lyses the parent ssRNA (ribonuclease activity) and forms complementary DNA strand taking the newly formed ssDNA as template, ultimately resulting in the dsDNA which then enters the host nucleus and binds to host DNA with the help of enzyme integrase. When the cell is actively replicating, viral mRNA is transcribed and protein synthesis occurs. (7) In Hepatitis B virus, which has partially dsDNA (circular -not shown in figure), the viral genome is first converted into covalently closed circular dsDNA (cccDNA), which serves as template for mRNA transcription, pre-genomic positive sense RNA is produce too which with the help of reverse transcriptase enzyme subsequently form the genomic partially dsDNA (not shown)

cells. IFN γ also causes activation of macrophages and NK cells.

Antibodies, produced by helper T-cells (CD4+) and B-cells can neutralize the viral attachment proteins. Complements also have neutralization action. Cytotoxic T cells (CD8+) play major role in controlling infection as they kill the virus infected cells (Delves et al. 2017; White et al. 1994).

## Evolution of Virus, Mutations, and Consequences

Different theories for origin of viruses have been proposed. Viruses may have originated from the genome of host cells or by degeneration of infecting intracellular parasites. DNA and RNA viruses have probably originated from different sources as they vary profoundly (Brooks 2010). The characteristic features of viruses of microbes are different from those of humans and other animals; however, evidences support that they evolved from the same source (Bamford et al. 2005).

Viruses keep evolving for fitness, i.e., "*ability of the virus to replicate infectious progeny*" (Domingo et al. 1996). Viruses have evolved to evade (escape) host immune system (Male et al. 2012) by various strategies like-

- Avoid being recognized by mechanisms like latency, infecting immunologically privileged sites
- Downregulate MHC I and MHC II as seen in HIV infection
- Change antigens by drift and shift as seen in influenza virus
- Affect antigen processing as seen in CMV infection

The RNA viruses are able to breach the boundary of species and capable of infecting new hosts. High mutation rates make them capable of evolving at a faster rate (Holmes 2009). Influenza virus has evolved by re-assortment (mixing of genetic material of one human, one bird, and two swine strains). This has altered its virulence, making it capable to develop a pandemic (Taubenberger and Kash 2010). The recent finding shows that HTLV-1 can cover itself in a carbohydrate-rich adhesive extracellular "cocoon," similar to bacterial biofilms. This novel mechanism of viral transmission ensures the efficient and protected viral transfer between cells (Thoulouze and Alcover 2011).

During evolution, changes in the viral genetics occur by means of mutation and recombination, which may alter the virulence power of the virus. An avirulent virus may turn virulent or a less virulent virus may become highly virulent. This leads to newly emerging diseases (Domingo et al. 1996; Roossinck 1997; Morse and Schluederberg 1990). Environmental changes (e.g., Global warming, ecological changes, demographic changes, migration) do play a role in activation or mutation in the viruses and may result in these emerging viral infections (Morse and Schluederberg 1990; Olival and Daszak 2005). The common emerging viral infections are those caused by – Nipah virus, paramyxoviridae, zika, and ebola viruses (Bishop 2015; Olival and Daszak 2005; Wikan and Smith 2016).

## Health Implications

Viruses can cause several diseases in humans (Table 2). Parvovirus B19 can have dangerous manifestation like aplastic anemia and carditis. Hemorrhagic fevers manifest as widespread bleeding from epithelial surfaces. Different hepatitis viruses are grouped under different families and differ greatly in pathogenicity. Cancers that can be caused by viral infection include cervical cancer by HPV 16 and 18, hepatocellular carcinoma by HBV & HCV, Burkitt's lymphoma and nasopharyngeal carcinoma by EBV, lymphomas by HIV virus, Kaposi Sarcoma by HHV8, and leukemias by HTLV. SARS & MERS have rapidly affected many people (reaching close to a pandemic) in recent past. H1N1 flu is the recent most pandemic infection caused by re-assorted influenza virus and is still continuing in India. Zika virus infection in the pregnant female may lead to microcephaly in the new-born child and Guillain- Barré syndrome in adults (White et al. 1994).

In-utero exposure to viruses has been hypothesized to increase the risk of development of schizophrenia, bipolar disorder, autism, and mental retardation in the child (Chess et al. 1978). Viral infection involving the central nervous system may present with psychiatric manifestations (psychosis, catatonia, mania, and depression) (Freudenreich et al. 2011). Viral infections like HIV, HSV can involve brain and produce cognitive deficits (Dickerson et al. 2004). Serious viral infections (HBV, HCV, and HIV) have been reported in patients with severe mental illnesses. Risky behavior and altered immune status in these patients might be responsible for such coinfections (Klinkenberg et al. 2003).

Certain viruses may remain latent in certain part of the body, after primary attack. JC virus, for example, commonly has subclinical or very mild manifestation in primary attack, and goes unnoticed. However, it remains latent in kidney and brain, and is a frequent cause of progressive multifocal leukoencephalopathy after renal transplantation. Subacute Sclerosing Panencephalitis (SSPE) is a late sequel of measles, though its occurrence has reduced due to vaccination (Garg et al. 2019). Mutated viral genome has been isolated from the brains of patients with SSPE. SSPE often has onset in the adolescence and manifest with cognitive impairment, myoclonus, ataxia, and visual disturbances (Garg et al. 2019).

**Virus, Table 2** Important groups of viral infections in humans

| Disease groups | Important causative viruses |
|---|---|
| Viral exanthems | Measles, Rubella, Mumps, Varicella viruses |
| Arthralgia and arthritis | Chikungunya, HBV, HIV, Zika viruses |
| Hemorrhagic fevers | Yellow fever, Dengue, Ebolavirus and Marburg viruses |
| Viral gastroenteritis | Rotavirus (common in childhood), caliciviruses, enteric adenoviruses |
| Hepatitis | Hepatitis viruses (A, B, C, D, E), yellow fever virus, HSV, EBV, CMV |
| Genitourinary infection | HSV-2, HPV- 6, HPV-11 |
| Oncogenic viruses | HPV types 16 and 18, HBV, HCV, EBV, polyoma virus, HHV8, HIV, HTLV |
| Cardiitis | Coxsackie B viruses, adenovirus, parvovirus B19 |
| Encephalitis | Japanese B encephalitis; Eastern, Western, and Venezuelan encephalitis; Herpesviridae family; Picornaviridae family; and Adenovirus |
| Respiratory infections | RSV, adenovirus, SARS-CoV MERS-CoV, Influenza, and Parainfluenza virus |

*SARS CoV* Severe acute respiratory syndrome, *MERS CoV* Middle east respiratory syndrome

## Laboratory Diagnosis

Samples like swabs (from throat, eye, and skin lesions), feces, CSF from suspected viral cases should be properly collected and transported in viral transport medium (VTM). Collection of the sample from the appropriate site during the course of disease is very critical for direct detection of virus.

Direct demonstration of the virus can be done under electron microscope. Detection of viral antigens can be done by ELISA, Latex agglutination, Immunofluorescence, and Immunochromatography can done depending upon the available formats. Viral nucleic acid can be detected by PCR, Microarray, and other molecular techniques. They are generally the most sensitive and rapid methods for diagnosis. Viral isolation is considered "gold standard," but the isolation of virus in cell lines (e.g., Vero cell line), animal inoculation, and egg inoculation are costly and time consuming and used mainly for research purpose (White et al. 1994).

Detection of antibodies against the viral antigens in the patient blood by ELISA are frequently used screening tools for detection of viral infections. A raised specific-IgM indicates recent infection, whereas, a raised specific IgG can detect past infection. A lot of viral diseases like JE, Dengue, Chikungunya, and Zika are diagnosed by detecting antibodies against them in the patient serum. They are also very sensitive and commonly employed tests.

## Advantages of Viruses

Certain vaccines are produced by the live attenuated strains of the viruses, which protects the individual from the infection by the virulent strains of similar viruses. Bio-engineering has used viruses for carrying and protecting genomic information (Li et al. 2010). Viruses can transfer genetic material to their host (e.g., Bacteriophages), which integrates with the host genome, there by facilitates the evolution of organisms (Roossinck 2011). An important example is evolution of antibiotic resistant bacteria. Many viruses have symbiotic relationships with their hosts and protect the host (Roossinck 2011).

## Conclusion

Viruses have abundant health implications including – cancer, neurological, and psychological implications. Viruses continuously interact with the environment and their host, through

which they evolve. Prevention of the serious health conditions need development of new and effective vaccines against viruses. There is a lot of scope for research in this field.

## Cross-References

► Viral Infections

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