Viruses: Definition, Structure, Classification 2

Contents

2.1 What is a Virus?

Viruses are infectious units with diameters of about 16 nm (circoviruses) to over 300 nm (poxviruses; Table 2.1). Their small size makes them ultrafilterable, i.e. they are not retained by bacteria-proof filters. Viruses have evolved over longtime period, and have adapted to specific organisms or their cells. The infectious virus particles, or virions, are composed of proteins and are surrounded in some species of viruses by a lipid membrane, which is referred to as an envelope; the particles contain only one kind of nucleic acid, either DNA or RNA. Viruses do not reproduce by division, such as bacteria, yeasts or other cells, but they replicate in the living cells that they infect. In them, they develop their genomic activity and produce the components from which they are made. They encode neither their own protein synthesis machinery (ribosomes) nor energy-generating metabolic pathways. Therefore, viruses are intracellular parasites. They are able to re-route and modify the course of cellular processes for the optimal execution of their own reproduction. Besides the genetic information encoding their structural components, they additionally possess genes that code for several regulatory active proteins (such as transactivators) and enzymes (e.g. proteases and polymerases).

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Table 2.1 Molecular biological characteristics of the different virus families, including some typical prototypes

Virus family	Subfamily/genus	Example	Envelope	Particle size/ shape of the capsid or nucleocapsid	Genome: kind and size
Picornaviridae (▶ Sect. 14.1)	Enterovirus	Poliovirus, coxsackievirus, human enteroviruses, human rhinoviruses	No	28–30 nm/ icosahedron	ssRNA; linear; positive strand; 7,200–8,400 nucleotides
	Cardiovirus	Encephalomyocarditis virus, mengovirus, theilovirus			
	Aphthovirus	Foot-and-mouth disease virus			
	Parechovirus	Human parechovirus			
	Hepatovirus	Hepatitis A virus			
	Erbovirus	Equine rhinitis B virus			
	Kobuvirus	Aichi virus			
	Teschovirus	Porcine teschoviruses			
Astroviridae (▶ Sect. 14.2)	Mamastrovirus	Human, bovine and feline astroviruses	No	27–30 nm/ icosahedron	ssRNA; linear; positive strand; 6,800–7,900 nucleotides
	Avastrovirus	Avian astroviruses			
Caliciviridae (▶ Sect. 14.3)	Norovirus	Norwalk virus	No	27–34 nm/ icosahedron	ssRNA; linear; positive strand; 7,500–8,000 nucleotides
	Sapovirus	Sapporo virus			
	Vesivirus	Feline calicivirus			
	Lagovirus	Rabbit haemorrhagic disease virus			
	Nebovirus	Newbury-1 virus			

Hepeviridae (▶ Sect. 14.4)	Hepevirus	Hepatitis E virus	No	27–34 nm/ icosahedron	ssRNA; linear; positive strand; 7,200 nucleotides
Flaviviridae (▶ Sect. 14.5)	Flavivirus	Yellow fever virus, dengue virus, West Nile virus, tick-borne encephalitis virus	Yes	40–50 nm/ icosahedron	ssRNA; linear; positive strand; 10,000 nucleotides
	Pestivirus	Classical swine fever virus, bovine viral diarrhoea virus			
	Hepacivirus	Hepatitis C virus			
Togaviridae (▶ Sect. 14.6)	Alphavirus	Sindbis virus, Semliki Forest virus, equine encephalitis viruses	Yes	60–70 nm/ icosahedron	ssRNA; linear; positive strand; 12,000 nucleotides
	Rubivirus	Rubella virus			
Arteriviridae (▶ Sect. 14.7)	Arterivirus	Equine arteritis virus, porcine reproductive and respiratory syndrome virus	Yes	40–60 nm/ icosahedron	ssRNA; linear; positive strand; 12,000–16,000 nucleotides
Coronaviridae (▶ Sect. 14.8)	Coronavirinae/ Alphacoronavirus	Human coronaviruses 229E and NL63, feline coronavirus, porcine transmissible gastroenteritis virus	Yes	120–160 nm/helix	ssRNA; linear; positive strand; 25,000–35,000 nucleotides
	Coronavirinae/ Betacoronavirus	SARS-associated coronavirus, mouse hepatitis virus, bat corinaviruses HKU5 and HKU9			
	Coronavirinae/ Gammacoronavirus	Avian infectious bronchitis virus			
	Torovirinae/Torovirus	Bovine and equine toroviruses			

(*continued*)

Table 2.1 (continued)

Virus family	Subfamily/genus	Example	Envelope	Particle size/ shape of the capsid or nucleocapsid	Genome: kind and size
Rhabdoviridae (▶ Sect. 15.1)	Vesiculovirus	Vesicular stomatitis virus	Yes	65–180 nm/helix	ssRNA; linear; negative strand; 12,000 nucleotides
	Lyssavirus	Rabies virus			
	Ephemerovirus	Bovine ephemeral fever virus			
	Novirhabdovirus	Infectious haematopoietic necrosis virus, viral haemorrhagic septicaemia virus			
Bornaviridae (▶ Sect. 15.2)	Bornavirus	Borna disease virus	Yes	90 nm/helix	ssRNA; linear; negative strand; 9,000 nucleotides
Paramyxoviridae (▶ Sect. 15.3)	Respirovirus	Parainfluenza virus	Yes	150–250 nm/helix	ssRNA; linear; negative strand; 16,000–20,000 nucleotides
	Rubulavirus	Mumps virus			
	Avulavirus	Newcastle disease virus			
	Morbillivirus	Measles virus, canine distemper virus, rinderpest virus			
	Henipavirus	Hendra virus, Nipah virus			
	Pneumovirus	Respiratory syncytial virus			
	Metapneumovirus	Human metapneumovirus			

Filoviridae (▶ Sect. 15.4)	Marburgvirus	Marburg marburgvirus	Yes	80–700 nm/helix	ssRNA; linear; negative strand; 19,000 nucleotides
	Ebolavirus	Zaire ebolavirus, Reston ebolavirus			
Arenaviridae (▶ Sect. 16.1)	Arenavirus	Lymphocytic choriomeningitis virus, Lassa virus, Junín virus	Yes	50–300 nm/helix	ssRNA; linear; 2 segments; ambisense strands; 10,000–12,000 nucleotides
Bunyaviridae (▶ Sect. 16.2)	Orthobunyavirus	California encephalitis virus	Yes	100–120 nm/helix	ssRNA; linear; 3 segments; negative strand (ambisense in phleboviruses); 12,000 nucleotides
	Phlebovirus	Rift Valley fever virus, sandfly fever virus			
	Nairovirus	Crimean-Congo fever virus, Nairobi sheep disease virus			
	Hantavirus	Hantaan virus, Puumala virus, Sin Nombre virus			
	Topsovirus	Tomato spotted wilt virus			
Orthomyxoviridae (▶ Sect. 16.3)	Influenza A virus	Influenza A virus	Yes	120 nm/helix	ssRNA; linear; 7 or 8 segments; negative strand; 13,000–14,000 nucleotides
	Influenza B virus	Influenza B virus			
	Influenza C virus	Influenza C virus			
	Thogotovirus	Thogoto virus, Dhori virus			
	Isavirus	Infectious salmon anaemia virus			
Birnaviridae (▶ Sect. 17.1)	Avibirnavirus	Gumboro virus	No	60 nm/ icosahedron	dsRNA; linear; 2 segments; 5,800–6,400 base pairs
	Aquabirnavirus	Infectious pancreatic necrosis virus			
	Entomobirnavirus	Drosophila X virus			

(*continued*)

Table 2.1 (continued)

Virus family	Subfamily/genus	Example	Envelope	Particle size/ shape of the capsid or nucleocapsid	Genome: kind and size
Reoviridae (▶ Sect. 17.2)	Orthoreovirus	Reoviruses	No	70–80 nm/ icosahedron	dsRNA; linear; 10/11/12 segments; 18,000–19,000 base pairs
	Orbivirus	Bluetongue virus, African horse sickness virus			
	Rotavirus	Rotaviruses			
	Coltivirus	Colorado tick fever virus			
	Aquareovirus	Golden shiner virus			
Retroviridae (▶ Sect. 18.1)	Alpharetrovirus	Rous sarcoma virus	Yes	100 nm/ icosahedron or cone	ssRNA; linear; positive strand, transcription into dsDNA; integration; 7,000–12,000 nucleotides
	Betaretrovirus	Mouse mammary tumour virus			
		Jaagsiekte sheep retrovirus (ovine pulmonary adenomatosis virus)			
	Gammaretrovirus	Feline leukaemia virus, murine leukaemia virus			
	Deltaretrovirus	Human T-lymphotropic viruses 1 and 2, bovine leukaemia virus			
	Epsilonretrovirus	Diverse fish retroviruses			
	Lentivirus	Human immunodeficiency viruses			
	Spumavirus	Simian foamy virus			

Hepadnaviridae (▶ Sect. 19.1)	Orthohepadnavirus	Hepatitis B virus	Yes	42 nm	DNA; partially double stranded; circular; 3,000–3,300 base pairs
	Avihepadnavirus	Duck hepatitis B virus			
	Deltavirus (virusoid); infection along with hepatitis B virus as helper virus	Hepatitis D virus	Yes, composition to similar the envelope of hepatitis B viruses		ssRNA; circular; 1,900 nucleotides
Polyomaviridae (▶ Sect. 19.2)	Polyomavirus	BK polyomavirus, JC polyomavirus, simian virus 40	No	45 nm/ icosahedron	dsDNA; circular; 5,000 nucleotides
Papillomaviridae (▶ Sect. 19.3)	Alphapapillomavirus	Human papillomaviruses 6, 10, 16, 18 and 32 (mucosa, oral/genital)	No	55 nm/ icosahedron	dsDNA; circular; 8,000 nucleotides
	Betapapillomavirus	Human papillomaviruses, 5, 9 and 49 (dermal)			
	Gammapapillomavirus	Human papillomaviruses 4, 48 and 50 (dermal)			
	Deltaapillomavirus	Ruminant papillomaviruses (cattle, sheep, deer)			
	Lambdapapillomavirus	Canine and feline papillomaviruses			
Adenoviridae (▶ Sect. 19.4)	Mastadenovirus	Human and canine adenoviruses	No	70–80 nm/ icosahedron	dsDNA; linear; 36,000–38,000 base pairs
	Aviadenovirus	Avian adenoviruses			
	Siadenovirus	Turkey haemorrhagic enteritis virus			
	Atadenovirus	Chicken egg drop syndrome virus			

(*continued*)

Table 2.1 (continued)

Virus family	Subfamily/genus	Example	Envelope	Particle size/ shape of the capsid or nucleocapsid	Genome: kind and size
Herpesviridae (▶ Sect. 19.5)	Alphaherpesvirinae	Herpes simplex viruses, varicella-zoster virus, bovine, equine, porcine, canine, feline and gallid herpesviruses	Yes	250–300 nm/ icosahedron	dsDNA; linear; 150,000–250,000 base pairs
	Betaherpesvirinae	Cytomegalovirus, human herpesvirus 6			
	Gammaherpesvirnae	Epstein-Barr virus, human herpesvirus 8, alcelaphine herpesvirus 1 (bovine malignant catarrhal fever virus)			
Poxviridae (▶ Sect. 19.6)	Orthopoxvirus	Variola viruses, vaccinia virus, bovine and simian variola viruses	Yes	350–450 nm/ complex	dsDNA; linear; 130,000–350,000 base pairs
	Parapoxvirus	Orf virus			
	Avipoxvirus	Canarypox virus			
	Molluscipoxvirus	Molluscum contagiosum virus			
	Suipoxvirus	Swinepox virus			
	Yatapoxvirus	Tanapox virus, Yaba monkey tumour virus			

Asfarviridae (▶ Sect. 19.7)	Asfivirus	African swine fever virus	Yes	200 nm/complex	dsDNA; linear; 180,000 base pairs
Parvoviridae (▶ Sect. 20.1)	Parvovirus	Feline panleucopenia virus, canine parvovirus, porcine parvovirus	No	20–25 nm/ icosahedron	ssDNA; linear; 5,000 nucleotides
	Erythrovirus	Parvovirus B19			
	Bocavirus	Human bocavirus, bovine bocavirus, canine minute virus			
	Amdovirus	Aleutian mink disease virus			
	Dependovirus	Adeno-associated viruses			
Circoviridae (▶ Sect. 20.2)	Gyrovirus	Chicken anaemia virus	No	16–24 nm/ icosahedron	ssDNA; circular; 1,700–2,000 nucleotides
	Circovirus	Porcine circovirus, beak and feather disease virus			
Anelloviridae (▶ Sect. 20.2)	Alphatorquevirus	Torque teno virus			
	Betatorquevirus	Torque teno mini virus			
	Gammatorquevirus	Torque teno midi virus			

ssDNA single-stranded DNA, *dsDNA* double-stranded DNA, *ssRNA* single-stranded RNA, *dsRNA* double-stranded RNA

Viruses exist in different conditions. They can actively replicate in cells, and produce a great number of progeny viruses. This is known as a replicationally active state. After infection, some virus types can transition into a state of latency by integrating their genetic information into the genome of the host cell, or maintain it as an episome in an extrachromosomal status within infected cells. Certain viral genes can be transcribed during that time, contributing to the maintenance of latency (herpesviruses). In other cases, the expression of the viral genome is completely repressed over long periods of time (e.g. in some animal pathogenic retroviruses). In both cases, cellular processes or external influences can reactivate the latent genomes, leading to a new generation of infectious viruses. Depending on the virus type, the infection can have different consequences for the host cell:

1. It is destroyed and dies.
2. It survives, but continuously produces small numbers of viruses and is chronically (persistently) infected.
3. It survives and the viral genome remains in a latent state without producing infectious particles.
4. It is immortalized, thus gaining the capability of unlimited cell division, a process that can be associated with malignant transformation into a tumour cell.

2.2 How are Viruses Structured, and what Distinguishes them from Virusoids, Viroids and Prions?

2.2.1 Viruses

Infectious virus particles – also referred to as virions – are constituted of various basic elements (Fig. 2.1): inside, they contain an RNA genome or a DNA genome. Depending on the virus type, the nucleic acid is single-stranded or double-stranded, linear, circular or segmented. Single-stranded RNA and DNA genomes can have different polarity, and in certain cases the RNA genome is similar to messenger RNA, e.g. in picornaviruses and flaviviruses. A single-stranded genome that has the same polarity as the messenger RNA is referred to as a positive or plus strand.

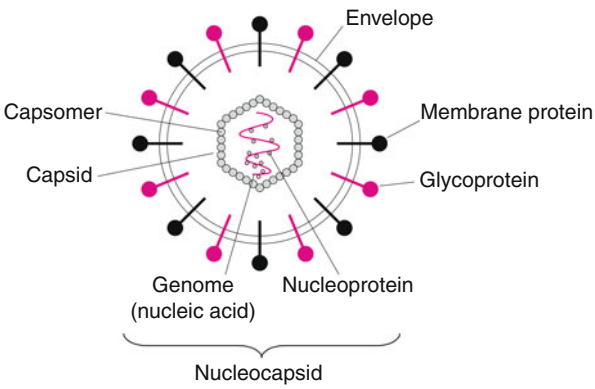

Fig. 2.1 Structure of an enveloped viral capsid

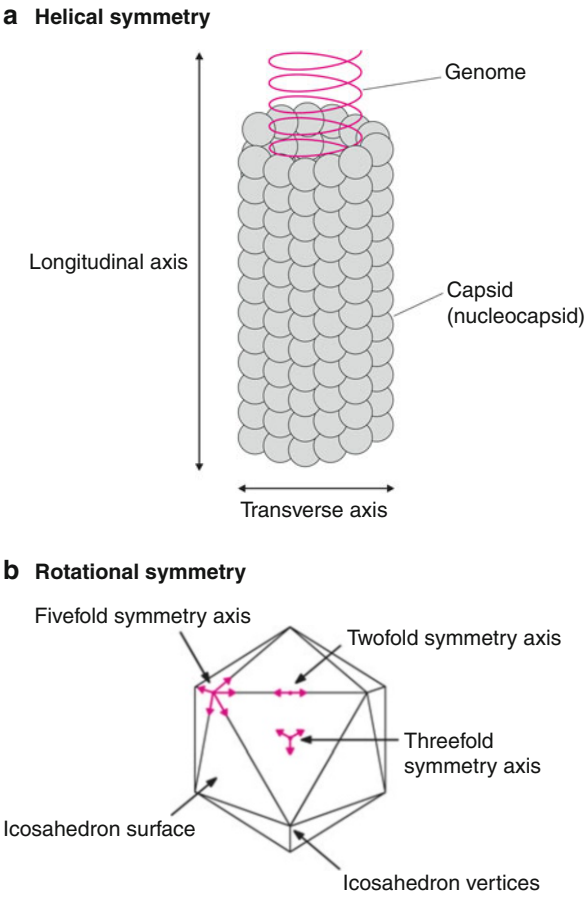

Fig. 2.2 Symmetry forms of viral capsids. (**a**) Helical symmetry; the symmetry planes run parallel to the longitudinal or transverse axis of the particle (e.g. tobacco mosaic virus capsid, nucleocapsid of paraviruses or orthomyxoviruses). (**b**) Cubic-spherical symmetry; icosahedron with rotational symmetry whose centres of the symmetry axes are at the vertices of the icosahedron (fivefold symmetry axis) in the middle of the triangle (threefold symmetry axis) and along the edges (twofold symmetry axis). Picornaviruses, parvoviruses and adenoviruses are examples of viruses with such capsid forms

The genome forms a nucleocapsid complex with cellular histones (polyomaviruses) or viral proteins (e.g. rhabdoviruses, paraviruses, orthomyxoviruses, adenoviruses and herpesviruses). This nucleic acid-protein complex can be surrounded by particular protein structures, the capsids (in polyomaviruses, papillomaviruses, adenoviruses and herpesviruses). In some cases (such as picornaviruses, flaviviruses, togaviruses and parvoviruses), the nucleic acid interacts directly with the capsids. In viruses containing an envelope, the capsid layer can be absent (as in coronaviruses, rhabdoviruses, paramyxoviruses, orthomyxoviruses, bunyaviruses and arenaviruses).

Capsids are rod-shaped or cubic-spherical protein structures. In some virus types, they consist of multimeric units of only one polypeptide, in other cases they are composed of heteromeric complexes. The capsid protein subunits can aggregate into discrete subunits or even into so-called capsomeres, i.e. morphologically distinct structural components. Rod-shaped capsids have a helical symmetry. The two planes of symmetry, i.e. the longitudinal and the transversal axes, differ in length (Fig. 2.2a). By contrast, spherical capsids have an icosahedral structure with

a rotational symmetry; an icosahedron consists of 20 equilateral triangles and 12 vertices (Fig. 2.2b). The symmetry axes have the same length: the fivefold symmetry axis is located at the vertices of the icosahedron; the threefold axis passes through the centre of a triangle, the twofold axis passes along the edges. The number of subunits of an icosahedron can be calculated by the formula $10(n-1)^2+2$, where n indicates the number of morphologically distinguishable structures on the face of a triangle.

The three-dimensional structures of the particles of a number of viruses have been resolved by X-ray structural analyses. Prerequisite is knowledge of the basic composition of the virus, i.e. information on which proteins form the capsid or the virus, as well as the nature of the viral genetic information and the sequence of the structural proteins. In addition, purification of virus particles must be possible and these must be available as a stable highly concentrated virus suspension on the order of several milligrams per millilitre. Finally, the purified virions or, alternatively, viral capsids, which are produced in cell culture or by genetic engineering, must be able to crystallize.

In some virus types, the capsids are surrounded by a lipid bilayer envelope, which is derived from cellular membrane systems. Viral and cellular proteins are embedded in the envelope, and are frequently modified into glycoproteins by sugar groups. Usually, viral surface components are clearly exposed, and they can protrude up to 20 nm from the particle surface. If such a membrane envelope is present, it renders the virus sensitive to inactivation by solvents and detergents. A tegument layer can be situated between the membrane and the capsid (herpesviruses), and contains additional viral protein components.

The exposed proteins and protein domains on the surface of the virus – either in the envelope or in the capsid – are subject to selection pressure by the immune system. Therefore, viruses change by mutation and selection preferentially the amino acid sequences of antibody-binding regions or epitopes, which are responsible for binding neutralizing immunoglobulins. In some species of viruses, this variability of the surface regions leads to the formation new subtypes. In addition to this continuous change of the surface of exposed regions that is determined by mutation and selection, in some virus types another source of variability is possible by genetic recombination, by which even large nucleic acid regions can be exchanged between different viruses. This can lead to substantial changes in the viruses involved and to the generation of new viral species.

2.2.2 Virusoids (Satellite Viruses), Viroids, Mimiviruses and Virophages

Satellite viruses, or virusoids, are small RNA or DNA molecules that code for one or two proteins with which they are associated. Their replication and spread is dependent on the presence of another virus. Virusoids are usually found together

with plant viruses, but also hepatitis D virus, which can only proliferate when the cell is simultaneously infected with hepatitis B virus, is a virusoid (▶ Sect. 19.1.5). Viroids are plant pathogens and consist of a circular RNA (about 200–400 nucleotides) that does not code for proteins and exhibits a complex two-dimensional structure. A central sequence motif is highly conserved and essential for replication of these nucleic acid molecules. Other regions are variable and may be responsible for virulence. These infectious RNA molecules are replicated by cellular polymerases in a rolling circle mechanism (▶ Sect. 3.4), whereby secondary structures are formed at the transitions, which are known as a hammerhead because of their form. They have RNase activity, and autocatalytically cleave the concatemeric RNA strands that result after replication. Ribozymes, small RNA species with sequence-specific RNase activity (▶ Sect. 9.3), are derived from the hammerhead-like RNA structures.

Mimiviruses are a family of very large DNA viruses which were discovered by Didier Raoult in the amoeba *Acanthamoeba polyphaga* only in 2004. These viruses were originally regarded as bacteria because of the extraordinary size of their spherical capsids (400 nm) and protein filaments, which protrude extremely from the surface, conferring the virions with an apparent size of up to 800 nm. Therefore, they were denominated "mimiviruses" as an abbreviation for "mimicking viruses". The DNA genome of mimiviruses comprises 1.2 million base pairs and encompasses more than 1,200 putative genes. Even larger mamaviruses have been discovered in amoebae, which can be infected by parasitic viruses. These significantly smaller viruses (sputnikvirus), also known as virophages, can multiply in amoebae only if they are concurrently infected by mamaviruses. However, sputniks do not use mamaviruses only as a helper virus, but also inhibit their proliferation and morphogenesis, thus making them virtually sick.

2.2.3 Prions

In animals and humans, prions always cause fatal neurodegenerative disorders. They can be transmitted within a species, and – albeit limited – to other organisms beyond species boundaries (▶ Chap. 21). The pathogen responsible (prion, from "proteinaceous infectious particle") does not require a coding nucleic acid in the infectious agent. Prions are composed of the pathological isoform (PrP^{Sc}), which exists especially in β-sheet conformation, and of a non-pathological cellular prion protein (PrP^{C}), which is present predominantly in α-helical conformation. The conversion of the PrP^{C} α-helical conformation into the β-sheet PrP^{Sc} variant is associated with completely different biochemical properties, and is the key pathogenetic basic principle of prion diseases. After its synthesis, the cellular protein PrP^{C} arrives in the cytoplasmic membrane. PrP^{C} is active at the cell surface only for a limited time, and is subsequently degraded in the endosomes. During this process, a small proportion of PrP^{C} proteins are constantly transformed into PrP^{Sc} variants. This process is referred to as prion conversion. PrP^{Sc} proteins cannot be efficiently degraded and accumulate in the cells. The function of PrP^{C} has not been completely resolved.

Experiments with knockout mice containing a deletion of the PrP coding genome sequences revealed that PrP^C appears to be dispensable for development and survival of the mice. However, without PrP^C they cannot develop a prion disease.

Human prion diseases include Creutzfeldt-Jakob disease, kuru and variant Creutzfeldt-Jakob disease. In animals, the most famous representatives are scrapie (sheep), bovine spongiform encephalopathy (cattle) and chronic wasting disease (deer). The peculiarity of prion diseases is that they appear in three manifestations: acquired infectious (exogenous), sporadic (endogenous) and genetic (endogenous). Inasmuch as prions are restricted to the central nervous system, their infectious transmission is generally limited.

2.3 What Criteria Determine the Classification System of Virus Families?

The taxonomic classification of viruses into different families is done by an international commission of virologists and is continuously adapted to current insights. It is based on the following main criteria:

1. The nature of the genome (RNA or DNA) and the form in which it is present, i.e. as a single or a double strand, in positive or negative sense, linear or circular, segmented or continuous; also the arrangement of genes on the nucleic acid is important for the definition of individual families.
2. The symmetry form of the capsids.
3. The presence of an envelope.
4. The size of the virion.
5. The site of viral replication within the cell (cytoplasm or nucleus).

The further subdivision into genera and virus types is largely based on serological criteria and the similarity of genome sequences. The different virus families and their important human and animal pathogenic prototypes are summarized in Table 2.1.

Further Reading

Chiu W, Burnett RM, Garcea RL (1997) Structural biology of viruses. Oxford University Press, New York

Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA (2005) Virus taxonomy. VIIIth report of the international committee on taxonomy of viruses. Academic, San Diego

Fraenkel-Conrat H (1985) The viruses. Catalogue, characterization, and classification. Plenum, New York

International Committee on Taxonomy of Viruses (2012) ICTV home. http://ictvonline.org/

Knipe DN, Howley PM (eds) (2006) Fields virology, 5th edn. Lippincott-Raven, New York

Nermuth MV, Steven AC (1987) Animal virus structure. Elsevier, Amsterdam

Richman DD, Whitley RJ, Hayden FG (2002) Clinical virology, 2nd edn. ASM Press, Washington, DC