Chapter 2. General properties of viruses

◉ Human viruses

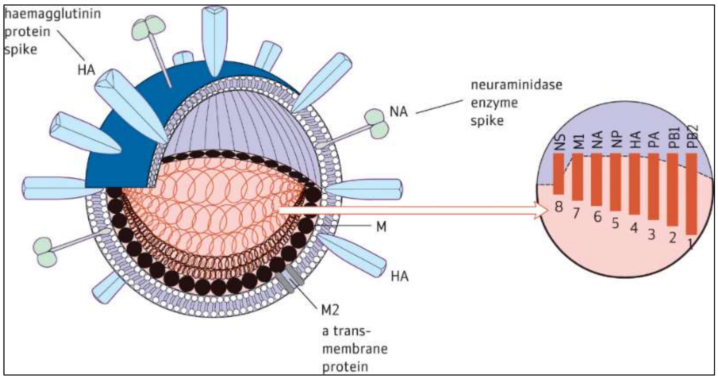
- Mostly small, from ~20 – 260 nm (~100X smaller than bacteria, ~1000X smaller than eukaryotic cells) → exceptions: poxviruses (200-400 nm), filoviruses like Ebola (~1000 nm)
- Detailed characterization by electron microscopy, cell culture, high-speed centrifugation, electrophoresis, and sequencing.
- Nowadays, first encountered by molecular biologists as novel nucleotide sequences in diseased tissues.
- Totally dependent on living cells, either DNA or RNA as a genome, receptor-binding proteins for docking to cells
  - ☞ Interesting non-human viruses: Bacteriophages such as λ. Viroids as very small circular ssRNA molecules, ~300 nt, too small to encode proteins, hardly regarded as true viruses, affect plants only.

The architecture of viruses

❖ Terms for the basic components of viruses

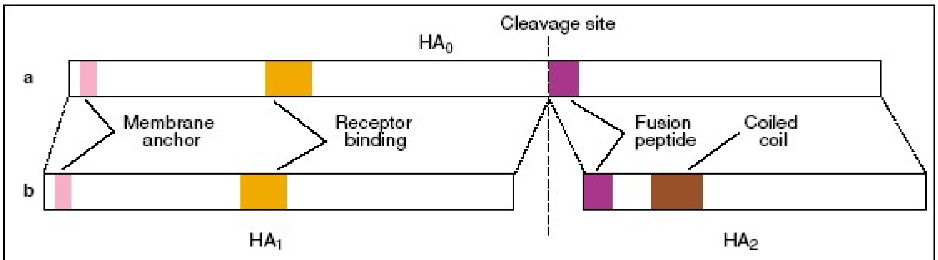
- Viral proteins: Structural and nonstructural proteins.
- Genomes: Nucleic acids.
- Capsid (meaning box): protein shell to function dually for the rigidity of itself and protection of nucleic acid.
- Capsomere (capsomer) is a morphological unit visible in the microscopes: formed by association of a definite number of individual proteins (often termed the structural subunits or protomers).
- Nucleocapsid: the internal complex of protective protein and viral nucleic acid.
- Envelope (the outer membrane derived from its host cell): many animal viruses as well as a few rare plant and bacterial viruses are surrounded by it.
- Membrane/matrix proteins: present beneath the envelope to stabilize it.
- Spikes: protruding usually through the envelope, commonly glycoproteins.
- Virion: the whole virus particle, that is the nucleocapsid with its outer envelope (if present).

⦿ Spikes of influenza



Haemagglutinin (HA): ~ 500 spikes/virion, the most investigated virus spike protein.

- ➢ 3 identical subunits (homo-trimer)/each spike.
- ➢ The glycosylated distant region (ectodomain) of HA is most exposed, contains five protruding antigenic sites, and a saucer-shaped depressed receptor-binding site.
- ➢ HA is cleaved by furin during transport into HA1/HA2, which are joined by S-S bonds and more infectious than the intact HA.
- ➢ HA2 has a **fusion motif**, normally buried deep near the proximal end → the contortion triggered by low pH places the motif nearer the far or distal end → carry out its fusion function with the endosome → viral RNA is released



Processing of influenza haemagglutinin (HA)
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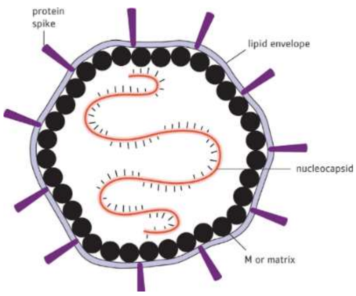
Figure 4. Processing of influenza haemagglutinin (HA). The key regions of HA are shown. (a) The protein is produced as a precursor molecule (HA_0). (b) HA_0 is cleaved by a protease into two active subunits, which are known as HA_1 and HA_2. HA_1 contains the receptor-binding domain, anchors the protein to the membrane and is held together with HA_2 by disulphide bonds. HA_2 contains the fusion peptide that is activated when a coiled coil of α helices is formed, a process that is dependent on a low pH (fig004gwn).

Neuraminidase (NA): homo-tetramer, ~100 spikes/virion): the mushroom-shaped 2^{nd} spike protein of influenza.

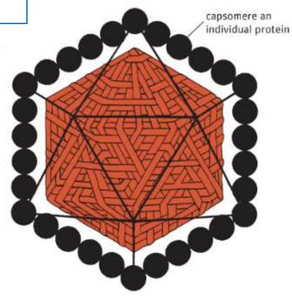
- ➢ Removing sialic acid from glycoproteins allows the virus to penetrate through mucus to reach a susceptible cell
- ➢ Prevent viral aggregation by removing sialic acid from viral glycoproteins (essential for the release of virus from infected cells)
- ➢ Enzyme active site on the head and its surrounding antigenic sites → anti-influenza drugs

❖ Virus symmetry

Helical



Icosahedral

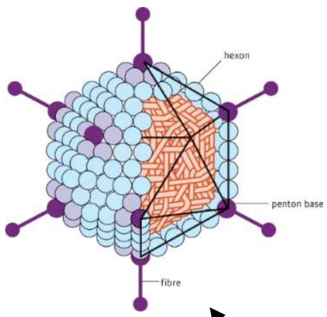


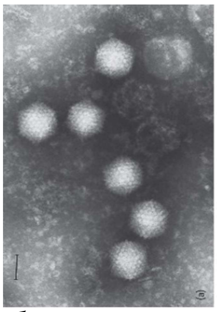
- Two basic patterns of nucleocapsids:

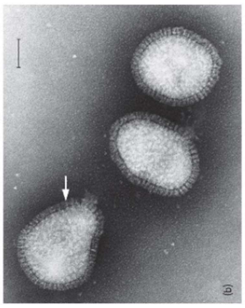
  Icosahedral: A protein shell of 20 equal triangular sides, rotational symmetry, like adenovirus. Some icosahedral viruses look to be spherical under EM.

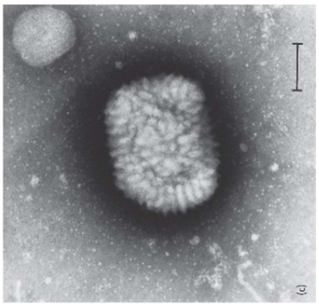
  Helical; **long and flexible helix** in the animal viruses, **rigid rod** in the plant viruses like tobacco mosaic virus.

  Many bacterial viruses like bacteriophages λ: both helical and icosahedral









Adenovirus (icosadedral) Influenza (helical) Poxvirus (complex)

Icosahedral symmetry, which permits **the greatest # of capsomeres** to be packed.

- 20 triangular facets/12 corners or apices/30 edges, spikes attached on the corners, each corner is intersection of five triangular faces.
- Small virions → each of triangular faces is constructed of 3 polypeptide subunits. (ex) Poliovirus: 3 polypeptides (protomers) → a capsomere.
- Large virions → multiples of 3 subunits in each capsomere (multiples of 60 subunits)
- **Except for the complex** poxviruses**, all DNA-containing animal viruses have these icosahedron-shaped capsids**, as do certain RNA viruses.
- DNA-containing herpesviruses have also icosahedral symmetry, but with an additional lipid envelope.

Helical symmetry, which has the advantage of a wide variety genome sizes by extension.

- Single-stranded RNA viruses such as (para)**influenza, rabies, coronaviruses.**

- The flexuous helical nucleocapsid is always contained inside a lipoprotein envelope, itself lined internally with a matrix protein.
- Lipid bilayer envelope is from host cell membrane, through which the virus matures by budding.
- Membrane or matrix (M) protein shell under the envelope → **rigid** as in the bullet-shaped rhabdoviruses or readily **distorted** as in influenza and measles viruses.
- M2 ion channel in influenza → H^+ flow-in → structural changes between four internal proteins surrounding the RNA genome → activate its infectiousness.

Complex symmetry (neither icosahedral nor helical) as in poxviruses → lipids in both the envelope and its outer membrane, its genome is linear dsDNA with closed ends.

Viral Genomes

- Double-stranded, single-stranded, linear, circular, continuous or segmented.
- Genome size minimization due to the difficulty of packaging.
- Extend genetic information by splicing and utilizing different reading frames.
- Human; ~30,000 genes/ E. coli; 4000 genes/ the largest human virus such as poxvirus; ~200 genes/the smallest human virus; 3 or 4 genes.
- All viruses, with an exception of retroviruses that are diploid, are haploid.
- In general, **RNA viruses have smaller genomes** and code for fewer proteins than DNA viruses, because **RNA genomes are** more **fragile** (**this feature limit their size**) than DNA.

DNA viruses

- All DNA viruses except parvoviruses are double stranded, but note that hepadnavirus DNA is partly ss when not replicating.
- Precisely regulated transcription with early and late switches which ensure that gene products involved in **DNA replication** are synthesized **early** in the cycle and viral **structural proteins much later**.

Adenovirus: linear dsDNA, 36 kbp, 30 genes.

Herpes and poxviruses: ~150 genes

- **No splicing in poxviruses that replicate in cytoplasm**, thus carry its unique enzymes.
- Herpes; replication and nucleocapsid assembly in the nucleus, and so the first budding through the nuclear membrane.

Hepatitis B virus: circular ds DNA genome with nicks (gaps), replication through RNA intermediate by a reverse transcriptase (RT).

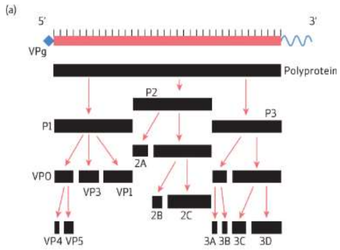
Parvoviruses; the smallest in terms of genome size and complexity.

- ssDNA → dsDNA → templates for transcription as well as ssDNA production.
- Genes are overlapped and their transcripts are spliced.

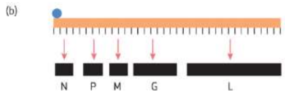
RNA viruses

- RNA viruses; divergence of RNA genomes (2% per year) → million times of eukaryotes.
- Viral RNA polymerase and reverse transcriptase → transcription error and lack of editing → RNA viruses are so heterogeneous.
- All RNA viruses are single stranded except reoviruses (rotaviruses; dsRNA)

◉ Positive-strand RNA viruses: viral RNA genome is directly used as mRNA.



Poliovirus
(positive-strand RNA)



Rabies virus
(negative-strand RNA)

Poliovirus:

- Polyadenylated at 3′ end, VPg at 5′ end.
- A single ORF → polyprotein → cleaved to produce viral capsid proteins (VP1-4), RNA polymerase, two viral proteases, and some minor viral proteins.
- 5' ntr (600 nucleotides) has a significant role in the initiation of viral protein synthesis, virulence, and encapsidation.
- 3' ntr is necessary for the synthesis of negative-strand RNA.

Coronaviruses:

- The largest of all human RNA viruses (30 kb)
- A nested set of 6 overlapping subgenomic RNAs with common 3′ ends, where only 5′ ends are translated.

◉ Negative-strand RNA virus (also, including ambisense group): more diverse, larger, more information than positive-stranded RNA viruses.

- Rabies; carry RNA transcriptase, which transcribes by a start-stop mechanism followed by reinitiation.
- Influenza: 8 ssRNA segments

Classification of viruses

As of 2014;

7 Order (-virales), *104 Family* (-*viridae*), 23 Subfamily (-virinae), 505 Genus, 3186 Species

Main criteria for classification

- Type of nucleic acid (genome, DNA or RNA, replication strategy)
- # of strands and physical construction (ss, ds, linear, circular, circular with breaks, segmented)
- Polarity (positive-stranded, negative-stranded)
- Symmetry of nucleocapsid
- Presence or absence of a lipid envelope

Further criteria;

Antigenic (genetic) similarity/virulence/cellular receptors/molecular structure (phylogenetic tree by nucleotide sequence comparison).

For example, measles virus is in the Order *Mononegavirales*, Family *Paramyxoviridae*, Subfamily *Paramyxovirinae*, Genus *Morbillivirus*, species Measles virus.

Nomenclature

Instead of formal names, viruses are usually called by the appropriate colloquial names.

- Type of disease; (ex) poxviruses and herpesviruses
- Acronyms; (ex) papovaviruses (papilloma-polyoma-vacuolating agent), picornaviruses (pico-RNA)
- Morphology; (ex) coronaviruses
- Places of isolation or outbreak; Coxsackie, Marburg, Hantavirus, West Nile, Ebola
- Discoverers; Epstein-Barr virus

❖ Families of viruses of medical importance

Family name	Etymology	Representative viruses	Approximate diameter of virion (nm)	Symmetry of nucleocapsid*	Genome (kb)
DNA viruses					
Parvoviridae	'Small'	Human parvovirus B19	20	I	5 ss
Papillomaviridae		Wart viruses	50	I	8 ds circular
Polyomaviridae		BK and MC viruses		I	5.3 ds circular
Adenoviridae	Adenoid	Adenoviruses	80	I	36 ds
Herpesviridae		Herpes simplex, varicella-zoster, CMV, Epstein–Barr, Kaposi	180	I	150 ds
Poxviridae	'Pox'	Vaccinia monkey pox, molluscum, variola (smallpox)	250	C	200 ds
Hepadnaviridae	Hepatitis DNA	Hepatitis B and D	40	I	3 ds circular (partial)
RNA viruses					
Astroviridae	'Star'	Astroviruses	30–60	I	8 ss
Picornaviridae	'Small' RNA	Polioviruses, hepatitis A, common cold	25	I	8 ss
Flaviviridae	'Yellow'	Yellow fever virus, dengue, TBE, hepatitis C, West Nile	30	I	10 ss
Togaviridae		Rubella virus, Ross River, Chikungunya	80	I	12 ss
Coronaviridae	'Crown'	MERS CoV, SARS CoV	100	H	30 ss
Bunyaviridae		California encephalitis, Crimean–Congo, Hantaan, Sin Nombre	100	H	16 ss
Hepeviridae		Hepatitis E	25	I	8 ss
Orthomyxoviridae		Influenza A, B, and C	100	H	13 ss
Paramyxoviridae		Measles, mumps, Hendra, Nipah, meta pneumovirus	150	H	15 ss
Rhabdoviridae	'Bullet-shaped'	Rabies	150	H	15 ss
Arenaviridae		Lassa fever (Old World); Machupo, Pichinde (New World)	100	H	12 ss
Retroviridae	RT enzyme	HIV-1, HTLV-1	100	I	10 ss
Reoviridae		Rotaviruses	70	I	20 ds
Filoviridae	'Thread'	Marburg, Ebola	Variable	H	19 ss
Caliciviridae		Norovirus	35	I	8 ss

BK; patient name, MC; Merkel cell, Kaposi: dermatologist's name.

◉ Range of diseases by viruses (**host ranges,** range of syndromes, **pathogenesis**/disease causing mechanisms, studying **the clinical picture as a whole** with the aid of virology lab for diagnosis).

➢ Tissue tropism: Affinity for various tissues within a given host (nerve, liver, respiratory tissues).

Acute infections of CNS

Predominant syndrome	Viruses	Predominant neurological lesions
Meningitis	Enteroviruses, especially ECHO, Coxsackie A and B, enteroviruses 70 and 71, poliovirus	Inflammation of the meninges, with or without some degree of encephalitis
	Mumps, lymphocytic choriomeningitis, louping-ill, Epstein–Barr virus, HSV-2, VZV	
Poliomyelitis	Polioviruses; occasionally other enteroviruses	Meningitis, lysis of lower motor neurons
Meningoencephalitis	HSV-1, arboviruses	Necrosis of neurons in grey matter of brain
Encephalitis	Rabies	Varying degrees of neuronal necrosis; perivascular and focal inflammation
AIDS dementia complex (ADC)	HIV-1	Meningitis cortical atrophy, focal necrosis; vacuolation, reactive astrocytosis and microgliosis in subcortical areas; demyelinating peripheral neuropathy
Tropical spastic paraparesis	HTLV-1	Upper motor neuron lesions

ECHO; enteric cytopathic human orphan

Viruses causing common respiratory infections

Virus family	Diseases
Rhinoviruses	Common cold
Picornaviridae *Coronaviridae*	Common cold
Herpesviridae	Pharyngitis
Myxoviridae	Influenza
Picornaviridae	
Adenoviridae	Pharyngitis
Myxoviridae	Bronchitis
Paramyxoviridae	Bronchitis
	Croup
	Influenza-like illness (ILI)
Myxoviridae *Paramyxoviridae*	Broncho pneumonia
Myxoviridae *Coronaviridae* *Paramyxoviridae*	Pneumonia

Viruses causing hepatitis

Virus family	Main route of transmission
Picornaviridae	Enteric HAV
Hepevirus	Enteric HEV
Hepadnaviruses	Parenteral HBV
Deltavirus	Parenteral HDV
Flaviviridae	Parenteral HCV
Flavi-like viruses	Enteric GBV

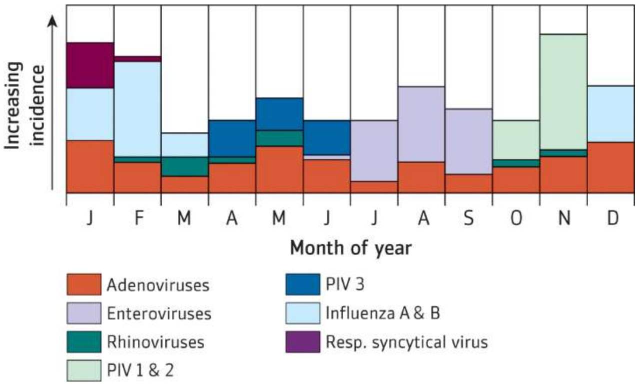
GB is the initial of surgeon's name who was infected with this virus.

Viruses causing sexually transmitted diseases

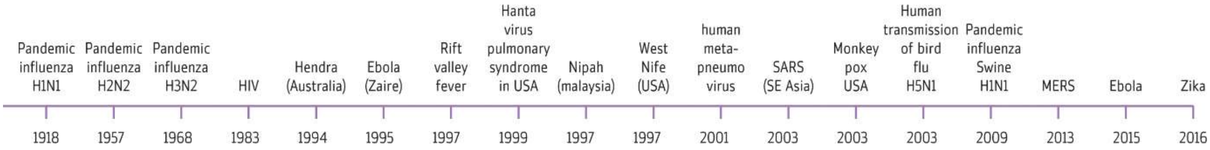
Virus family	Main clinical features
(a) Localized infections	
Herpesviridae	HSV-2 more severe than HSV-1. Painful, itchy vesicular lesions on genitalia, anal, perineal areas, possibly mouth. Urethritis, proctitis, cervicitis
Papillomaviridae	Warts, anogenital mucosa, cervix, possibly larynx
Adenoviridae	Types 19 and 37 cause ulcers on external genitalia, urethritis
Poxviridae	Characteristic lesions on genitalia
(b) Generalized infections	
Picornaviridae	Hepatitis A may be transmitted by anal sex
Hepeviridae	Risk difficult to quantify, probably not high
Hepadnaviridae	Very high risk of acquisition from HBsAg-positive carriers if intercourse is unprotected
Flaviviridae	Risk difficult to quantify probably not high, recorded with Zika
Retroviridae	Male to female transmission of HIV more efficient than female to male. Spread favoured by presence of genital lesions due to, e.g. herpes, syphilis, chancroid

syphilis and chancroid; bacterial infections

➢ Seasonal incidence



➢ New or re-emergence



Recently emerged viruses

Virus family	Disease in humans	Location	Reservoir
Poxviridae	Pox lesions	USA	Gambian giant rats and prairie dogs
Paramyxoviridae	Respiratory disease in Nipah	Malaysia	Bats
Coronaviridae	Respiratory disease SARS	South-east Asia	Civet cat or bat
Retroviridae	AIDS	Africa	Chimpanzee
Flavividae	Mild rash hvt teratogenic	S. America	Mosquitos
Togaviridae West Nile	Encephalitis	USA and Europe	Wild birds
Paramyxoviridae	Respiratory disease Hendra	Australia	Horses
Myxoviridae	Respiratory disease of influenza A H5N1	South-east Asia	Migrating ducks and geese, domestic ducks and chickens
Filoviridae	Ebola haemorrhagic fever	West Africa	Bats
Coronaviridae	Respiratory disease MERS	Saudi Arabia	Camels

Factors influencing the emergence of viral infections

Factor	Example
Breakdown of species barriers	Probable transfer of HIV from a simian reservoir to humans. Spread of influenza viruses from animals or birds to humans, and most recently H1N1 virus from pigs to humans. Transfer of BSE to humans.
Genetic	RNA viruses, particularly HIV and influenza, have extremely high mutation rates, which favour the spread of strains resistant to immune barriers or chemotherapy.
Host factors	
Ecology and modern agriculture	New farming practices encourage human contact with rodents carrying Hantaan and other exotic RNA viruses.
Medical or surgical interventions	Immunosuppressive drugs have encouraged latent herpesviruses to emerge, such as CMV. Brain surgery can spread CJD.
Human behaviour	Changes in sexual habits have enhanced the spread of sexually transmitted diseases.
Intermediate hosts	Hantaviruses, carried harmlessly in rodents, infect humans when rodent populations expand because of increased availability of food. Recently, fruit-eating bats have been recognized as a source of novel viruses, such as Hendra and Nipah, and Ebola. Migrating birds carry potential pandemic influenza A viruses such as H5N1 (bird flu).
Population increase	Increasing population densities and urban poverty encourage the spread of water- and airborne viruses.
Global warming	Mosquitos carrying Chikungunya, formerly an African arbovirus, have moved northwards to Italy. Similarly, the veterinary virus Blue Tongue has moved out of Africa to Europe and the UK and Zika virus from Africa to S. America.
Defects in public health infrastructure	Poor control of mosquitos because of worries about the insecticide DDT or poor public health structure, or both, have allowed the re-emergence of dengue, West Nile and Zika, and other classic insect-borne viruses.

BSE; bovine spongiform encephalopathy (mad cow disease), by prion but not virus

Rashes in the skin

Genital herpes (Herpes simplex virus)

Lip herpes (Herpes simplex virus)

Small pox

Chicken pox (varicella-zoster virus)

Measles