BIOCHEMISTRY

Molecular Virology
March 1st – 10th 2022

Dr. MULINGE
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Course Outline

WEEK	TOPIC	LECTURER (S)
WEEK 20 **21-25/02/2022**	**Gene regulation: Structural and transcriptional regulation of gene expression in prokaryotes and eukaryotes repression and induction of transcription of prokaryotic gene, bacterial operon concept, negative vs positive control, other regulatory mechanisms.**	**Dr. Mulinge**
WEEK 21 28-04/03/2022	DNA repair and DNA recombination. Disease/syndromes associated with DNA repair	,,
WEEK 22 07 - 11/03/2022	Molecular virology: Classification and properties of viruses, replication and life cycle of viruses. Interferons, Oncogenes and oncogenic viruses. Viroids and prions. Application –HIV	,,
WEEK23 14 - 18/03/2022	Molecular virology: Classification and properties of viruses, replication and life cycle of viruses. Interferons, Oncogenes and oncogenic viruses. Viroids and prions. Application –HIV	,,
WEEK 24 21 - 25/03/2022	Bacterial Biochemistry: Bacterial cell structure: Cell envelope; Cell cytoplasm; Cellwall and its biosynthesis. Bacterial toxins, virulence and pathogenesis.	,,
WEEK 25 28 - 01/04/2022	Bacterial chemotherapy: Mechanisms of action of antibiotics Bacterial resistance to antimicrobial chemotherapy.	,,
WEEK 26 04 - 08/04/2022	Biochemical endocrinology: Endocrine, paracrine and autocrine mode of secretions. Classification of hormones. Mechanism of hormone action: Signal and signal transduction, Receptors: intracellular and membrane bound receptors. Second messenger role in signal transduction: cAMP, cGMP, lipids, Calcium ions.	,,
WEEK 27 11 - 15/04/2022	Biochemical endocrinology: Synthesis, storage, release, transport, mode of action and degradation of peptide, steroid and prostaglandins derived hormones	,,
12/04/2022	MID 2nd SEMESTER CAT	Dr Mulinge

What are viruses

- ✓ Obligate intracellular parasites that deliver their genome into host cells for replication.
- ✓ Once introduced into host cells, their genome is transcribed and translated by host synthetic machinery.
- ✓ Viruses are not cells, but rather sub-microscopic particles that require an electron microscope to be seen.
- ✓ Viruses infect all forms of life: bacteria (bacteriophage), plants, fungi, insects, fish, reptiles, bird, mammals.

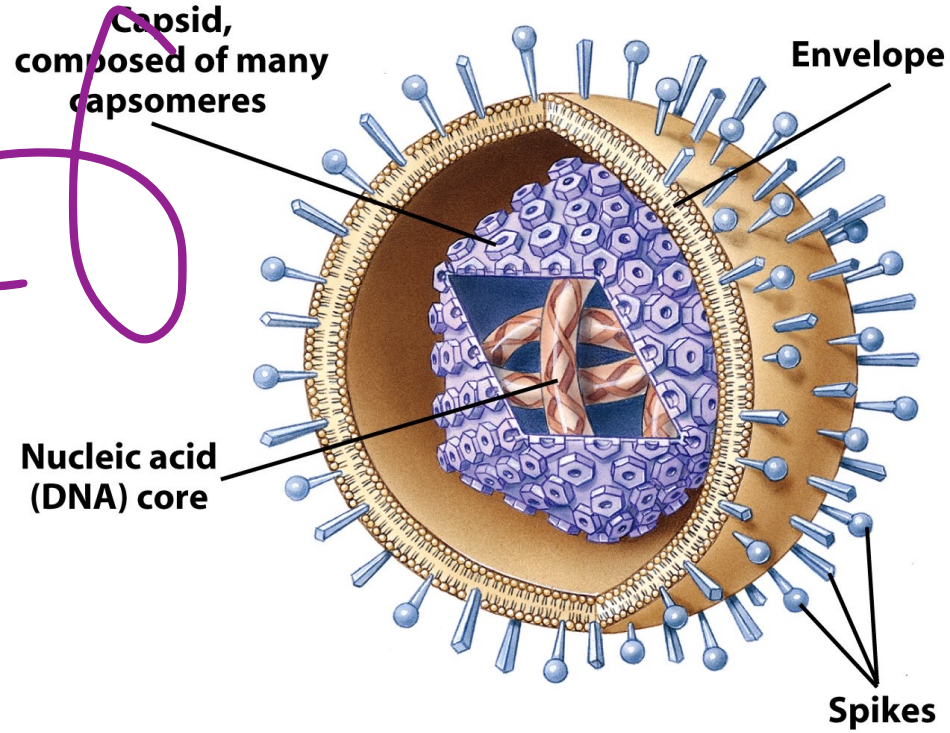
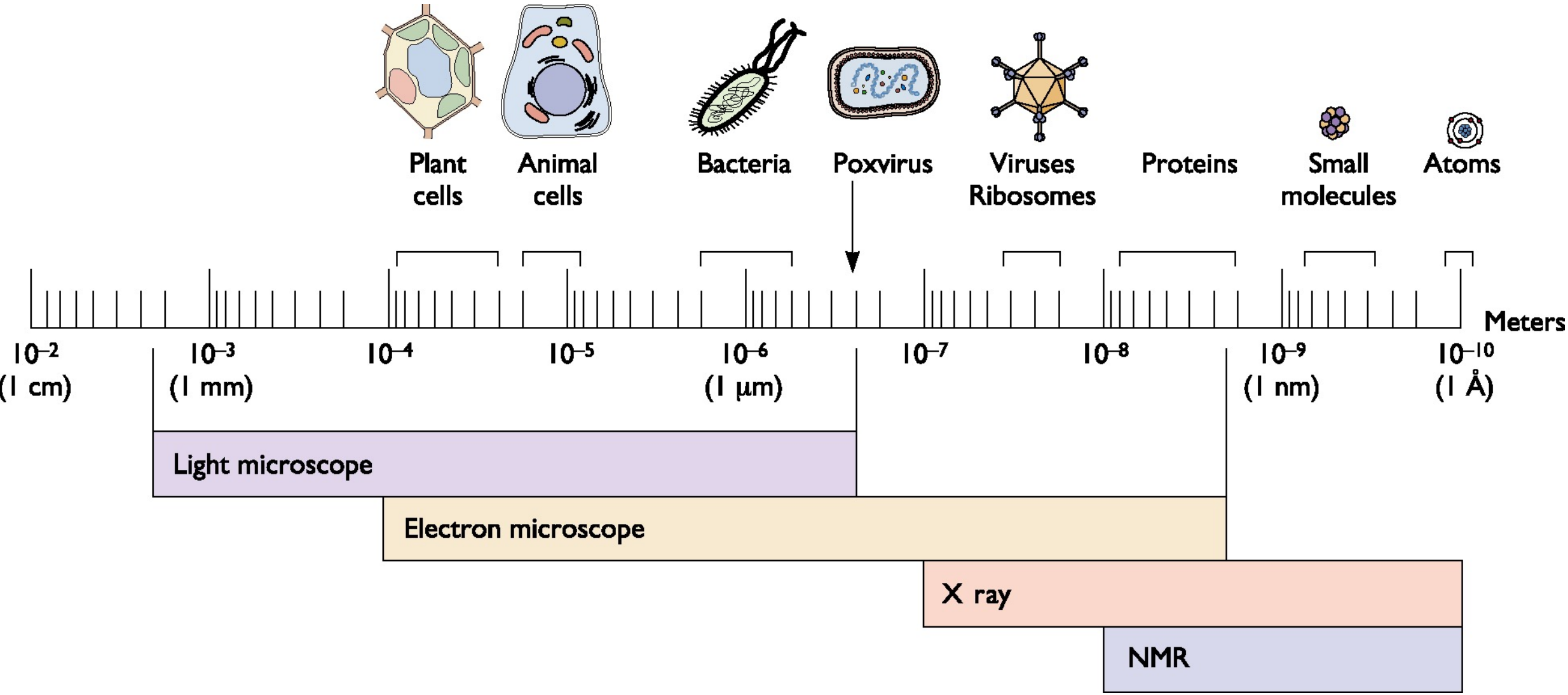


Figure 10-1 Microbiology, 6/e

Introduction



Emerging Viruses

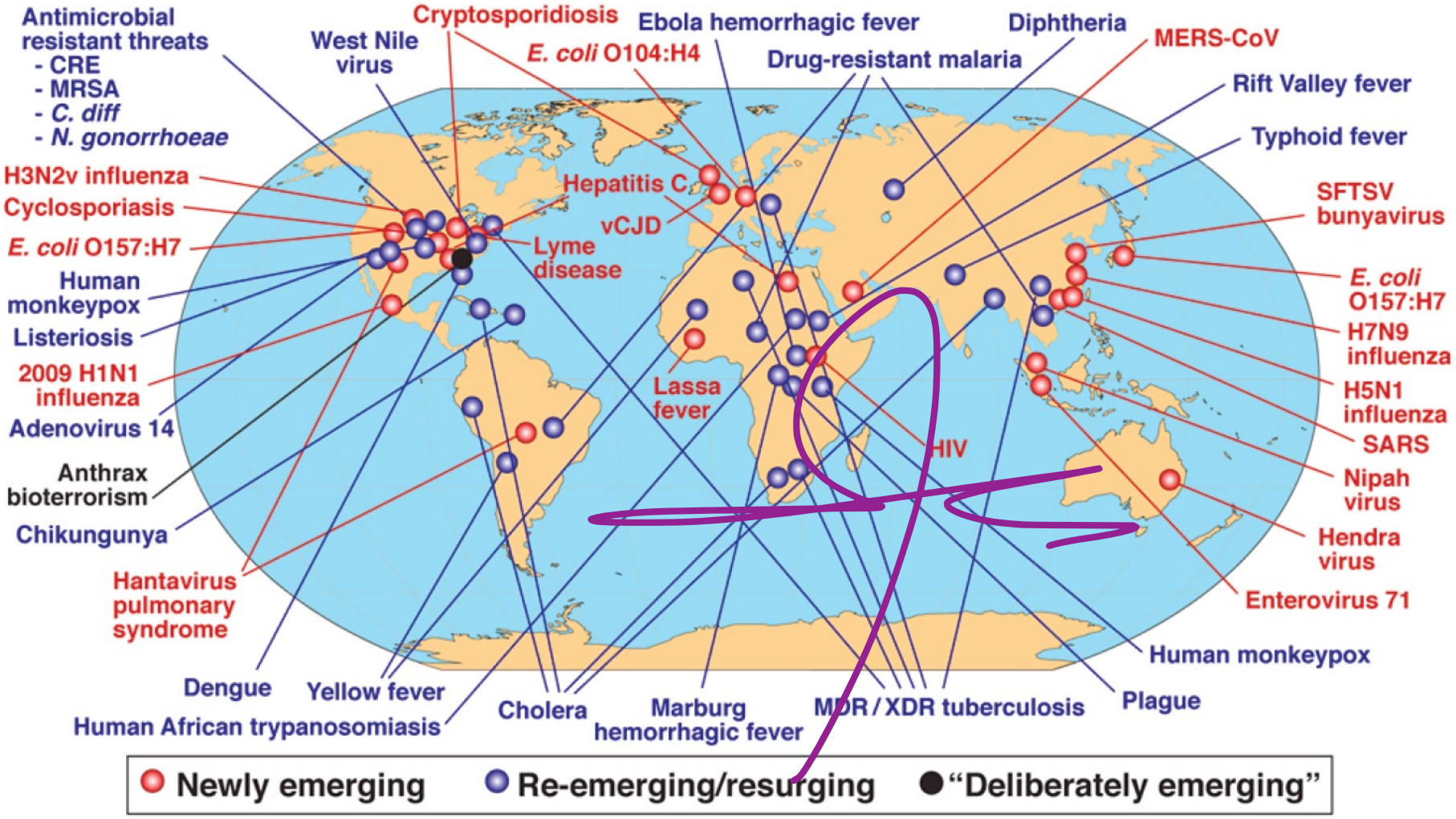
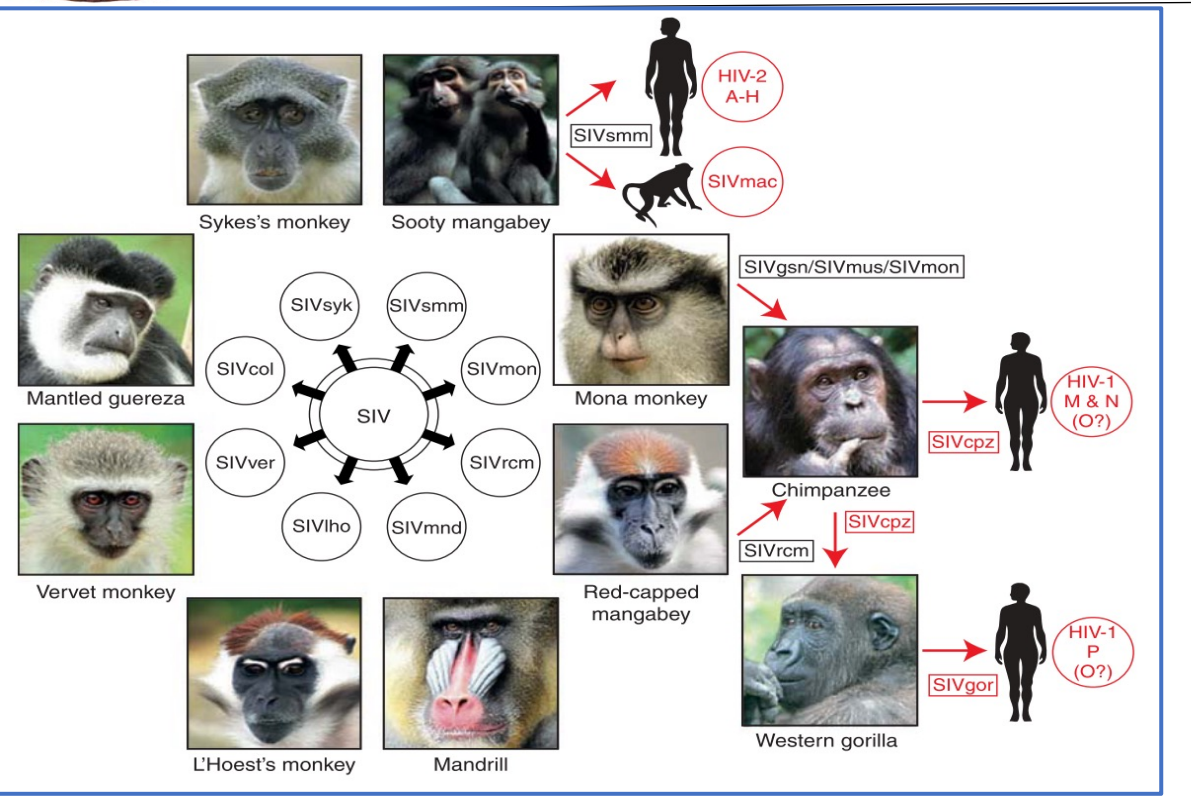
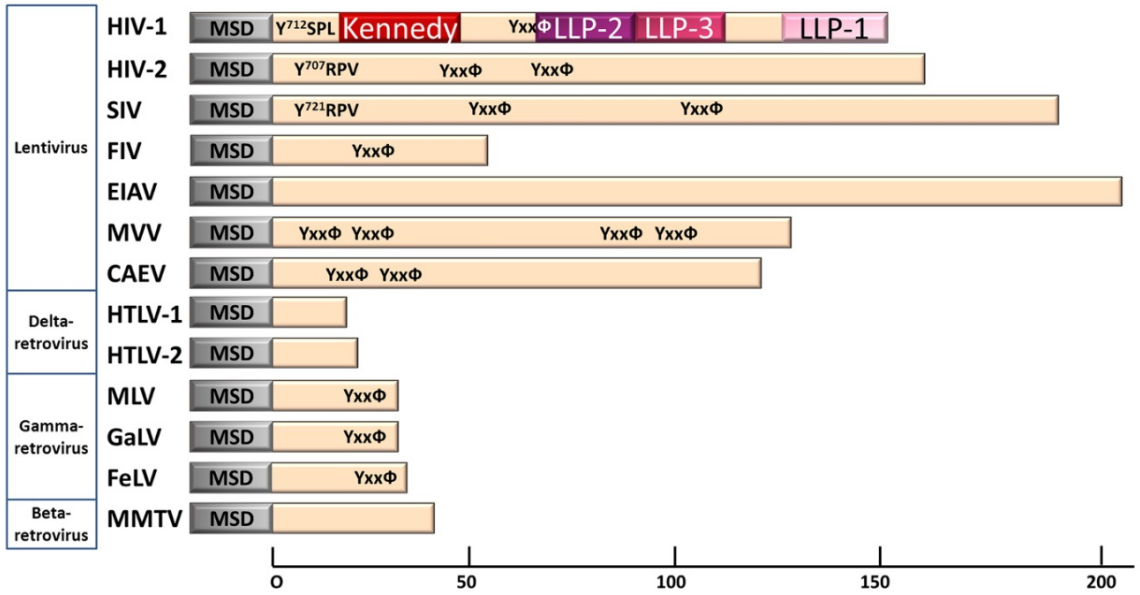


FIGURE WO-1 Global examples of emerging and reemerging infectious diseases.
SOURCE: Morens et al., 2004.

HIV – controversial origins





PLOS | ONE

RESEARCH ARTICLE

The Envelope Cytoplasmic Tail of HIV-1 Subtype C Contributes to Poor Replication Capacity through Low Viral Infectivity and Cell-to-Cell Transmission

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CrossMark click for updates

Santos da Silva *et al. Retrovirology* 2013, **10**:54
http://www.retrovirology.com/content/10/1/54

RETROVIROLOGY

REVIEW Open Access

The frantic play of the concealed HIV envelope cytoplasmic tail

Eveline Santos da Silva, Martin Mulinge and Danielle Perez Bercoff*

Quantifying viral pandemics

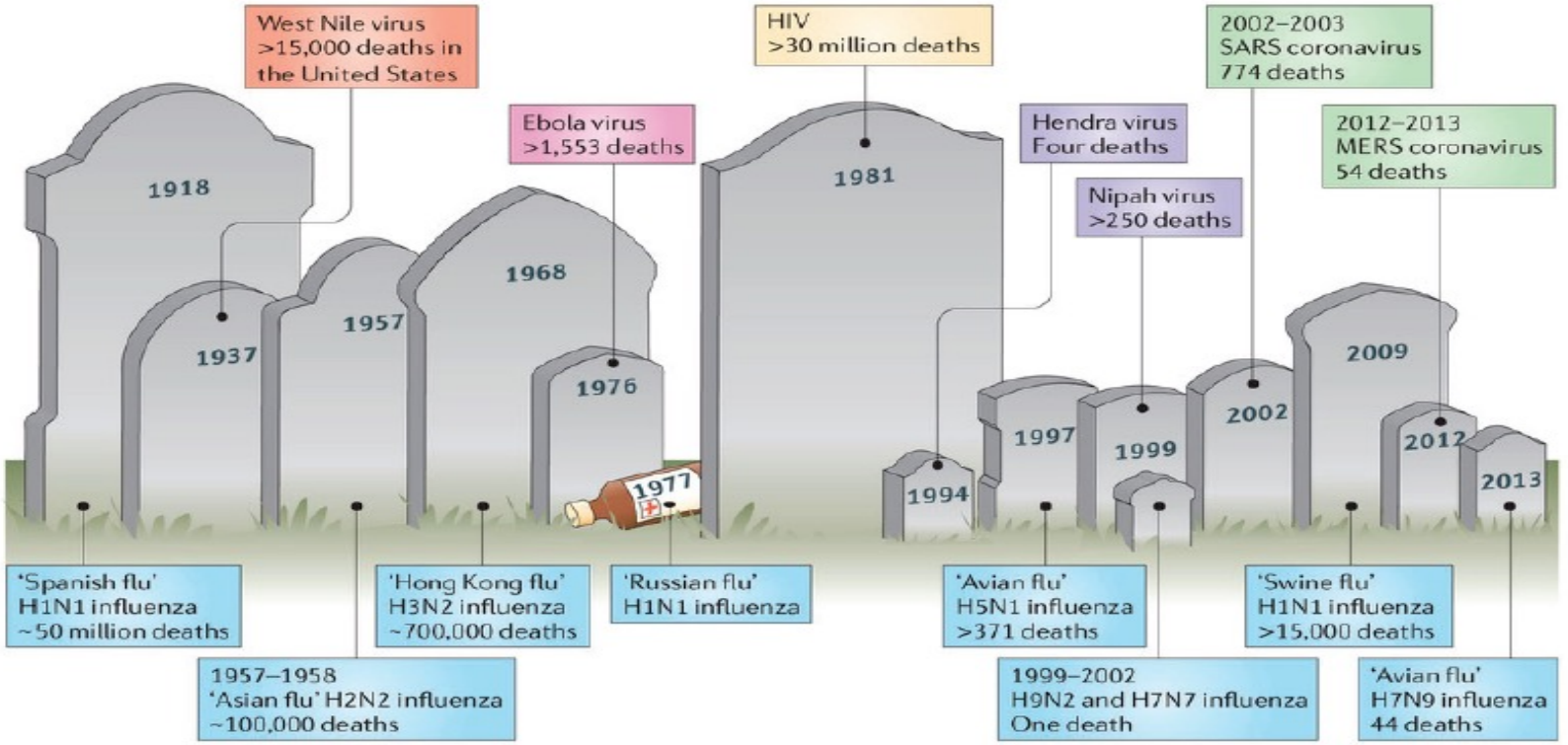

FIGURE WO-2 Emergence of zoonoses. Over the past century, humanity has witnessed the emergence of numerous zoonotic infections that have resulted in varying numbers of human fatalities. Influenza viruses that originate from birds account for an important proportion of these deaths, and recently many new zoonotic viruses that originate in bats, such as Hendra virus, Nipah virus, and the SARS coronavirus, have caused outbreaks with high mortality rates.
NOTE: As of June 2, 2014, the Centers for Disease Control and Prevention (CDC) reports that there were 39,557 cases of West Nile virus in the United States resulting in 1,668 deaths between 1999 and 2013. Source: http://www.cdc.gov/westnile/resources/pdfs/cummulative/99_2013_CasesAndDeathsClinicalPresentationHumanCases.pdf (accessed February 19, 2015).
SOURCE: Bean et al., 2013.

Then came – SARS-CoV-2

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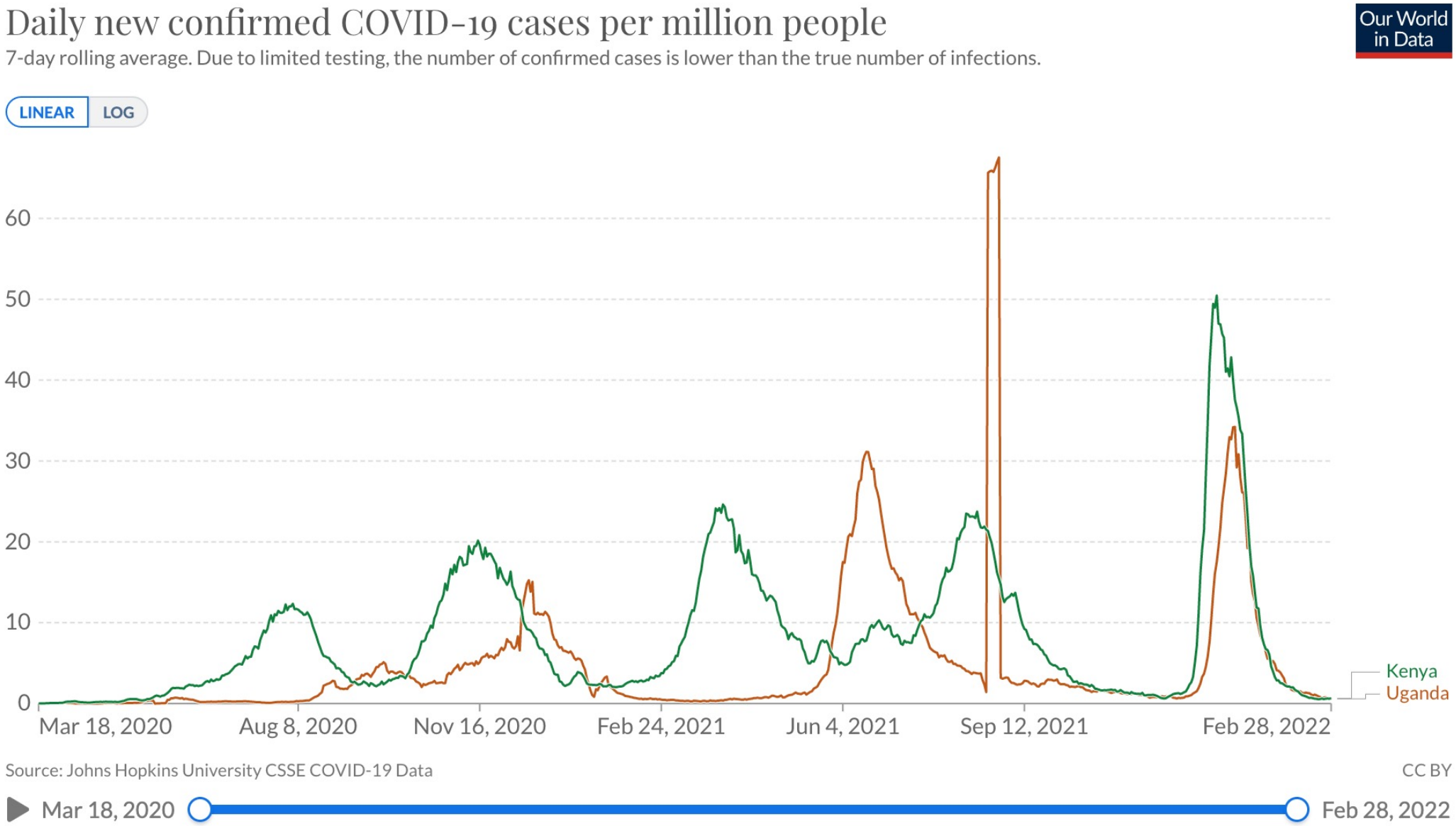

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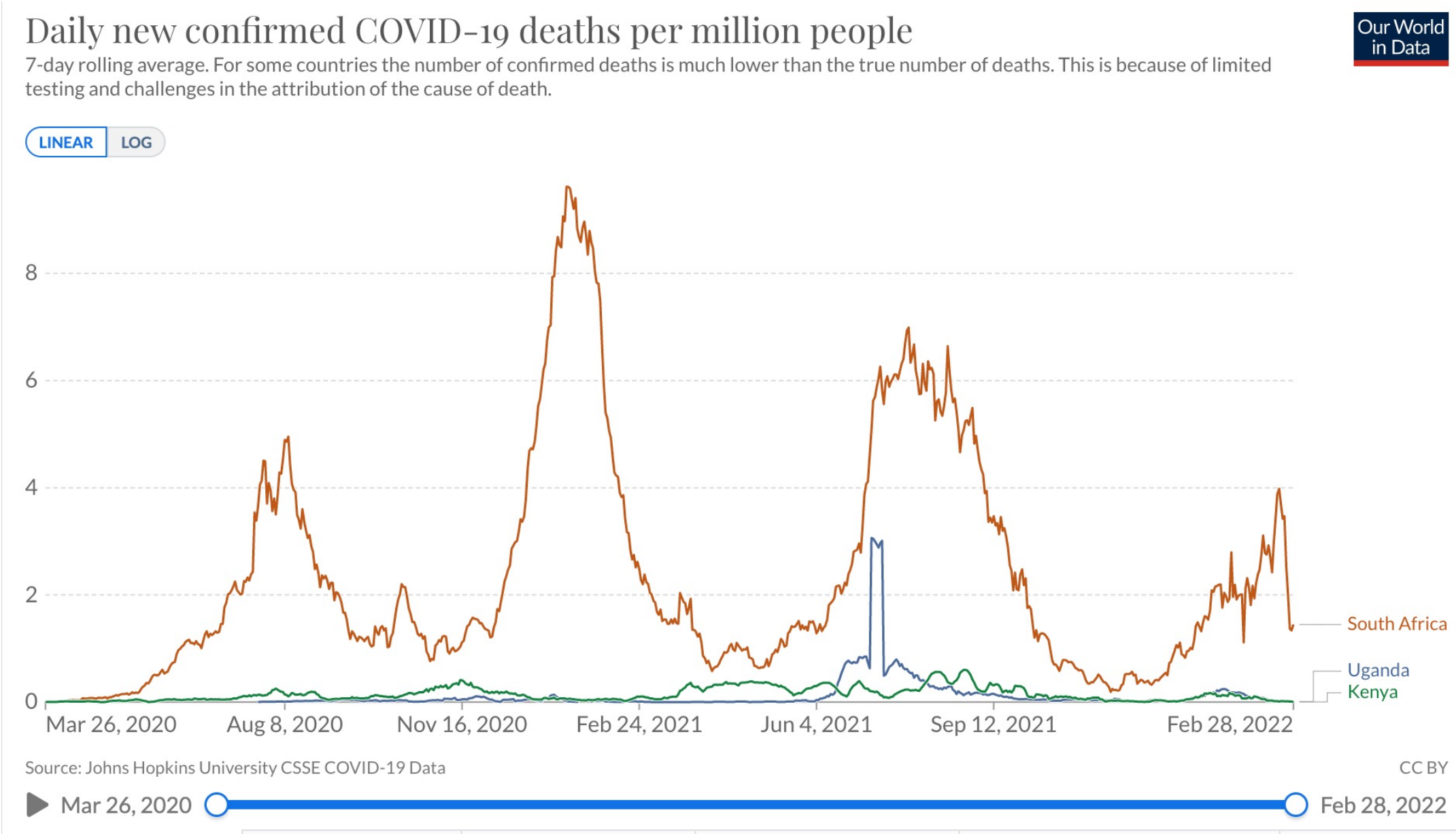

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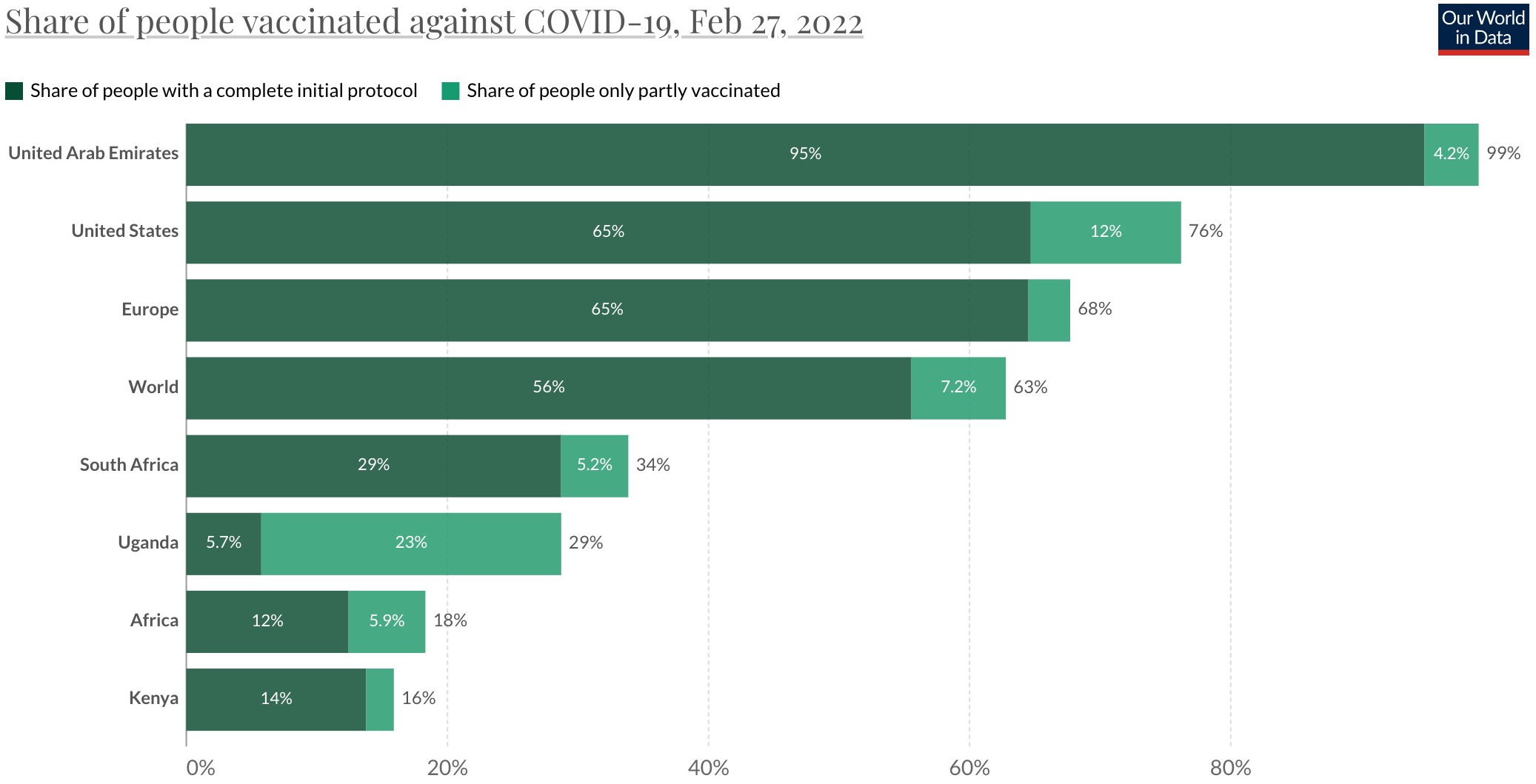
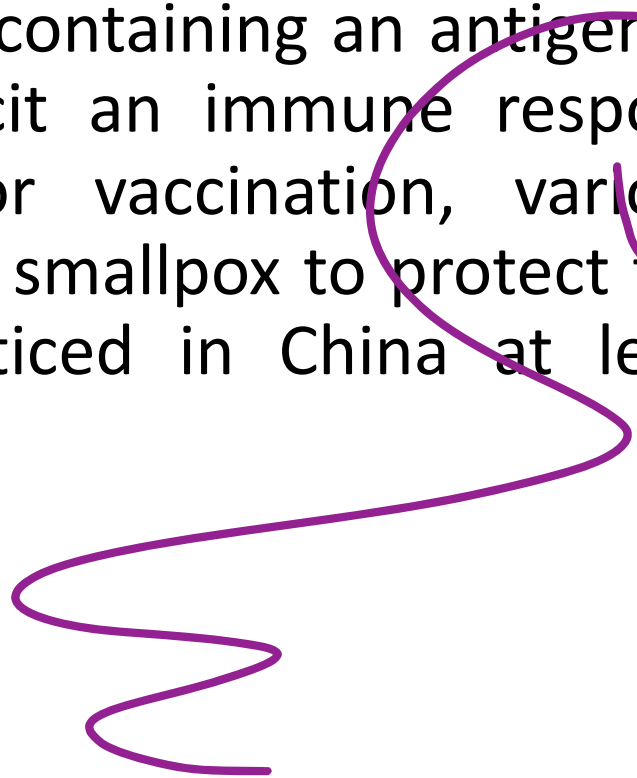


History of Virology

- **1796**: **Edward Jenner** (1749-1823) used **cowpox to vaccinate against smallpox**. In 1774, a farmer named Benjamin Jesty had vaccinated his wife and two sons with cowpox taken from the udder of an infected cow and had written about his experience (see 1979).
- Jenner was the first person to deliberately vaccinate against any infectious disease, i.e. to use a preparation containing an antigenic molecule or mixture of such molecules designed to elicit an immune response. Although Jenner is commonly given the credit for vaccination, variolation, the practice of deliberately infecting people with smallpox to protect them from the worst type of the disease, had been practiced in China at least two thousand years previously.



History of Virology

- **1885**: **Louis Pasteur** (1822-1895) experimented with **rabies vaccination**, using the term "**virus**" (Latin, poison) to describe the agent. Although Pasteur did not discriminate between viruses and other infectious agents, he originated the terms "virus" and "vaccination" (in honour of Jenner) and developed the scientific basis for Jenner's experimental approach to vaccination.

History of Virology

- **1892**: Dmiti Iwanowski (1864-1920) described the first **"filterable" infectious agent - tobacco mosaic virus (TMV)** - smaller than any known bacteria. Iwanowski was the first person to discriminate between viruses and other infectious agents, although he was not fully aware of the significance of this finding.

History of Virology

- 1898: **Martinus Beijerinick (1851-1931)** extended Iwanowski's work with TMV and formed the first clear concept of the virus "contagium vivum fluidum" - soluble living germ. Beijerinick confirmed and extended Iwanowski's work and was the person who developed the concept of the **virus as a distinct entity**.

- Freidrich Loeffler (1852-1915) and Paul Frosch (1860-1928) demonstrated that **foot and mouth disease** is caused by such "filterable" agents. Loeffler and Frosch were the first to prove that **viruses could infect animals as well as plants**.

History of Virology

- *1900*: **Walter Reed** (1851-1902) demonstrated that **yellow fever is spread by mosquitoes**. Although Reed did not dwell on the nature of the yellow fever agent, he and his coworkers were the first to show that **viruses could be spread by insect vectors** such as mosquitoes.

History of Virology

- **1908: Karl Landsteiner** (1868-1943) and **Erwin Popper** proved that **poliomyelitis** was **caused by a virus**. Landsteiner and Popper were the first to prove that viruses could infect humans as well as animals.

History of Virology

- **1911**: Francis Peyton Rous (1879-1970) demonstrated that a virus (**Rous sarcoma virus**) can **cause cancer in chickens** (**Nobel Prize, 1966**) (see 1981). Rous was the first person to show that a virus could cause cancer.

History of Virology

- **1915**: **Frederick Twort** (1877-1950) discovered **viruses infecting bacteria**.

- **1917**: Felix d'Herelle (1873-1949) independently discovered viruses of bacteria and coins the term **bacteriophage**.

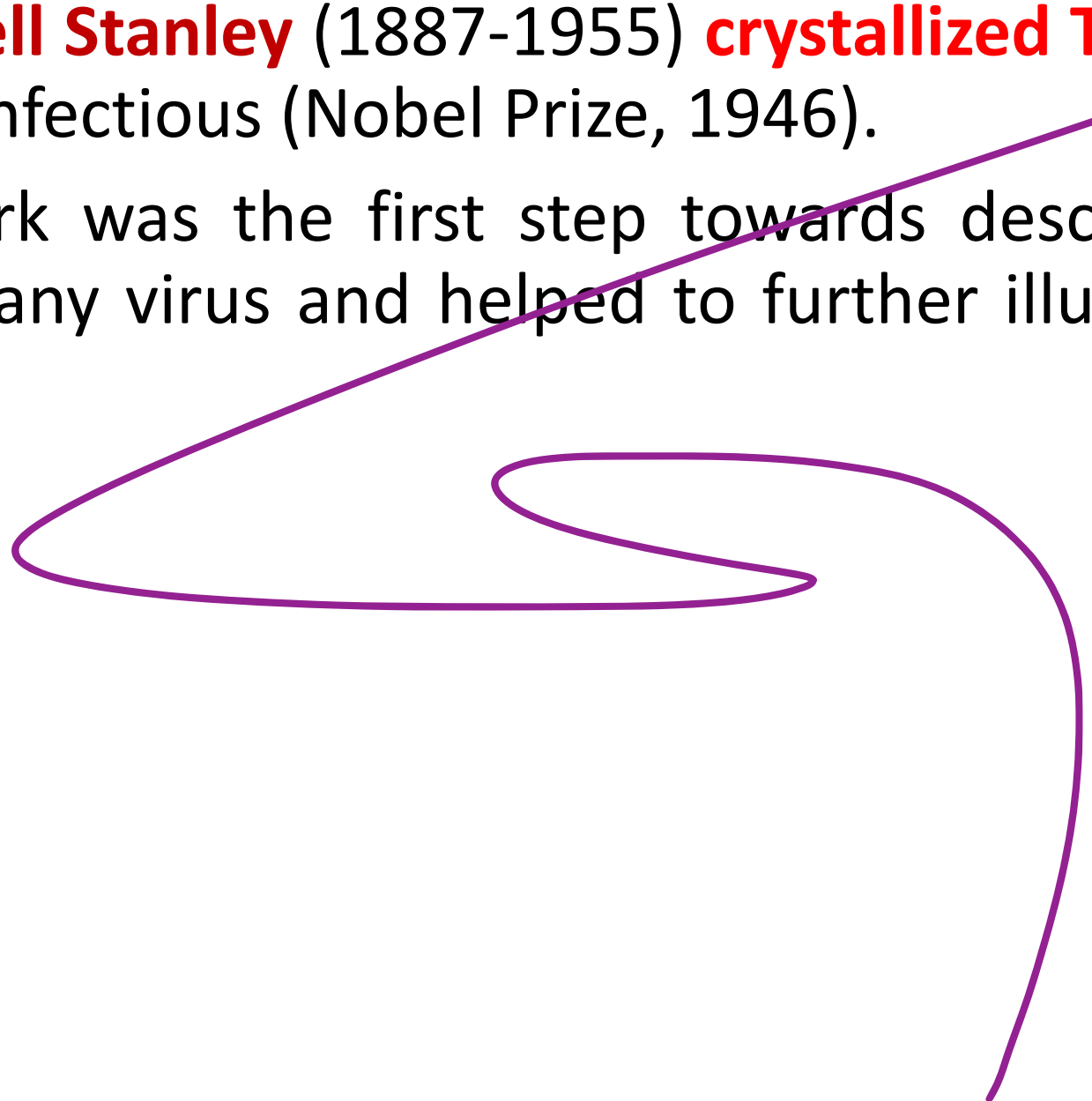
- The discovery of bacteriophages provided an invaluable opportunity to study virus replication at a time prior to the development of tissue culture when the only way to study viruses was by infecting whole organisms.

History of Virology

- **1933**: Isolation of **human influenza virus**
- Pandemics 1918 (Spanish flu, H1N1), 1957 (Asian, H2N2), 1968 (Hong Kong, H1N2).
- Influenza A virus infects chicken embryos
    - Production of virus
    - Production of influenza vaccines

History of Virology

- **1935**: **Wendell Stanley** (1887-1955) **crystallized TMV** and showed that it remained infectious (Nobel Prize, 1946).
- Stanley's work was the first step towards describing the **molecular structure** of any virus and helped to further illuminate the nature of viruses.



History of Virology

- **1938: Max Theiler** (1899-1972) developed a **live attenuated vaccine against yellow fever** (Nobel Prize, 1951).
- **** Theiler's vaccine was so safe and effective that it is still **in use today!** This work saved millions of lives and set the model for the production of many subsequent vaccines.

History of Virology

- **1940**: Helmuth Ruska (1908-1973) used an **electron microscope** to take the first pictures of virus particles.
- Along with other physical studies of viruses, direct visualization of virions was an important advance in **understanding virus structure**.

History of Virology

- **1949**: John Enders (1897-1985), Thomas Weller (1915-) and Frederick Robbins (1916-) were able to **grow poliovirus *in vitro*** using human tissue culture (Nobel Prize, 1954).
- This development led to the isolation of many new viruses in tissue culture.

History of Virology

- **1952: Renato Dulbecco** (1914-) showed that **animal viruses can form plaques** in a similar way to bacteriophages (Nobel Prize, 1975). Dulbecco's work allowed rapid quantitation of animal viruses using assays which had only previously been possible with bacteriophages.

- Alfred Hershey (1908-1997) and Martha Chase showed that **DNA was the genetic material of a bacteriophage.** Although the initial evidence for DNA as the molecular basis of genetic inheritance was discovered using a bacteriophage, this principle of course applies to all cellular organisms (though **not all viruses!**).

History of Virology

- **1957**: Alick Isaacs and Jean Lindemann discovered **interferon**. Although the initial hopes for interferons as broad spectrum antiviral agents equivalent to antibiotics have *faded*, interferons were the first cytokines to be studied in detail.

History of Virology

- **1957**: Carleton Gajdusek proposes that a "slow virus" is responsible for the **prion disease kuru** (Nobel Prize, 1976).
- Gajdusek showed that the course of the kuru is similar to that of scrapie, that kuru can be transmitted to chimpanzees and that the agent responsible is an atypical virus.

History of Virology

- **1963**: **Baruch Blumberg** discovered **hepatitis B virus (HBV)** (Nobel Prize, 1976).
- Blumberg went on to develop the first **vaccine** against the HBV, considered by some to be the first vaccine against cancer because of the strong association of hepatitis B with **liver cancer.**

History of Virology

- **1967**: Theodor Diener discovered **viroids**, agents of plant disease which have no protein capsid.
- Viroids are infectious agent consisting of a low molecular weight **RNA** that contains no protein capsid responsible for many **plant diseases**.

History of Virology

- **1970**: Howard Temin (1934-1994) and David Baltimore independently discovered **reverse transcriptase in retroviruses** (Nobel Prize, 1975).
- The discovery of reverse transcription established a pathway for genetic information flow from **RNA to DNA**, refuting the so-call *"central dogma"* of molecular biology.

History of Virology

- **1972**: Paul Berg created the first **recombinant DNA molecules**, circular SV40 DNA genomes containing λ phage genes and the galactose operon of *E. coli* (Nobel prize, 1980). This was the beginning of recombinant DNA technology.

History of Virology

- **1973**: Peter Doherty and Rolf Zinkernagl demonstrate the basis of **antigenic recognition** by the **cellular immune system** (Nobel Prize, 1996).
- The demonstration that **lymphocytes recognize** both **virus antigens and major histocompatibility antigens** in order to kill virus-infected cells established the specificity of the cellular immune system.

History of Virology

- **1976**: J. Michael Bishop and Harold Varmus determined that the **oncogene** from **Rous sarcoma virus** can also be **found in cells of normal animals, including humans** (Nobel Prize, 1989).
- Proto-oncogenes are essential for normal development but can become cancer genes when cellular regulators are damaged or modified, e.g. by virus transduction.

History of Virology

- **1979**: **Smallpox** was officially declared to be **eradicated** by the World Health Organization (WHO).
- The last naturally occurring case of smallpox was seen in Somalia in 1977. This was the first microbial disease ever to be completely eliminated.

History of Virology

- **1982**: Stanley Prusiner demonstrates that **prions are infectious proteins.** Prions cause scrapie, a fatal neurodegenerative disease of sheep (Nobel Prize, 1997).
- This was the most significant advance in understanding of what were previously called **"slow virus" diseases** and are now known as transmissible spongiform encepthalopathies (TSEs).

History of Virology

- **1983**: Luc Montaigner and Robert Gallo announced the discovery of **human immunodeficiency virus (HIV)**, the causative agent of **AIDS**. The ***2008 Nobel Prize in Medicine*** was awarded to Montagnier and Françoise Barré-Sinoussi for the discovery of HIV.

History of Virology

- **1989**: **Hepatitis C virus (HCV)**, the source of most cases of nonA, nonB hepatitis, was definitively identified.
- This was the first infectious agent to be identified by **molecular cloning** of the genome rather than by more traditional techniques.

History of Virology

- **2019**: **SARS-CoV-2**, the causative agent for **COVID-19** disease identified.
- The advances in biotechnology occasioned developed vaccines within a year of discovery.

Virus Classification

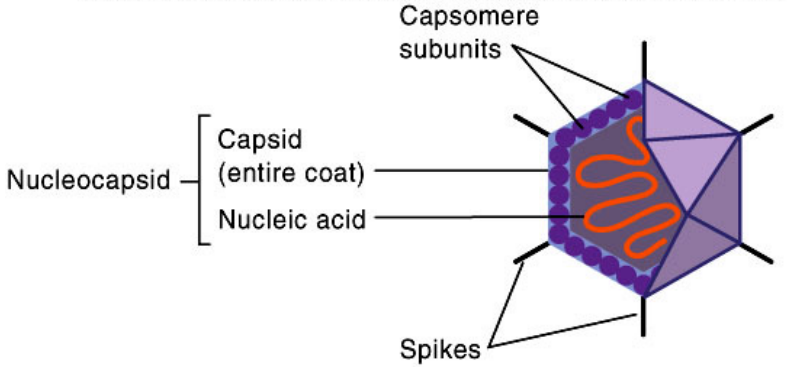
- ✓ Virus are classified according to:
- ✓ Morphology – size, shape, symmetry, +/- peplomers, +/- envelope
- ✓ Genome – DNA/RNA, single stranded/double stranded, Sense or antisense, size and +/- segments
- ✓ Physiochemical properties – molecular mass, density, stability, susceptibility
- ✓ *** International Committee on Taxonomy of Viruses (ICTV)

Virus components

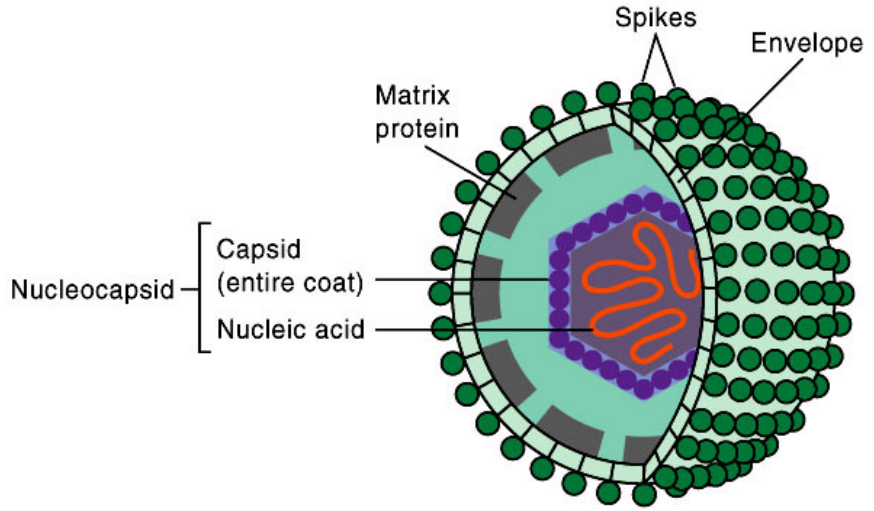
- ✓ A fully assembled infectious virus consists of at least two components: capsid (protective protein coat) and genome (DNA or RNA, single stranded or double stranded, sense or antisense).

- ✓ Viruses may have an envelope, the outermost layer that protects their genetic material when they travel between host cells as part of their life-cycle. The envelopes are typically derived from portions of the host cell membranes (phospholipids and proteins), but also include some viral glycoproteins.

- ✓ Viruses have peplomers which are glycoprotein spikes on the viral envelope, coded by the viral genome and determine viral host range.



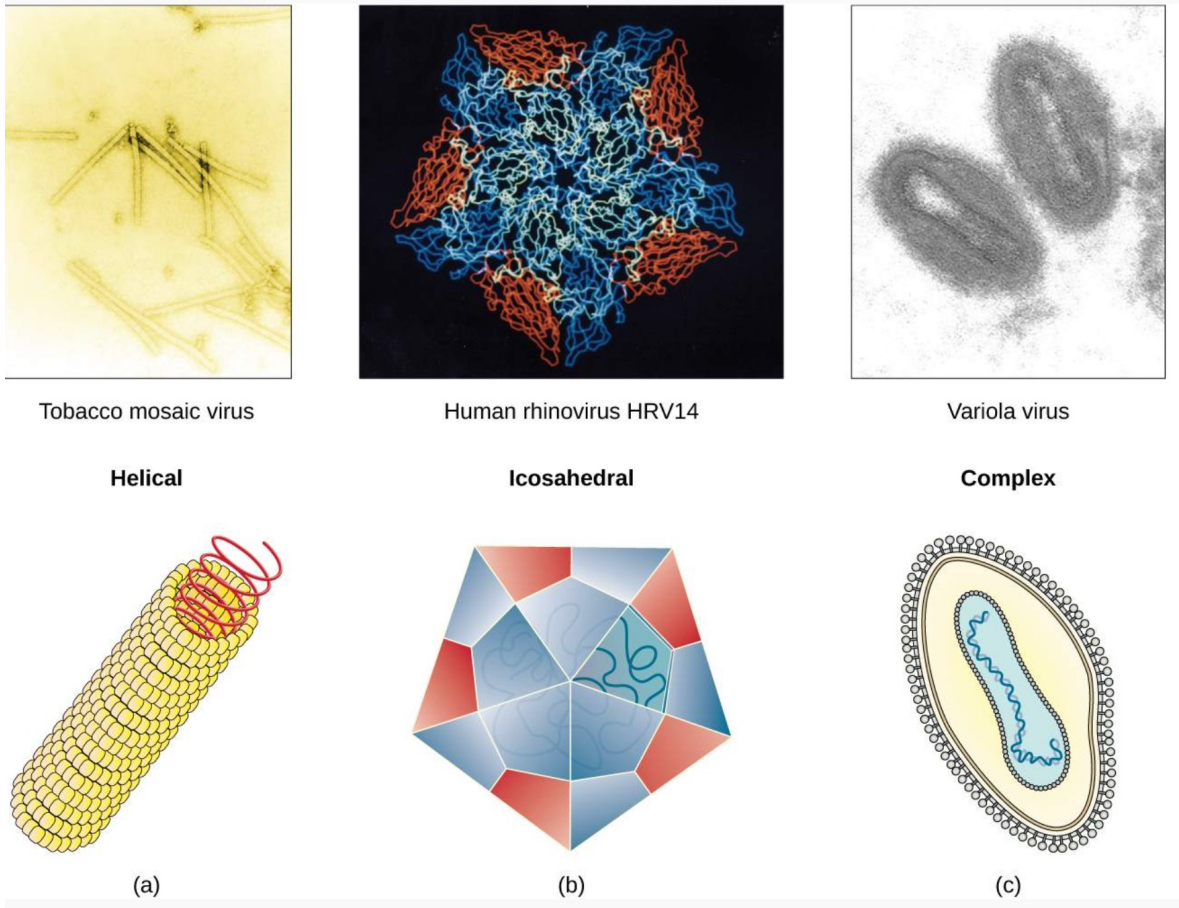
(a) Naked virus



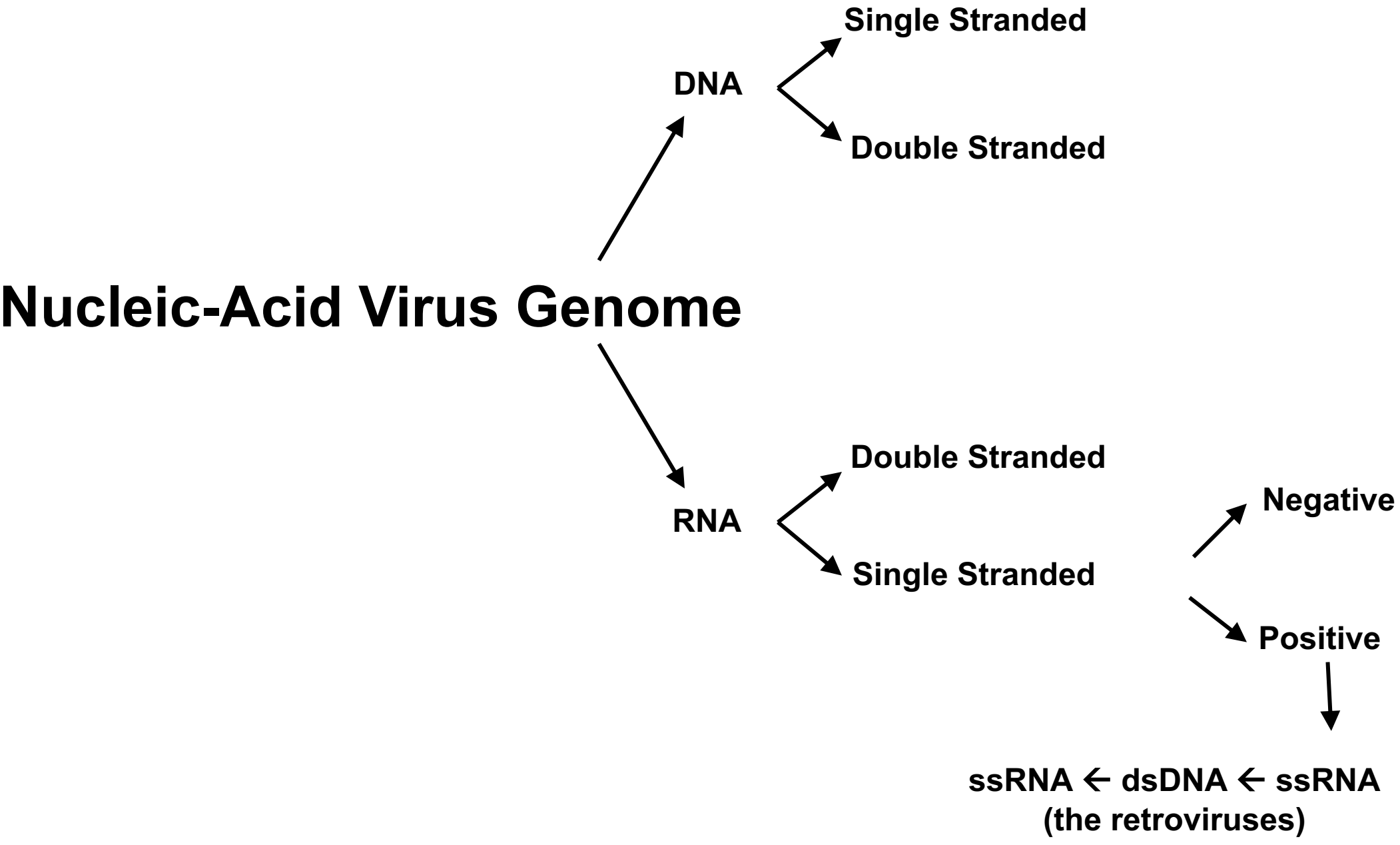
(b) Enveloped virus

Virus Morphology

- ✓ **Three main virus morphological groups** are characterised by:
- ✓ Helical symmetry (Filovirus, Rhadovirus)
- ✓ Icosahedral symmetry (Cubical symmetry, 20 equilateral triangles, 12 vertices, e.g., adenovirus, picornavirus)
- ✓ Complex symmetry (poxvirus, bacteriophages)
- ✓ *** Bacteriophages are the most complex viruses. They consist of a head, +/- tail (long, short-contractile/non contractile, +/- tail fibers).



Virus Classification



Virus Classification➔ GENOME

DNA viruses

i. Contain double-stranded DNA (except for parvovirus).
ii. Are naked viruses (except for herpesviruses, poxviruses, and hepadnaviruses).
iii. Have icosahedral capsids and replicate in the nucleus (except for poxviruses).

RNA viruses

i. Contain **single-stranded** RNA (*except* for *reoviruses*).
ii. Are **enveloped** (except for *caliciviruses, picornaviruses, and reoviruses*).
iii. Have **helical** capsids (*except* for picornaviruses, reoviruses, and togaviruses).
iv. Are classified **positive, negative, or ambisense** depending on the ability of virion RNA to act as messenger RNA (mRNA).
v. Replicate in the **cytoplasm** (*except* for *orthomyxoviruses and retroviruses*, which have both a cytoplasmic and a nuclear phase).

DNA VIRUSES

DNA viruses that cause human disease are classified into **seven families.** The **replication of all viral DNA occurs in the nucleus except for poxviruses,** which replicate entirely in the cytoplasm. *Some DNA viruses can produce latent infections* and all except parvoviruses can transform cells.

table 5.6 Virion and Nucleic Acid Structure of DNA Viruses

Virus Family	Prominent Examples	Virion Structure	Virion Polymerase	Capsid Symmetry	DNA Structure
Adenoviridae	Adenoviruses	Naked	No	Icosahedral	Linear, double stranded
Herpesviridae	Herpes simplex virus Varicella-zoster virus Epstein-Barr virus Cytomegalovirus	Enveloped	No	Icosahedral	Linear, double stranded
Poxviridae	Smallpox virus Vaccinia virus Molluscum contagiosum virus	Brick shaped, enveloped	Yes	Complex	Linear, double stranded
Papillomaviridae	Human papillomavirus	Naked	No	Icosahedral	Circular, double stranded
Polyomaviridae	JC virus	Naked	No	Icosahedral	Circular, double stranded
Hepadnaviridae	Hepatitis B virus	Enveloped	Yes	Icosahedral	Circular, double stranded
Parvoviridae	B19 virus	Naked	No	Icosahedral	Linear, single stranded

DNA VIRUSES ➔ NAKED VIRUSES

1. Human adenoviruses: naked viruses with an **icosahedral nucleocapsid** composed of hexons, pentons, and fibers.

Virulence factors: toxic activity associated with pentons and hemagglutinating activity associated with pentons and fibers.

Classification: are classified into nearly 50 serotypes.

Genome: contains **double-stranded DNA** that replicates asymmetrically.

Replication: replicate in the nucleus of epithelial cells.

Clinical disease

i. Cause localized infections of the eye, respiratory tract, gastrointestinal (GI) tract, and urinary bladder.
ii. Frequently cause subclinical infections and can cause latent infections of lymphoid tissue (e.g., tonsils).
iii. Can cause tumors because **E1A and E1B** gene products bind to cellular tumor suppressor proteins **p110Rb and p53.**

Diagnosis: Virus isolation from the eyes, throat, or urine or ELISA procedures on fecal specimens from patients with GI infections.

2. Papillomaviruses: naked viruses with an icosahedral capsid and double-stranded circular DNA.

Classification: exist in more than 100 different subtypes.

Replication: replicate in epithelial cells of epithelial and mucosal tissue; form koilocytotic cells (cytoplasmic vacuoles and enlarged nuclei) during replication.

Clinical disease

i. May cause lytic, latent, or transforming human infections depending on the host cell.
ii. Types **16 and 18** are associated with **cervical intraepithelial neoplasia** (CIN) involving the **inactivation of tumor suppression proteins, p53 and p110Rb,** by early viral proteins **E6 and E7**, respectively.

3. Parvoviruses: small, naked viruses with **icosahedral** capsids containing single-stranded DNA.

Clinical disease: includes one human virus (B19) that causes disease involving cytolytic replication in erythroid precursor cells.

4. Polyomaviruses: naked viruses with an **icosahedral** capsid containing double-stranded circular DNA.

Clinical disease: includes two human viruses, BK virus and JC virus, which infect the kidney where they usually do not cause disease but become **latent**; when reactivated by immunosuppression, BK causes a urinary tract infection and JC travels to and replicates in oligodendrocytes to cause a neurological disease (progressive multifocal leukoencephalopathy).

1. Hepadnaviruses (only one representative infects humans: **HBV):** icosahedral capsid containing a partially double-stranded DNA surrounded by an envelope.

Replication: have a virion-associated multifunctional enzyme complex with reverse transcriptase, DNA polymerase, and ribonuclease activity, which is necessary for viral DNA replication.

Clinical disease: can cause acute and symptomatic or asymptomatic chronic liver disease and is implicated in primary hepatocellular carcinoma.

Diagnosis: produces unique antigens (**HBsAg**, a surface antigen, and **HBcAg** and **HBeAg** core-associated antigens) associated with infections or their antibodies that are monitored by **serological tests** to determine the source of HBV infections.

2. Herpesviruses: an icosahedral nucleocapsid containing double stranded DNA.

a. Herpes simplex type 1 and 2 (HSV-1 and 2)

Cytopathology: can cause cell rounding and polykaryocyte formation or inclusion bodies (Cowdry type A inclusions) in infected cells.

Replication: produce a viral-specific thymidine kinase necessary for DNA replication; it is the target of several antiherpes nucleoside analog drugs like acyclovir.

Clinical disease:

i. Latently infect neurons.
ii. Produce both acute and latent infections whose clinical lesions occur primarily on mucosal surfaces (lip and genitals), but can cause encephalitis and eye infections as well.

b. Varicella-zoster virus

Cytopathology: produces similar cytopathology as HSV and also latently infects neurons.

Clinical disease: causes vesicular lesions in both acute (chickenpox) and recurrent (shingles) disease.

c. Cytomegalovirus

Cytopathology: causes swelling of infected cells (cytomegalic cells) and ‘‘owl’s eye’’ intranuclear inclusion bodies.

Replication: replicates in epithelial cells of oropharynx, but latently infects monocytes, macrophages, and lymphocytes.

Clinical disease

i. May depress immune response during initial infection due to interaction of cells involved in cellular immunity.
ii. Causes a heterophile-negative mononucleosis and is a potentially serious congenital infection.
iii. Latent infections are usually reactivated to asymptomatic disease, but reactivation in immunosuppressed individuals can be serious (e.g., giant cell pneumonia in AIDS patients).

d. Epstein-Barr virus (EBV)

Pathobiology: can productively infect and abortively infect human B lymphocytes; abortive infection induces B-cell proliferation and potential transformation.

Virulence factors: uses complement receptor 3 (CS-21 or CR-2) as the cellular receptor.

Clinical disease

i. Produces several distinct antigens, including latent membrane proteins (LMPs), nuclear antigens (EBNAs), early antigens (EAs), a membrane antigen (MA), and a viral capsid antigen (VCA).
ii. Usually causes clinically inapparent infections, but may cause heterophile positive infectious mononucleosis and is associated with **Burkitt's lymphoma and nasopharyngeal carcinoma.**

Diagnosis: is associated with the production of atypical lymphocytes (Downey cells) and IgM heterophile antibodies (antibodies detected using antigens from a source different from the one used to induce them) identified by the mononucleosis spot test.

e. Human herpesviruses types 6 and 7 (HHV 6 and 7)

Description: T-lymphotrophic viruses associated with roseola diseases and febrile seizures in infants.

Clinical disease

i. cause latent infections of peripheral blood lymphocytes and can reactivate during immunosuppression of transplant and AIDS patients.

f. Human herpesvirus type 8 (Kaposi's sarcoma–associated herpesvirus; HHVS or KSHV)

Pathobiology: preferentially infects B lymphocytes and appears to be sexually transmitted.

Genome: contains more than 10 homologues of cellular genes (e.g., cyclin D, interleukin 6, and so forth) in its genome.

Clinical disease

i. Associated with Kaposi's sarcoma.
ii. Linked to some AIDS-associated B-cell lymphomas.
iii. Implicated in multiple myeloma.

3. Poxviruses

i. **Complex brick-shaped** virion that consists of an outer envelope enclosing a core containing linear, double-stranded DNA, and two lateral bodies.
ii. Have more than 100 structural polypeptides, including many enzymes and a transcriptional system associated with the virion.

Replication: replicate in the cytoplasm of the cell.

Cytopathology: produce eosinophilic inclusion bodies called Guarnieri bodies and membrane hemagglutinins in infected cells.

Classification: include human viruses (vaccina, variola, and molluscum contagiosum) and animal viruses (cowpox virus, paravaccinia virus [in cows], and orf virus [in sheep]);

* **Variola virus** ➔ causes smallpox.
** **Vaccinia virus** is the variant of variola virus that generally produces only a mild disease and is used as the immunogen in smallpox vaccination.

RNA VIRUSES

Although both naked and enveloped RNA viruses exist, they are usually discussed based on the nature of their RNA genome, which may be single stranded or double stranded.

Using this criterion, there are, therefore, four categories of RNA viruses:

i. **positive sense** (virion s.s. RNA can serve as mRNA),
ii. **negative sense** (s.s. RNA complementary to the virion RNA serves as mRNA),
iii. Ambisense (virion RNA has portions of both positive-sense and negative-sense RNA), and
iv. **Double stranded** (virion RNA is double stranded).

- ✓ **All of these viruses except the influenza viruses and HIV replicate entirely in the cytoplasm of the cell,** and since cells lack cytoplasm RNA polymerase, they must code for and produce their own.
- ✓ All **negative sense RNA viruses are enveloped** and a RNA polymerase that acts as a transcriptase or replicase associated with the virion.

RNA VIRUSES ➔ POSITIVE SENSE

table 5.7 Virion and Nucleic Acid Structure of Positive-Sense RNA Viruses

Virus Family	Prominent Examples	Virion Structure	Virion Polymerase	Capsid Symmetry	RNA Structure
Caliciviridae	Norwalk agent	Naked	No	Icosahedral	Linear single stranded, nonsegmented
Picornaviridae	Coxsackieviruses Echoviruses Enteroviruses Hepatitis A virus Polioviruses Rhinoviruses	Naked	No	Icosahedral	Linear, single stranded, nonsegmented
Flaviviridae	Dengue virus Hepatitis C virus St. Louis encephalitis virus Yellow fever virus	Enveloped	No	Icosahedral	Linear, single stranded, nonsegmented
Togaviridae	Eastern, Western, and Venezuelan equine encephalomyelitis viruses	Enveloped	No	Icosahedral	Linear, single stranded, nonsegmented
Retroviridae	Human immunodeficiency virus Leukemia viruses Sarcoma viruses	Enveloped	No*	Helical	Linear, single stranded, nonsegmented*
Coronaviridae	Coronaviruses SARS-CoV	Enveloped	No	Helical	Linear, single stranded, nonsegmented

*Retroviruses are diploid and have reverse transcriptase.

1. **Caliciviruses:** naked viruses with an **icosahedra**l nucleocapsid that contain positive-sense, **single-stranded** RNA.

Classification: have been classified in four genera, of which two infect humans to cause gastroenteritis; those belonging to the Norovirus genus (previously called ‘‘Norwalk agents’’) cause epidemics of gastroenteritis associated with contaminated food and is transmitted via the fecal–oral route.

2. Coronaviruses

i. Enveloped viruses with a helical nucleocapsid that contains single-stranded RNA with positive (messenger) polarity.
ii. Have distinctive club-shaped surface projections that give the appearance of a solar corona to the virion.

Clinical disease: most frequently associated with the common cold in adults and gastroenteritis in infants, a variant strain, SARS-CoV, emerged to cause a severe acute respiratory syndrome

*** In 2019 SARS-CoV-2 has caused one of the economically important pandemic in the world…… second to HIV-1 pandemic

3. Flaviviruses: enveloped viruses with a single-stranded, positive-sense RNA and no discernible capsid structure.

Replication: replicate in the cytoplasm of the cell, where the RNA is translated into a large polyprotein that is subsequently cleaved (by posttranslational cleavage) into individual proteins.

** **Dengue virus:** arbovirus transmitted from monkeys to humans by mosquitoes.

Clinical disease

i. Four serotypes exist; antibodies to one serotype increase efficiency of infection by another serotype, resulting in more serious disease.
ii. Causes characteristic skin lesions as well as fever and muscle and joint pain.

iii. Continued …. * Hepatitis C virus**

3. Flaviviruses: enveloped viruses with a single-stranded, positive-sense RNA and no discernible capsid structure

*** **Hepatitis C virus:** also known as non-A, non-B hepatitis virus; exist in **six genotypes** with different worldwide distribution.

Clinical disease

i. Infects the body after parenteral entry and causes **90% of blood transfusion–associated or blood product administration–associated hepatitis**.
ii. Can cause chronic infections involving carrier state individuals and is implicated in primary **hepatocellular carcinoma**.

Diagnosis: diagnosed by ELISA serology and **molecular genotyping of circulating virions** to determine patient's likelihood to respond to treatment with INF-a and ribavirin since only two genotypes respond.

3. Flaviviruses

*** **Yellow fever virus:** an arbovirus that is usually transferred from monkeys to humans by mosquitoes.

Clinical disease

i. Causes a biphasic disease with clinical signs involving the vascular endothelium during initial virus replication and involving the liver during later replication.
ii. Can cause chronic infections; therefore, individuals with the virus are in a carrier state.

Diagnosis: diagnosed by eosinophilic hyaline masses called Councilman bodies in the cytoplasm of infected liver cells.

Prevention: prevented by immunization with the attenuated vaccine strain 17D.

4. Hepevirus (Hepatitis E-like viruses): naked viruses with a single-stranded, positive-sense RNA genome, which has been divided into four genotypes.

Clinical disease:

produce a hepatitis transmitted by the fecal–oral route, but not endemic in the United States.

RNA VIRUSES ➔ POSITIVE SENSE

5. Picornaviruses: small, naked viruses with an icosahedral nucleocapsid that contains single stranded, positive-sense RNA covalently linked to a small protein (VPg in poliovirus).

Replication: replicate in the cytoplasm of the cell, where RNA is translated into a large polyprotein that is subsequently cleaved (posttranslational cleavage).

Classification: classified into nine genera, but only five cause human disease.

- enteroviruses
- hepatoviruses
- kobuviruses
- parechoviruses
- rhinoviruses

5. Picornaviruses: small, naked viruses with an icosahedral nucleocapsid that contains single stranded, positive-sense RNA covalently linked to a small protein (VPg in poliovirus).

- **Enteroviruses** cause a variety of human diseases involving infections of the alimentary tract (are stable at acidic pH 3 to 5). They include polioviruses and coxsackie A and B viruses, and echoviruses.

***** Coxsackie viruses:**

Classification: divided into two groups, depending on the type of paralysis they cause into mice (group A cause flaccid paralysis; group B cause spastic paralysis).

Clinical disease:

i. Group B are cardiotrophic and can cause severe chest pain due to infection of muscles between the ribs.
ii. Are most often not identified during infections, but are simply classified as enteroviral disease disease: are the leading cause of the common cold.

5. Picornaviruses….contimued

**** Polioviruses

Classification: exist in three serotypes.

Pathobiology: spreads in the body by hematogenous and neural routes.

Clinical disease

i. Replicate in the intestine where they usually produce an asymptomatic infection, but can spread to the spinal cord and CNS via neural pathways.
ii. Destroy anterior horn cells of the spinal cord as a result of replication there.
iii. May cause a **rare paralytic disease as a result of invasion of the CNS.**

Prevention: the three serotypes have been inactivated and combined in a trivalent vaccine (Salk vaccine);

5. Picornaviruses

**** **Hepatovirus:** contains the hepatitis A viruses that replicate in hepatocytes where they cause a food-borne or water-borne hepatitis.

Treatment and prevention: may be treated prophylactically with immune human globulin or prevented by immunization with killed virus vaccines (Havrix or VAQTA) containing formalin-inactivated virions.

Rhinoviruses
Description: exist in more than 100 serotypes; are acid labile.

Replication: bind to ICAM-1 and replicate best at 33C/91F

Clinical disease: are the leading cause of the common cold.

6. Retroviruses: enveloped viruses with an icosahedral capsid.

Genome

i. Contain two identical copies of ss positive-sense RNA (diploid genome) with viral specified **reverse transcriptase enzyme complex** (RNA-dependent DNA polymerase and RNAse activity), integrase enzyme, and protease enzyme.
ii. Have 3 notable genes: gag, pol & env flanked by LTR (regulatory functions).
iii. Use posttranslational cleavage processes during the synthesis of gag and env gene products.

Classification: Divided morphologically into four types (A, B, C, and D).

*** Classified into three groups: **lentiviruses** (visna and maediviruses of sheep, **HIV**); **spumaviruses**; and **oncoviruses** (types B, C, and D RNA tumor viruses).

Clinical disease: cause mostly "slow" diseases of animals and various cancers, except for HIV, which causes AIDS.

6. Retroviruses

*** **HIV-1 and -2:** members of the lentivirus subfamily and exist as lymphotrophic and macrophage trophic strains.

Pathobiology

i. Initiate infection by interaction of an envelope glycoprotein (gp120) with the CD4 T cell receptor and coreceptors (CCR5 and CXCR4(.
ii. Synthesize core proteins (p17, p24, and RT) and transregulatory proteins (tat, rev, and nef) plus regulatory genes
iii. Infect and kill T-helper cells, resulting in depression of both humoral and cell mediated immunity.

Clinical disease: causes immunosuppression, lending to opportunistic infections, cancers, and neurologic disorders.

Treatment: replication may be inhibited by six classes of antivirals: nucleoside analogs and nonnucleoside inhibitors of reverse transcriptase; integrase inhibitor; protease inhibitors; attachment inhibitor; and fusion inhibitor.

6. Retroviruses

****** Human T-cell lymphotrophic viruses (HTLV-1 and -2)** belong to the oncovirus sub family and are associated with human cancers:

- adult T-cell leukemia [HTLV-1],
- hairy cell leukemia [HTLV-2]),
- neurologic myelopathy (tropical spastic paraparesis [HTLV-1]).

7. Togavirus: enveloped viruses with an icosahedral nucleocapsid containing single-stranded, positive-sense RNA; have hemagglutinins associated with their envelope.

Classification: divided into four groups of which two (alphaviruses and rubiviruses) are human pathogens.

****** Alphaviruses:** arboviruses with mosquito vectors and animal reservoirs.

Clinical disease

i. Cause encephalitis or moderate systemic disease following the bite of a mosquito that has fed on an animal viral reservoir.
ii. Lead to more serious encephalitis than do flaviviruses.
iii. Include eastern equine encephalomyelitis virus, western equine encephalomyelitis virus, and Venezuelan equine encephalomyelitis virus.

Diagnosis: diagnosed by serologic tests, usually ELISA for IgM, because virus isolation is difficult.

RNA VIRUSES → NEGATIVE SENSE

table 5.8 Virion and Nucleic Acid Structure of Negative-Sense RNA Viruses

Virus Family	Prominent Example	Virion Structure	Virion Polymerase	Capsid Symmetry	RNA Structure
Paramyxoviridae	Mumps virus Measles virus Parainfluenza virus Respiratory syncytial virus	Enveloped	Yes	Helical	Linear, single stranded, nonsegmented
Rhabdoviridae	Rabies virus Vesicular stomatitis virus	Enveloped	Yes	Helical	Linear, single stranded, nonsegmented
Filoviridae	Ebola virus Marburg virus	Enveloped	Yes	Helical	Linear, single stranded, nonsegmented
Orthomyxoviridae	Influenza viruses	Enveloped	Yes	Helical	Linear, single stranded, eight segments
Bunyaviridae	California encephalitis virus Hantavirus	Enveloped	Yes	Helical	Circular, single stranded, three segments
Unclassified (genus: delta virus)	Hepatitis D virus	Naked	No	Helical	Circular, single stranded

1. Bunyaviruses: Enveloped arboviruses with three circular helical nucleocapsids, each containing a unique piece of single-stranded, negative-polarity RNA, viral nucleoprotein, and transcriptase enzyme.
Can interact with viruses that are closely related serologically to produce recombinant viruses by genetic reassortment.

Replication: replicate within the cytoplasm and bud from the membranes of the Golgi apparatus.

Clinical disease

i. Have rodent hosts and infect humans during an arthropod bite.
ii. Cause mosquito-borne encephalitis (California and LaCrosse encephalitis viruses); sandfly and mosquito-borne fever (sandfly fever virus and Rift Valley fever virus); rodent-borne hemorrhagic fiver (Hantaan virus); and respiratory distress syndrome (Hantavirus).

2. Orthomyxoviruses (influenza): enveloped, spherical, or filamentous viruses with eight helical nucleocapsids containing a unique singe-stranded, negative-sense RNA.

Components: have a hemagglutinin (H), a neuraminidase (N), a matrix protein (M) associated with the envelope, a transcriptase (P) that is associated with the nucleocapsid, and a nucleoprotein (NP) associated with the RNA.

Influenza virus hemagglutinin.

i. This envelope glycoprotein contains a virus receptor that binds to the cellular receptor site. Agglutinates many species of red blood cells.
ii. It induces neutralizing antibodies. Has fusion activity that allows the virion envelope to fuse with the host-cell plasma membranes.
iii. Antigenic changes are responsible for influenza epidemics. Frequent minor mutations result in antigenic changes, leading to antigenic drift; major antigenic changes resulting from reassortment between the hemagglutinin-coding RNA segments of animal or human viruses cause antigenic shift.

2. Orthomyxoviruses (influenza): enveloped, spherical, or filamentous viruses with eight helical nucleocapsids containing a unique singe-stranded, negative-sense RNA.

Influenza virus neuraminidase

i. This envelope glycoprotein removes terminal sialic acid residues from oligosaccharide chains, resulting in less viscous mucous secretions thereby facilitating virus spread.
ii. It is involved in the release of virions from infected cells.
iii. It can undergo antigenic shift and drift mutations; however, epidemics do not result from these changes.
iv. Its activity is inhibited by the antivirals oseltamivir and zanamivir.

Influenza virus M2 protein

i. This protein forms a proton channel during replication that facilitates uncoating and is rendered nonfunctional in influenza A virus infections by the antivirals amantadine and rimantadine.
ii. They are assembled in the cytoplasm but have a nuclear phase since they depend on host nuclear functions, including RNA polymerase II, for transcription.

2. Orthomyxoviruses (influenza)

Classification

i. Are classified as type A, B, or C, depending on a nucleocapsid antigen; A is the only one infecting both animals and humans.
ii. Are designated by the nomenclature, which indicates virus type, species isolated from (unless human), site of isolation, strain number, year of isolation, and hemagglutinin and neuraminidase subtype; for example, A/swine/NewJersey/8/76 (H1N1) and A/Phillippines/2/82 (H3N2).

Influenza is a localized infection of the respiratory tract that may result in pandemics due to reassortment of the hemagglutinin.

d. Avian flu is a contagious disease of animals caused by influenza A viruses that normally infect birds and occasionally pigs, but have rarely crossed species lines to infect humans.

3. Paramyxoviruses: spherical, enveloped viruses with a single helical nucleocapsid containing single-stranded, negative-sense RNA; exist in few antigenic types.

Components: have a hemagglutinin-neuraminidase (HN), a fusion protein (F), a matrix protein (M) associated with the envelope, and a nucleocapsid-associated transcriptase (P).

Paramyxovirus hemagglutinin-neuraminidase (HN): **L**arge surface glycoprotein with hemagglutinating and neuraminidase activity, except in measles virus, which lacks neuraminidase activity, and in respiratory syncytial virus, in which both activities have been lost. HN is responsible for **virus adsorption.**

Paramyxovirus fusion protein: surface glycoprotein has fusion and hemolysin activities, except in respiratory syncytial virus, in which hemolysis activity is lost. It is responsible for **virus penetration**

Replication: replicate in the cytoplasm of the cell.

Clinical disease: cause acute and persistent infections.

Classification: divided into **three genera** on the basis of chemical and biologic properties:

i. paramyxoviruses (parainfluenza and mumps viruses)
ii. morbilliviruses (measles virus),
iii. pneumoviruses (respiratory syncytial virus and metapneumovirus).

3. Paramyxoviruses

***Parainfluenza viruses

Classification: exist in four serotypes.

Clinical disease: cause a variety of fall and winter upper and lower respiratory tract illnesses; croup (type 2 virus) is a well-known infant disease.

Diagnosis: may be diagnosed using fluorescent antibody (FA) techniques on nasopharyngeal washes or swab to detect viral antigens.

****Mumps virus

Classification: exists in one serotype.

Clinical disease: often causes asymptomatic infections, but can cause a generalized disease involving enlargement of the parotid glands.

Diagnosis: usually diagnosed clinically.

Prevention: infections are inhibited by a live attenuated vaccine containing the Jeryl Lynn strain of virus (usually included with live attenuated measles and rubella virus strains).

3. Paramyxoviruses

**** Measles virus

Description: exists in one serotype.

Components: has hemagglutinin, but no neuraminidase activity (H protein rather than HN protein).

Pathobiology: uses the CD46 molecules as its cellular receptor.

Replication: frequently forms giant multinucleated cells (syncytia) as part of its replication process (called Warthin-Finkeldey cells in nasal secretions).

Clinical disease: causes an acute generalized disease characterized by a maculopapular rash, fever, respiratory distress, and Koplik's spots on the buccal mucosa.

Prevention: infections can be prevented by a live attenuated measles vaccine (Moraten strain) that is part of the trivalent (measles,mumps, and rubella) vaccine given to children.

3. Paramyxoviruses

**** **Respiratory syncytial virus**

Description: exists in one serotype.

Components: has only hemagglutinin activity (H protein), no neuraminidase activity.

Replication: induces syncytia formation during replication.

Clinical disease: causes a potentially serious respiratory tract pathogen of infants.

Diagnosis: diagnosed by enzyme immunoassay (EIA) for viral antigens in nasopharyngeal washes.

RNA VIRUSES ➔ NEGATIVE SENSE

4. Rhabdoviruses: enveloped, bullet-shaped viruses with a helical nucleocapsid containing singe-stranded, negative-sense RNA.

Replication: have a virion-associated transcriptase and replicate in the cytoplasm.

Classification: includes the human pathogen rabies virus and the bovine pathogen vesicular stomatitis virus.

***** Rabies virus**

Replication: has a virion-associated transcriptase or replicase.

Cytopathology: produces specific cytoplasmic inclusion bodies, called Negri bodies, in infected cells.

Pathobiology: Uses acetylcholine receptors on muscle cells to initiate infection, Has a predilection for the hippocampus (Ammon's horn cells), Can travel throughout the nervous system in nerve fibers.

Clinical disease

i. Produces disease after inoculation by an animal bite (zoonotic disease) or, occasionally, inhalation.
ii. Causes fatal disease unless the infected person was previously immunized or receives postexposure prophylaxis consisting of passive immunization with human rabies immune globulin and immunization with a vaccine.

Diagnosis: identified in suspected tissues by a direct immunofluorescent test for viral antigens.

5. Filoviruses: enveloped viruses with a helical nucleocapsid containing single-stranded, negative- sense RNA.

Classification: include Marburg and Ebola viruses.

Clinical disease: cause African hemorrhagic fevers, which then lead to death.

RNA VIRUSES ➔ Double stranded

Reoviruses: naked viruses with a double-shelled (outer shell and core) icosahedral capsid containing 10, 11, or 12 segments of double-stranded RNA.

Replication: replicate in the cytoplasm; have a core-associated transcriptase or replicase.

Classification: classified into five groups; orthoreoviruses, **rotaviruses,** orbiviruses, and coltiviruses have strains that infect humans.

RNA VIRUSES ➔ Double stranded

Reoviruses

***Rotaviruses

Genome: have 11 segments of double-stranded RNA; virion has wheel-and-spoke morphology.

Classification: exist in at least seven serotypes, with type A being involved in most human infections.

Clinical disease: cause infantile diarrhea and are the most common cause of gastroenteritis in children; are frequent causes of nosocomial infections.

Diagnosis: diagnosed by demonstrating virus in the stool or by serologic tests, particularly ELISA.

Prevention: have been modified and genetically manipulated for preparation of live attenuated vaccines (Rotateg and Rotarix).

RNA VIRUSES ➔ AMBISENSE

Description: enveloped viruses with two string-of-beads nucleocapsids, each containing a unique single-stranded, circular RNA.

2. Genome: have two molecules (L, or large and S, or small) of single-stranded, ambisense RNA.

3. Replication: replicate in the cytoplasm and have host-cell ribosomes in their virion.

4. Clinical disease

i. Infect mice, rats, or both as their natural hosts; are initially passed from rodents to humans but can be transferred by direct human contact.

ii. Cause highly contagious hemorrhagic fevers (Junin, Machupo, and Lassa viruses) that are not endemic to the United States and a meningitis or flulike illness (lymphocytic choriomeningitis virus) that is endemic.

table 5.9 Virion and Nucleic Acid Structure of Other RNA Viruses

Virus Family	Prominent Example	Virion Structure	Virion Polymerase	Capsid Symmetry	RNA Structure
Arenaviridae	Lassa fever virus Lymphocytic choriomeningitis virus	Enveloped	Yes	Helical	Circular, single stranded, two ambisense segments

Viroids

- ✓ are very small (200-400 bases) circular RNA molecules with a rod-like secondary structure
- ✓ They have no capsid or envelope and are associated with certain plant diseases
- ✓ Their replication strategy is like that of viruses
  - ✓ they are obligate intracellular parasites

Virusoids

- ✓ Are satellite, viroid-like molecules somewhat larger than viroids (approximately 1000 nucleotides)
- ✓ Are dependent on the presence of virus replication for multiplication
- ✓ They are packaged into virus capsids as passengers

Virus-related entities

Prions

1. Description

a. Not viruses but are proteinaceous material lacking nucleic acid that may be acquired or inherited and is identical or closely related to a 30 to 35 kDa host membrane glycoprotein(PrPc).

b. PrPc can undergo a change in its tertiary structure (e.g., the PrP of scrapie [PrPsc] that causes an aggregation of itself and PrPc on neuronal cell surfaces); the aggregates (amyloid) are released and cause slow diseases called spongiform encephalopathies.

2. Clinical disease: associated with several degenerative CNS diseases (subacute spongiform virus encephalopathies): kuru and Creutzfeldt-Jakob disease of humans, scrapie of sheep, bovine spongiform encephalopathy (or mad cow disease), and transmissible encephalopathy of mink.

Viral replication – (general)

General characteristics of viral replication

Replication involves many host-cell enzymes and functions, including attachment, penetration, uncoating of the viral genome, synthesis of early proteins involved in genome replication, synthesis of late proteins (structural components of the virion), assembly, and release

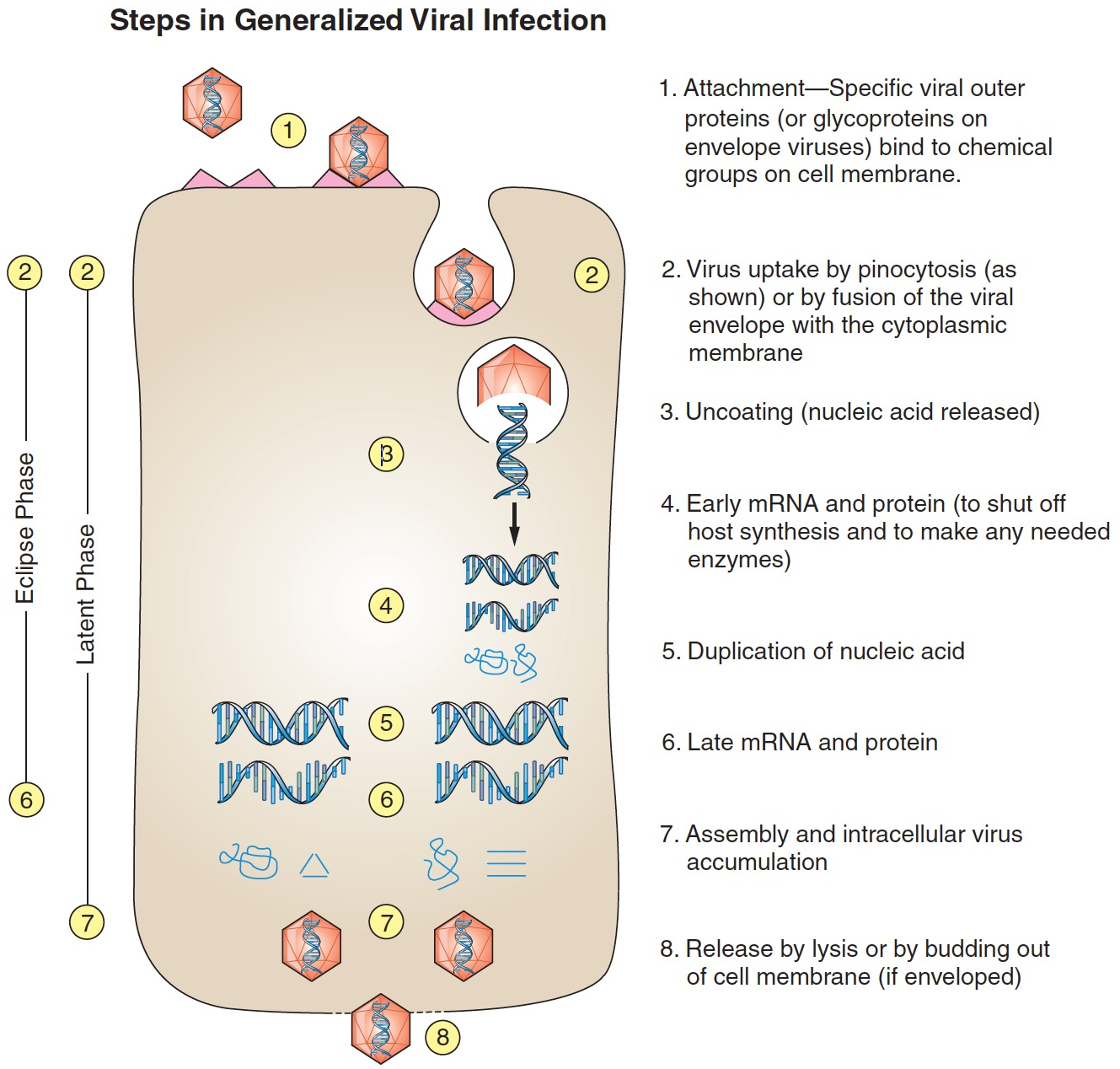
1. Attachment involves the interaction of viral attachment proteins (VAPs) and specific host-cell receptor sites. It plays an important role in viral pathogenesis, determining viral cell tropism; it may be inhibited by antibodies (neutralizing antibodies) against viral receptors or cellular receptor sites.

2. Penetration can occur by a cellular mechanism called receptor-mediated endocytosis. The virus envelope may fuse with the plasma membrane of the host cell.

3. Uncoating refers to the separation of the capsid from the viral genome. It results in the loss of virion infectivity.

4. Genome replication is conducted by virally encoded enzymes

4. Budding is the process by which enveloped viruses obtain their envelope and confers infectivity to enveloped viruses. It is preceded by the insertion of virus-specific glycoproteins into the membranes of the host cell.



Viral replication – (general)

Replication in DNA viruses

1. Transcription occurs in the host-cell nucleus *(except for poxviruses)* and is regulated by host cell DNA-dependent RNA polymerases (except for virion-associated RNA polymerase of poxviruses). It occurs in a specific temporal pattern ➔ immediate early, delayed early, and late mRNA transcription. It may be followed by posttranscriptional processing of primary mRNA transcripts (late adenovirus transcripts).

2. Translation occurs on cytoplasmic polysomes and is followed by transport of newly synthesized proteins to the nucleus (except for poxviruses).

3. Genome replication occurs after the synthesis of the early proteins. It is semiconservative and is performed by a DNA-dependent DNA polymerase, which may be supplied by the host cell (adenoviruses) or may be virus specific (herpesviruses).

4. Assembly takes place in the nucleus (except for poxviruses).

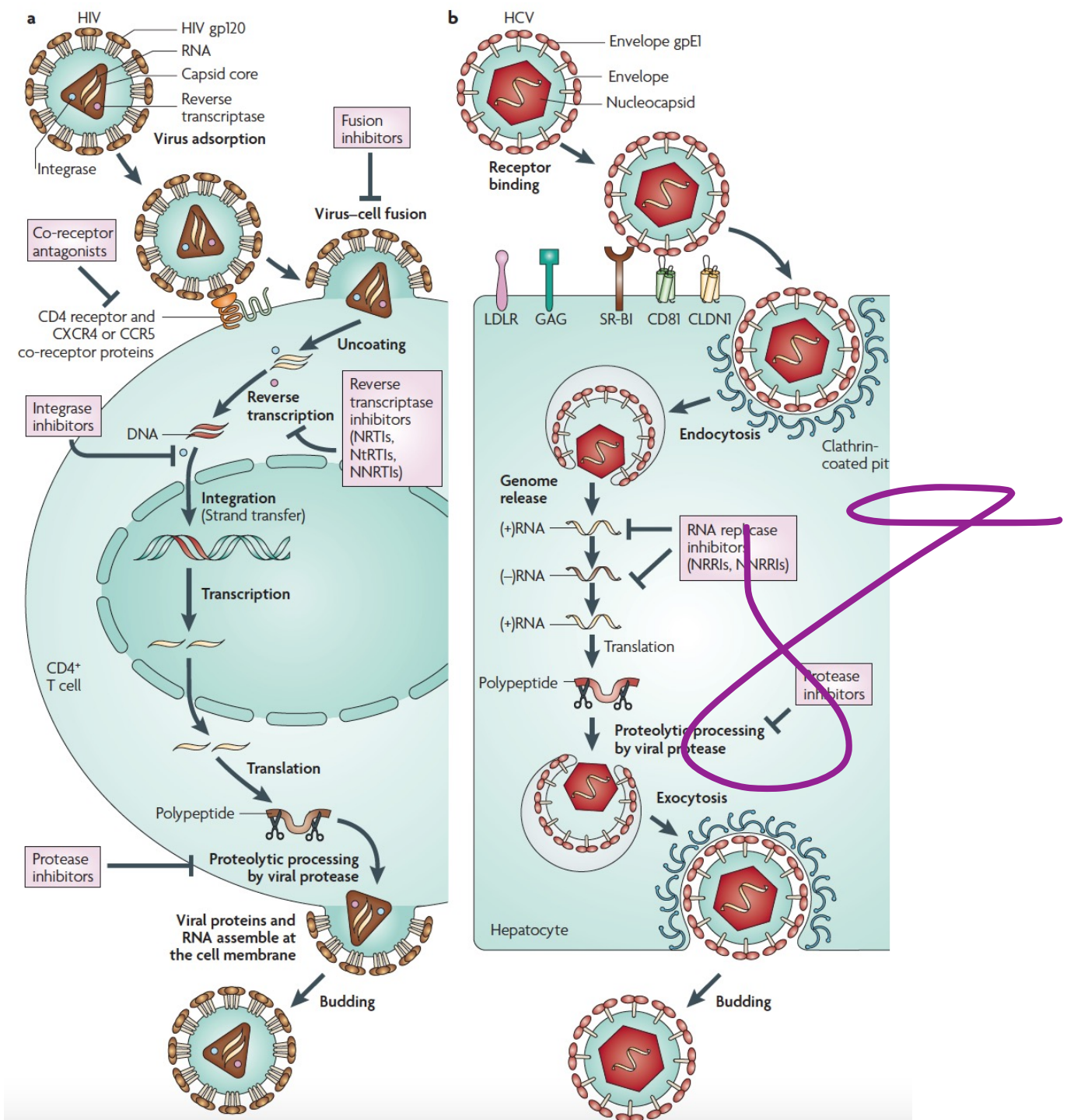
Replication in RNA viruses

1. The **viral genome** may be single stranded or double stranded and segmented or nonsegmented. It may have: messenger **(positive-sense)** (picornaviruses and retroviruses) antimessenger (**negative-sense**) (orthomyxoviruses and paramyxoviruses) or ambisense (arenaviruses).
2. **Transcription** involves a viral-specified RNA-dependent RNA polymerase for all viruses, except retroviruses, which use a host-cell, DNA-dependent RNA polymerase. Negative-sense viruses use a virion-associated enzyme (transcriptase).

3. Translation occurs on cytoplasmic polysomes. It may result in the synthesis of a large polyprotein that is subsequently cleaved (in posttranslational processing) into individual viral polypeptides (picornaviruses and retroviruses).

4. Genome replication occurs in the cytoplasm (except for orthomyxoviruses and retroviruses) and is performed by a viral-specific replicase enzyme (except for retroviruses). A replicative intermediateRNA structure is required for all single-stranded RNA genomes. RNA viruses have a higher mutation rate than DNA viruses.

Viral replication ➔ HIV & HCV (RNA viruses)



What is the host for?

- ✓ Viruses cannot replicate by themselves:
- ✓ Viral DNA replication always requires synthesis of at least one viral protein, sometimes many (hence always delayed after infection).
- ✓ Simple viruses require more host proteins - genetic economy.
- ✓ Complex viruses encode many, but not all proteins are required for replication.
- ✓ Small DNA viruses do not encode an entire replication system. They generally encode proteins that orchestrate the host (Papillomaviridae, Polyomaviridae, Parvoviridae).
- ✓ Large DNA viruses encode most of their own replication systems (Herpesviridae, Adenoviridae, Poxviridae).

ONCOGENIC VIRUSES

General characteristics: Oncogenic viruses cause cancers when they infect appropriate animals. They are classified as DNA or RNA tumor viruses.

Pathobiology

i. Oncogenic viruses transform infected cells by altering cell growth, cell surface antigens, and biochemical processes.
ii. When they enter cells, these viruses introduce “transforming”’ genes or induce expression of quiescent cellular genes, which results in the synthesis of one or more transforming proteins.
iii. The RNA viral genome is converted to DNA by reverse transcriptase and integrated into host cell chromosome, forming a provirus.

DNA TUMOUR VIRUSES

General characteristics

Cause transformation in nonpermissive cells (infected cells that do not support total virus replication).

Classification

i. **Human viruses** include human papillomaviruses: adenoviruses, HBV, EBV, molluscum contagiosum virus, JC and BK viruses, and possibly HSV-2.

ii. **Animal viruses** include chicken Marek's disease virus (a herpesvirus), mouse polyomavirus (a papovavirus), and monkey SV40 virus (a papovavirus).

Protein products of some DNA tumor viruses (e.g., adenovirus, papillomavirus, and polyomavirus) interact with cellular **tumor suppressor gene** products that suppress oncogene expression.

DNA TUMOUR VIRUSES

2. SV40 virus

Replication: undergoes productive replication in monkey cells but transforms nonpermissive hamster& mouse cells.

Pathobiology: (i) Synthesizes an early protein called large tumor (T) antigen, which associates with two antioncogene proteins, p53 and p110Rb, and the retinoblastoma gene product, and establishes and maintains SV40-induced transformation.
(ii) Synthesizes two other tumor antigens: middle T and small T antigen.

Polyomavirus grows permissively in mouse cells but transforms nonpermissive hamster and rat cells. It synthesizes a transforming large T antigen.

Human adenovirus may be highly oncogenic (types 12, 18, and 31) or weakly oncogenic (types 3, 7, 14, 16, and 21) when injected into hamsters. It synthesizes an E1A protein that binds to cellular p53 and E1B protein that binds to cellular p110Rb if highly oncogenic.

Human papillomavirus may have a strong association (types 16 and 18) or a moderate association (types 31, 33, 35, 45, 51, 52, and 56) with cervical carcinoma. HPV synthesizes an E6 protein that binds to cellular p53 and E7 protein that binds to cellular p110Rb.

EBV is a cofactor in the etiology of Burkitt's lymphoma and nasopharyngeal carcinoma. It can immortalize and transform B lymphocytes due to specific EBNA and LMP proteins.

HBV is associated with primary hepatocellular carcinoma. It synthesizes an X protein, which binds to cellular p53.

RNA TUMOUR VIRUSES

Description: retroviruses (oncovirus group); are also called oncornaviruses.

Pathobiology: infect permissive cells, but transform rather than kill.

Clinical disease: cause tumors of the reticuloendothelial and hematopoietic systems (leukemias), connective tissues (sarcomas), or mammary gland.

Type B tumor viruses have an eccentric electron-dense core structure in their virion. They are best exemplified by mouse mammary tumor virus, also called Bittner virus.

Type C tumor viruses have electron-dense cores in the center of the virion. They include most RNA tumor viruses.

Genome: may contain a cellular-derived oncogene (which codes for a cancer-inducing product) as well as virogenes (gag, pol, and env); however, a few nondefective murine leukosis viruses (AKR and Moloney viruses) and HTLV-1 and -2 lack oncogenes.

RNA TUMOUR VIRUSES

(1) Oncogenes are genes that cause cancer.

i. Copies are found in viruses (v-onc) and cells (c-onc or proto-oncogene).

ii. In normal cells, oncogenes are ‘‘switched off’’ or down-regulated by antioncogeneproteins (e.g., p53 andp110Rb).

iii. Their products are essential to normal cell function or development and include:

1. Tyrosine protein kinases (src gene-Rous sarcoma virus, ab1 gene-Abelson leukemia virus).
2. Guanine-nucleotide–binding proteins (Ha-ras-Harvey sarcoma virus).
3. Chromatin-binding proteins (myc-MC29 myclocytomatosis virus and fos-FBJ osteosarcomavirus).
4. Cellular surface receptors such as epidermal growth factor receptor (erb-B product of avian erythroblastosis virus).
5. Cellular growth factors such as platelet-derived growth factor (SIS gene product of simian sarcoma virus).

Classification: are classified as **nondefective** or **defective** based on replicative ability.

(1) Nondefective viruses: Have all their virogenes and can therefore replicate themselves, Have high oncogenic potential if they also contain an oncogene (Rous chicken sarcoma virus),Have low oncogenic potential if they do not have an oncogene (e.g., AKR and Moloney murine leukemia viruses and human T-cell leukemia viruses [HTLV] 1 and 2).

(2) Defective viruses: Have a virogene or part of a virogene replaced by an oncogene, Need helper viruses to provide missing virogene products for replication, Have high oncogenic potential, for example, murine sarcoma viruses (Kirsten and Harvey viruses) and murine leukemia viruses (Friend and Abelson viruses).

4. HTLV-1 and -2

a. Are nondefective human retroviruses with no identifiable oncogene that transform T4 antigen-positive cells.

b. Are associated with human adult acute T-cell lymphocytic leukemia and tropical spastic paraparesis (HTLV-1) and some forms of hairy cell leukemia (HTLV-2).

Host defenses to Viruses

A. Host defense mechanisms are responsible for the self-limiting nature of most viral infections.

1. Defense mechanisms have both immune and nonimmune aspects.
2. They operate during all stages of a viral infection and may contribute to the clinical pattern of disease (immunopathology).

B. Nonimmune defenses

1. Innate immunity includes anatomic barriers (dead cells of the epidermis) and chemical barriers (mucous layers) that limit contact of the virus with susceptible cells. They are dependent on the complex parameters associated with the age and physiologic status of the host.

2. Cellular resistance involves nonpermissive cells, which lack factors (e.g., viral receptor sites) necessary for virus replication.

3. Inflammation limits the spread of virus from an infection site and results in unfavorable environmental conditions for viral replication (e.g., antiviral substances, low pH, elevated temperature).

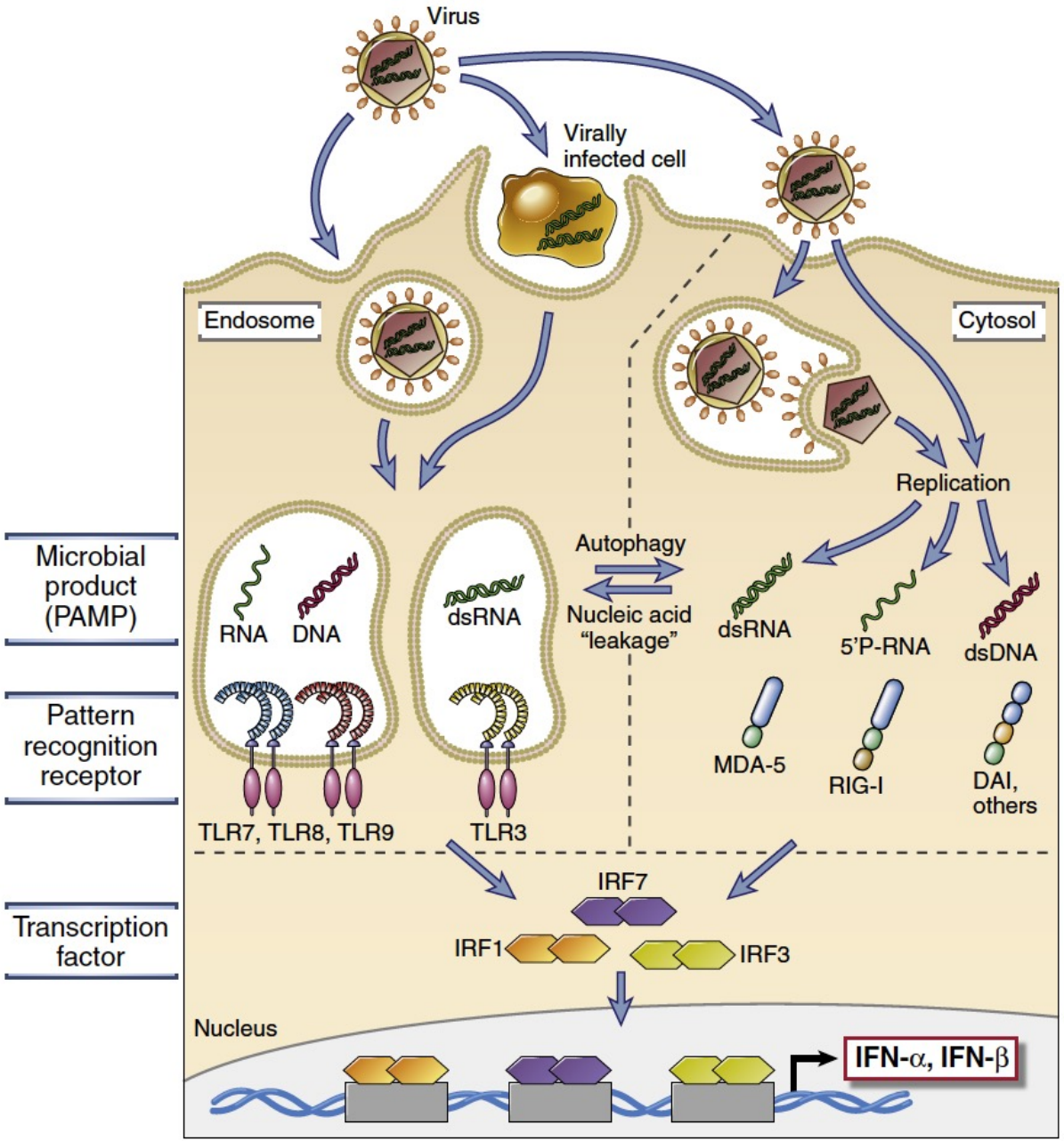
4. **IFN** is a host-specific, viral-induced glycoprotein that inhibits viral replication by inducing the synthesis of several antiviral proteins including 20,50A synthetase and specific protein kinases.

   i. Although it is not viral specific, IFN is fairly species specific.
   ii. It is the first viral-induced defense mechanism at the primary site of infection in nonimmune individuals.

Interferons

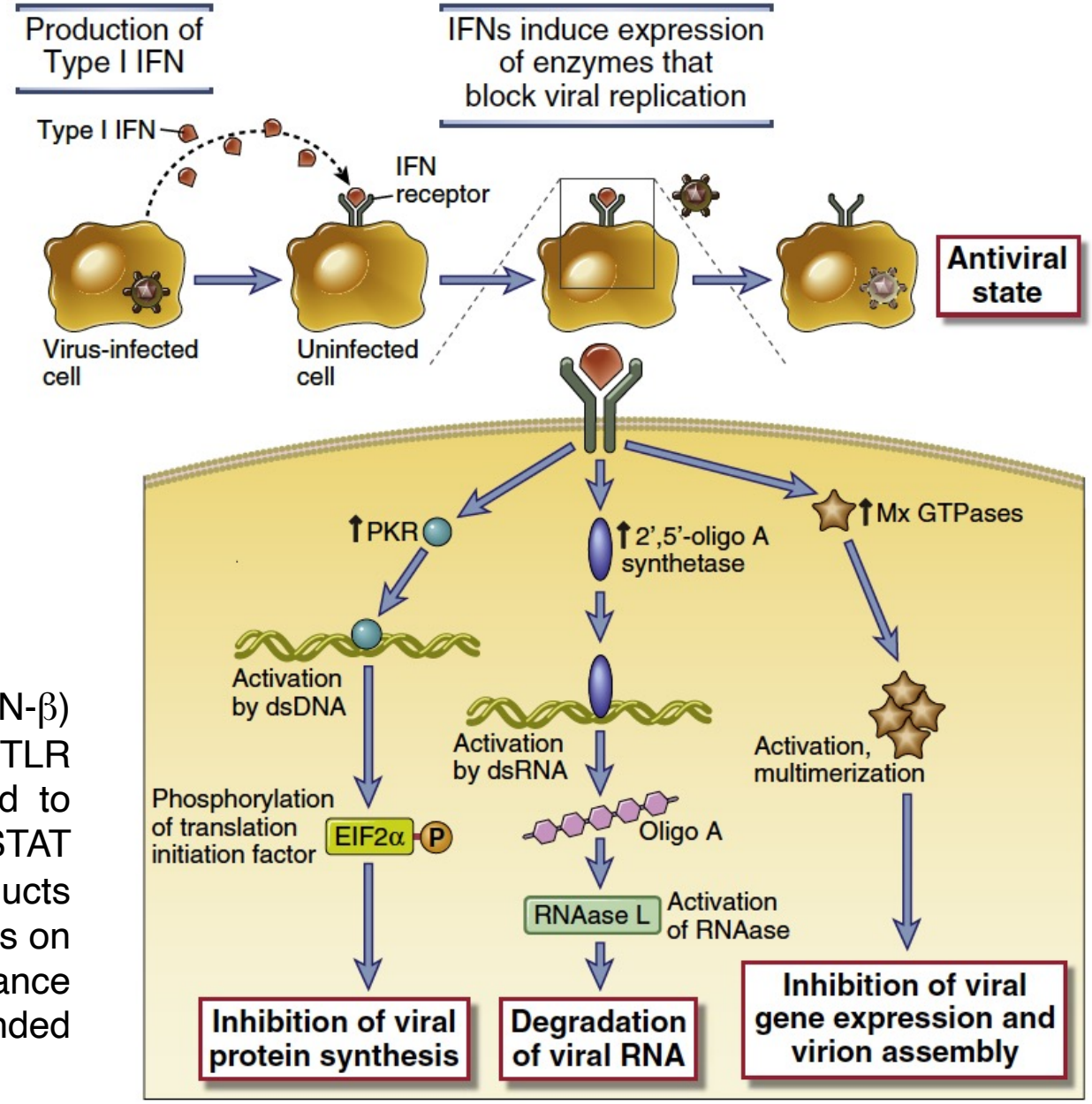
i. IFNs are host-coded proteins, or glycoproteins, produced in and secreted from virus-infected cells in response to virus infection, synthetic nucleotides, and foreign cells.
ii. IFNs bind to cell-surface receptors and induce antiviral proteins, including a protein kinase and 2',5' A synthetase (which synthesizes an oligoadenylic acid), leading to the destruction of viral mRNA.
iii. They are host specific but not viral specific.
iv. Three groups or families are recognized: IFN-α, IFN-β, and IFN-γ.
v. IFN-α (Intron-A) is licensed for treatment of chronic HBV and HCV infections and can produce adverse effects at high doses or with chronic therapy.
vi. They have toxic side effects, including bone marrow suppression.

Interferons



Mechanisms of induction of type I interferons by viruses. Viral nucleic acids and proteins are recognized by several cellular receptor families (TLRs, the family of cytosolic RIG-like receptors, or RLRs, which include MDA-5, RIG-I, DAI and others, and cytosolic DNA sensors), which activate transcription factors (the IRF proteins) that stimulate the production of type I interferons IFN-α and IFN-β.

Interferons



Biologic actions of type I interferons. Type I interferons (IFN-α, IFN-β) are produced by virus infected cells in response to intracellular TLR signaling and other sensors of viral RNA. Type I interferons bind to receptors on neighboring uninfected cells and activate JAK-STAT signaling pathways, which induce expression of genes whose products interfere with viral replication. Type I interferons also bind to receptors on infected cells and induce expression of genes whose products enhance the cell's susceptibility to CTL-mediated killing. PKR, double stranded RNA-activated protein kinase

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