GENETICS OF VIRUSES

Learning Outcome

Candidates should be able to:

Core Topic 3 – Genetics of Viruses and Bacteria

(a) Discuss whether viruses are living or non-living organisms and explain why viruses are obligate parasites.

(b) Describe the structural components of viruses.

(c) Describe the reproductive cycles of the following virus types:

  i. bacteriophages that reproduce via a lytic cycle, e.g. T4 phage;

  ii. bacteriophages that reproduce via a lysogenic cycle, e.g. lambda phage;

  iii. an enveloped virus, e.g. influenza;

  iv. retroviruses, e.g. HIV.

(d) Explain how viral infections cause disease in animals, e.g. mammals, through the disruption of host tissue and functions (e.g. HIV and T helper cells [details of the immune system are not required], influenza and epithelial cells of the respiratory tract).

Content Outline

1. Introduction
2. Definition of Life – Are Viruses Living or Non-living?
3. Structure of Viruses
   (a) Genome
   (b) Capsid
   (c) Envelope
4. Viral Reproductive Cycles
   (a) Reproductive cycle of bacteriophages, e.g. T4 phage, lambda phage
   (b) Reproductive cycle of enveloped viruses, e.g. influenza
   (c) Reproductive cycle of retroviruses, e.g. HIV
5. Viral Infections and Diseases
6. Course of HIV Infection in Humans

References

1. Campbell N. A. & Reece J.B. (2008). Biology. Chapter 19: Viruses. Eighth Edition. Pearson Education, Inc.
2. Brooker R.J. (2008). Biology. Chapter 18: Genetics of Bacteria and Viruses. International Edition. The McGraw-Hill Companies.

1. Introduction

All living organisms, either eukaryotes or prokaryotes, have nucleic acids which make up their genomes. Viruses possess nucleic acids but require the assistance of living cells to reproduce. As such, it becomes a debate as to whether viruses are living or non-living.

Viruses are **obligate parasites** as they can **reproduce only within a host cell as they lack organelles and metabolic enzymes necessary for protein synthesis and replication of the viral genome**. Thus, isolated viruses, i.e. **virions** (**infectious viral particles found outside a host cell**), are merely packaged sets of genes in transit from one host cell to another. In this topic, we will explore the structure of viruses, their reproductive cycles as well as the diseases caused by them.

2. Definition of Life – Are Viruses Living or Non-living?

It has been an ongoing debate in the scientific world as to whether the virus is a living organism or a non-living particle. The consensus is that life is a characteristic of organisms that exhibit all or most of the following phenomena:

- Organisation – Being structurally composed of one or more cells which are the basic units of life.
- Metabolism – Consumption of energy by converting chemicals into cellular components (anabolism) and decomposing organic matter (catabolism). Living things require energy to produce phenomena associated with life.
- Growth – A growing organism increases in size of all of its parts, rather than simply accumulating matter. The particular species begins to multiply and expand as the evolution continues to flourish.
- Homeostasis – The ability to regulate and maintain a constant internal environment.
- Adaptation – A population of living organisms has the ability to change over a period of time in response to the environment, an ability that is fundamental to the process of evolution.
- Response to stimuli – A response that can take on many forms from contraction of a unicellular organism to external chemicals to complex reactions involving senses of higher animals. A response is often expressed by motion for example the leaves of a plant turning towards the sun, otherwise known as phototropism.
- Reproduction – The ability to produce new organisms.

A virus is considered as a **living organism** as it is able to:

- **Reproduce**: It takes over the genetic machinery of its host cells to replicate more viral particles.
- **Adaptable**: Viruses have high mutation rates so as to have genetic variation and have a higher chance of survival in unfavourable environments.
- **Metabolism**: Viruses direct its host cells to provide the energy needed to produce more viral particles.

Yet, scientists have also argued that virus is **not a living organism** as it:

- **Does not grow or increase in size**. It merely replicates to produce more viruses in terms of numbers.
- **Is not a cell or composed of cells,** thus does not carry out metabolism on its own.
- **Does not have the ability to carry out homeostasis** since it usually contains no more than a genome in a protein coat.
- **Does not seem to have the ability to response to stimuli**, since it does not move on its own.

Therefore the answer as to whether viruses are living or non-living **remains inconclusive**.

3. Structure of Viruses

Viruses are **20 – 400nm** in diameter. For comparison, a typical bacterium is 1000nm in diameter and the diameter of most eukaryotic cells is 10 to 1000 times that of a bacterium. A ribosome has a diameter of about 20nm.

Viruses can differ in many aspects from host range (number of species and cell types that they can infect), types of genome and structural features. Thus, viruses have a wide variety of shapes. All viruses have a **genome** and **capsid** but can be categorized as **enveloped** or **non-enveloped**.

(a) Genome

The genome of a virus varies according to the type of virus:

- A virus is called a **DNA virus** or an **RNA virus**, depending on whether the genome consists of DNA or RNA respectively.
  - For viruses with RNA genome, they may possess either **positive-sense RNA** (i.e. identical to viral mRNA and thus can be immediately translated) or **negative-sense RNA** (i.e. complementary to viral mRNA and thus must be converted to positive-sense RNA by RNA polymerase before translation).
- The genome is usually organized as a **linear** or **circular** molecule of nucleic acid, depending on the type of virus.
- In some viruses, the nucleic acid is **single-stranded**, whereas in others, it is **double-stranded**.
- Some kinds of viruses **may have more than one copy of the genome**.
- Viral genomes also vary considerably in size, **ranging from a few thousand to more than a hundred thousand nucleotides in length**. Fewer genes have been related to a less complex viral structure:
  - The genomes of some simple viruses, such as phage Qβ are only a few thousand nucleotides in length and contain only a few genes.
  - Other viruses, particularly those with a complex structure, contain more genes. Phage T4 is an example of a complex virus having many genes. These extra genes are largely involved in the formation of the elaborate protein coat.

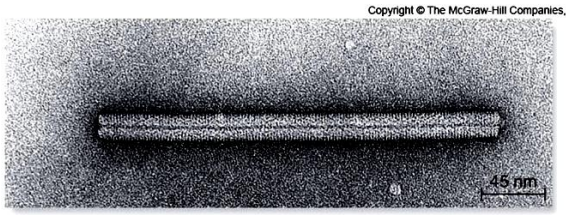
(b) Capsid

- The **capsid** is a **protein coat enclosing the viral genome**.
  - There is a **variety of shapes**, including helical and polyhedral.
  - Capsids are built from a large number of protein subunits called **capsomeres**.
- Some viruses carry a few viral enzyme molecules within their capsids.
- The most complex capsids are found among viruses that infect bacteria, called **bacteriophages** / **phages**.
  - The capsids of phages have elongated **icosahedral heads** enclosing their genome.
  - Attached to the head is a **tail shaft with fibres** that the phages use to **attach to a bacterial cell wall**.
- Generally, capsids serve to **protect the viral genome**.

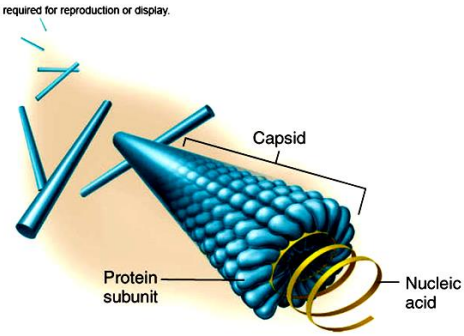
(c) Envelope

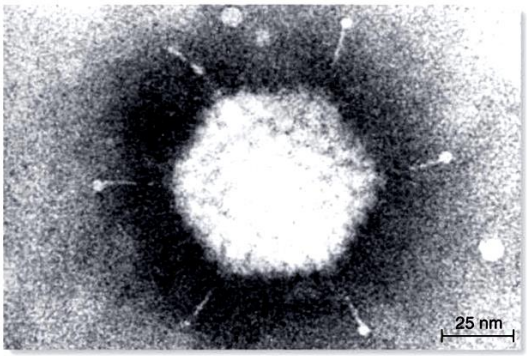
- The **viral envelope encloses the capsids of many viruses which infect animals**.
  - These viral envelopes comprise of:
    - **host cell phospholipids from the cell surface membrane of the host cell**
    - **embedded with virally encoded spike glycoproteins**
  - The viral envelope **protects the virion from enzymes and other chemicals**, giving them an advantage over capsid-only virions.
- Glycoproteins on viral envelopes **help viruses enter host cells by functioning as receptor molecules** – Virions recognize and bind to specific host cells, resulting in possible uptake of virion into cell.
- Each type of virus can infect only a limited host range. This **host specificity** results from the evolution of recognition systems by the virus, via a **"lock-and-key" fit between glycoproteins on the surface of the virus and specific receptor molecules on the surface of host cells.**
  - Some viruses have broad host ranges. West Nile virus, for example, can infect mosquitoes, birds, and humans.
  - Other viruses have very narrow host ranges of only a single species. For example, measles virus and polio virus can infect only humans.
  - Infection by viruses of higher eukaryotes is usually limited to specific tissues. Human influenza virus infects only epithelial cells lining the upper respiratory tract, and HIV binds to specific receptors on certain types of white blood cells (T cells).

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

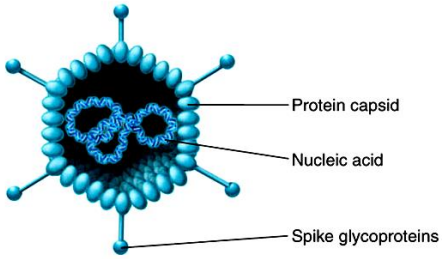


(a) Tobacco mosaic virus, a nonenveloped virus with a helical capsid

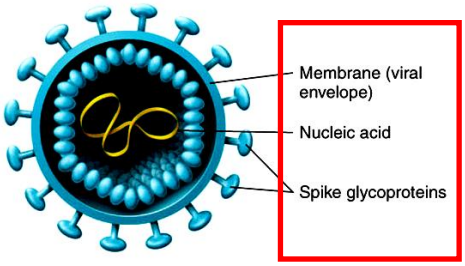


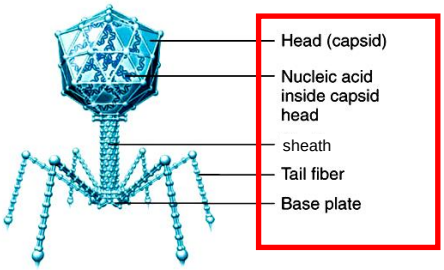


(b) Adenovirus, a nonenveloped virus with a polyhedral capsid



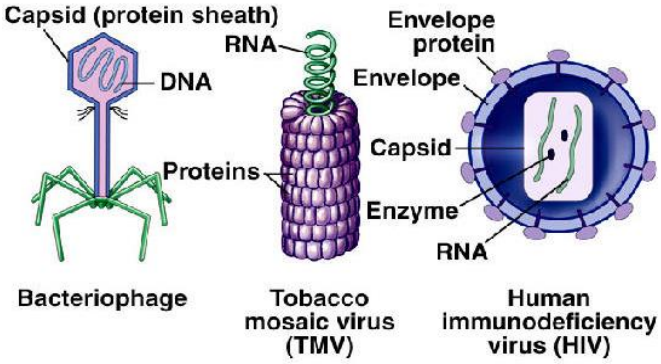
(c) Influenza virus, an enveloped virus with spikes





(d) T4, a bacteriophage

a: © Robley C. Williams/Biological Photo Service; b: Reprinted from Journal of Molecular Biology, 13, R.C. Valentine and H.G. Pereira, Antigens and Structure of the Adenovirus, 1965, with permission from Elsevier.; c:Chris Bjornberg/Photo Researchers, Inc.; d: © Omikron/Photo Researchers, Inc.



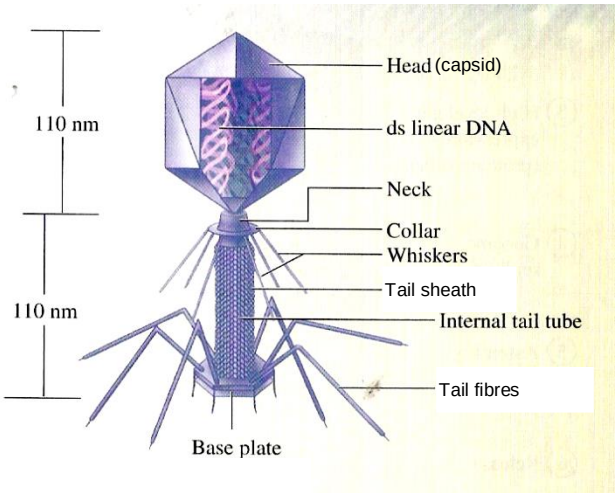
Non-enveloped virus	Enveloped virus

Examples of Viruses

(http://faculty.southwest.tn.edu/rburkett/classi16.jpg)

4. Viral Reproductive Cycles

(a) Reproductive cycle of bacteriophages (Lytic and Lysogenic Cycles)



Structure of T4 phage

(i) The Lytic Cycle (using T4 phage as an example)

- A phage reproductive cycle that **culminates the death of the host cell** is known as a **lytic cycle**. The bacterium lyses and releases the phages that were produced within the cell.
- **Phage T4** / **T4 phage** is a **virulent phage** (i.e. **a phage that reproduces only by lytic cycle**) with about 100 genes which are transcribed and translated using the host cell's machinery. The main steps of its reproductive cycle are as follows:
  - **Attachment / Adsorption:**
    - T4 phage uses its **tail fibres bind to specific receptor sites** on the outer surface of an *Escherichia coli* (host cell).
  - **Entry / Penetration:**
    - The **sheath of the tail contracts, injecting the phage DNA into the cell** and leaving the empty capsid outside.
  - **Synthesis of viral components:**
    - **The phage DNA directs synthesis of phage proteins and replication of phage DNA** by the host cell machinery.
    - One of the first phage genes expressed codes for an enzyme that **degrades the host cell's DNA**. The phage DNA is protected from degradation because it contains a modified form of cytosine that is not recognized by the enzyme.
  - **Viral assembly / Maturation:**
    - Phage components (head, tail and tail fibres) are **assembled** with the help of non-capsid proteins to form new phages.
    - The **phage DNA is packaged inside the capsid** as the head is being formed.
  - **Release:**
    - The phage directs **production of an enzyme called lysozyme that damages the bacterial cell wall, allowing fluid to enter**.
    - The host cell **swells** and **lyses**, releasing 100 to 200 new phages.

The Lytic Cycle

Schematic Representation of Synthesis of Viral Components and Assembly

5. Viral Infections and Diseases

The link between a viral infection and the symptoms it produces is often obscure. The **extent of damage a virus causes** depends partly on the **ability of the infected tissue to regenerate by cell division:**

- People can recover completely from influenza infections because the epithelium of the respiratory tract, which the viruses infect, can efficiently repair itself.
- Permanent damage is inflicted by polio virus to mature nerve cells as these cells do not divide and usually cannot be replaced.

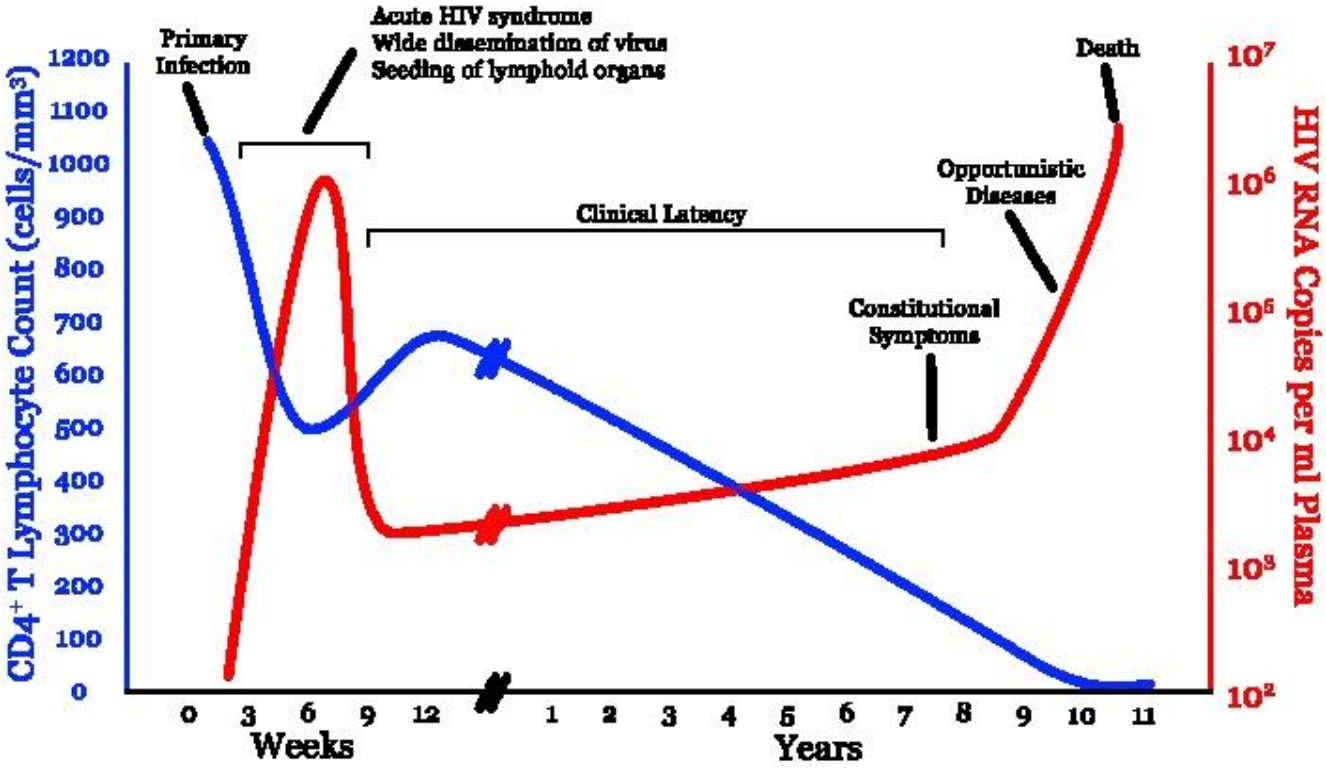
There are several mechanisms through which viral infections can cause diseases in animals:

- **Change in antigenic surface of host cell surface membrane**, resulting in it being **recognized as foreign and destroyed by the host's immune system**
  - HIV causes gp120 fragments to be exhibited on the cell surface membrane of infected helper T-cells, causing these T-cells to become targets for destruction by killer T-cells.
  - Helper T-cells, a type of white blood cell, play an important role in the immune system. The loss of helper T-cells caused the immune system to fail and thus unable to mount a response against foreign particles.
  - Influenza virus causes viral antigens to be exhibited on cell surface membrane of infected epithelial cells and causes the death of epithelial cells by necrosis and sloughing of the dead cells.
  - Respiratory epithelial cells are armed with cilia, mucus and antibodies for protection against bacterial infection. The loss of epithelial cells caused the person to be more susceptible to bacterial pneumonia.
- **Inhibition of expression of host cell's genes**
  - Adenovirus interferes with the transport of mRNAs from nucleus to cytoplasm.
  - Influenza virus cleaves the capped ends from cellular mRNA's causing them to be degraded by exonucleases.
  - Herpes virus also degrades host cell's mRNA's.
- **Inhibition of normal DNA, RNA or protein synthesis**
  - Poxvirus codes for a protein that degrades single-stranded DNA, disrupting host cell DNA synthesis by destroying DNA used as template at replication forks.
  - Herpes virus displaces host chromatin from its normal association with nuclear matrix proteins, inhibiting replication and transcription.
- Viral genome may be expressed in the host to **produce toxins that disrupts host organism's homeostatic mechanisms.**
  - Rotavirus produces toxins that cause severe diarrhoea in the host organism.
- Some viruses are **oncogenic**, causing normal cells to become malignant, resulting in **cancers**, e.g. Human papillomavirus and polyomavirus.
- **Trigger release of hydrolytic enzymes from host cell's lysosomes** leading to **lysis of infected host cells**
- **Depletion of host cell's cellular materials** e.g. amino acids, nucleotides, that are essential for normal functioning.

6. Course of HIV Infection in Humans

During the past decades, the most devastating example of an emerging virus has been **Human Immunodeficiency Virus (HIV)**, the causative agent of **Acquired Immune Deficiency Syndrome (AIDS).**

The process of HIV infection resulting in disease in human occurs in phases:



Course of HIV Infection in Humans

1. Window period

The window period is the **incubation period of HIV shortly after exposure to the virus**. It can range from as short as four weeks to as long as six months. During this period, **HIV replicates in the blood** of the infected individual but the **infected person exhibits no detectable physiological response**. Virus cannot be detected by laboratory tests to detect the HIV antigen during this period.

2. Acute primary infection phase

This takes place one to two weeks after the window period and patients can **experience flu-like symptoms**: fatigue, fever, headache and muscle aches caused by **large numbers of free HIV particles and decreasing number of $CD4^+$ T cells in the bloodstream** during this time. **Towards end of acute phase, the number of HIV particles in the blood declines**. Virus becomes **localized in the lymphatic system**.

3. **Asymptomatic phase**

Following the initial events of the acute phase, the **symptoms disappear** and the infected person becomes asymptomatic. This phase lasts on average eight to ten years. There is a **gradual decline in the number of helper T-cells** during this period. Some infected cells continue to produce HIV particles during this time, but the **immune system is still capable of managing the free viruses and the infected cells**. Due to the asymptomatic nature of this phase, few individuals realized that they are infected with HIV. Current anti-retroviral therapies have been shown to be successful in extending this phase in a bid to improve quality of life for infected patients.

4. **Symptomatic phase**

This phase is characterized by an **onset of immune suppression**. Eventually, the **immune system wears down and symptoms results from failure of immune system to defend against pathogens and direct attack by virus on host's cells**. Symptoms include fever, night sweats, weight loss and swelling of lymph nodes. The population of **helper T-cells diminishes**, so that the load of HIV particles is not cleared from the system.

5. **AIDS**

This phase lasts one to three years. The normal function of the T-cells is to direct the other cells of the immune system. When the T-cells are destroyed, the **entire immune system fails and opportunistic infections occur**. **Most patients die** within three years of prognosis.

Origins of Viruses

Viruses have been found to infect every form of life. As they depend on cells to reproduce, viruses are not descendants of precellular forms of life and have probably existed **after** living cells first evolved.

The origin of viruses is unclear because they do not form fossils so molecular techniques have been most useful means of investigating how they arose. There are however three main theories of the origin of viruses.

(a) Regressive theory

Viruses may have **once been small cells that parasitized larger cells**. Over time, genes are no longer required by them as they can depend on the host cells for survival. Their dependence on parasitism is likely to have caused the loss of genes that enabled them to survive outside a cell. This is also known as the **degeneracy theory**.

(b) Cellular origin theory

Some viruses may have evolved from bits of **DNA or RNA that "escaped" from the genes of a larger organism**. The escaped DNA could have come from plasmids or transposons. This is also known as the vagrancy theory.

(c) Co-evolution theory

Viruses may have evolved from complex molecules of protein and nucleic acid **at the same time as cells first appeared** on earth and would have been dependent on cellular life for millions of years.

Computer analysis of viral and host DNA sequences is giving a better understanding of the evolutionary relationships between different viruses and may help to identify the ancestors of modern viruses. To date, such analyses have not helped to decide on which of the theories are correct.

Evolution of Viruses

There are many different types of virus depending on the cells that they infect. It seems unlikely that all currently known viruses have a common ancestor. Thus it can be postulated that viruses have probably arisen numerous times in the past by one or more mechanisms. Viruses are therefore considered to be **polyphyletic** in origins i.e. having a number of **independent origins** almost certainly at **different times** from cellular organisms. Therefore, there is **no common ancestor**.

Viruses evolve together with their host. This would explain why viruses in the different types of hosts are generally so different as they have had a long period of time to adapt to each "life niche" since divergence from the respective common ancestor. Thus, bacteria / archaea and eukaryotes share no virus types, as they have been diverged so long.

Processes that Contribute to Emergence of Viral Diseases

(i) The **mutation of existing viruses** is a major source of these new diseases. RNA viruses tend to have an unusually high rate of mutation because errors in replicating their RNA genomes are not corrected by proofreading. Some mutations enable existing viruses to evolve into new strains that can cause disease in individuals who had developed immunity to the ancestral virus. Flu epidemics, for instance, are caused by new strains of influenza virus genetically different enough from earlier strains that people have little immunity to them.

(ii) **Existing viruses can spread from one host species to another**.

- e.g. hantavirus in rodents (especially deer mice). The population of deer mice in southwestern United States exploded in 1993 after unusually wet weather increased the rodents' food supply. Many people who inhaled dirt containing traces of urine and feces from infected mice become infected with hantavirus, and dozens died.
- e.g. SARS-causing virus started from southeast Asia in 2002 where people were infected with a flu virus that originated in bats and spread to humans either directly or through civet cats. If this coronavirus evolved so that it can spread easily from person to person, the potential for a major human outbreak is significant.

(iii) The **dissemination of a viral disease from a small isolated population** can lead to widespread epidemics.

- e.g. AIDS caused by HIV went unnamed and virtually unnoticed for decades before it began to spread around the world in the 1980s due to technological and social factors, such as affordable international travel, blood transfusions, sexual promiscuity, and the abuse of intravenous drugs.

(iv) **Changes in host behaviour or environmental changes can increase the viral traffic** responsible for emerging diseases.

- e.g. new roads through remote areas can allow viruses to spread between previously isolated human populations.
- e.g. destruction of forests to expand cropland brings humans into contact with other animals that may host viruses capable of infecting humans.

Use of Vaccines

Many of the temporary symptoms associated with viral infections such as fever and aches, actually result from the body's own efforts at defending itself against infection. The immune system is a complex and critical part of the body's natural defenses. The immune system is also the base for the major medical tool for preventing viral infections, i.e. **vaccines**.

(i) Vaccines are **harmless variants or derivatives of pathogenic microbes that stimulate the immune system to mount defenses against the actual pathogen**.

(ii) The viruses that cause smallpox, polio, and measles infect only humans. This very narrow host range has allowed for the eradication of smallpox. The World Health Organization is also currently campaigning to eradicate the viruses that cause polio and measles as well.

(iii) There are also effective vaccines against rubella, mumps, hepatitis B, and a number of other viral diseases.

Although vaccines can prevent certain viral illnesses, medical technology can hardly do much to cure viral infections.

(i) Antibiotics kill bacteria by inhibiting specific enzyme-catalyzed processes, but viruses have few or no enzymes of their own. Thus, antibiotics are powerless against viruses. However, a few drugs effectively combat certain viruses.

(ii) Most antiviral drugs resemble nucleosides and thus **interfere with viral nucleic acid synthesis**.

- e.g. acyclovir impedes herpes virus reproduction by inhibiting the viral polymerase that synthesizes viral DNA.
- e.g. azidothymidine (AZT) curbs HIV reproduction by interfering with the synthesis of DNA by reverse transcriptase.

(iii) Currently, multi-drug treatments, known as "cocktails", have been found to be most effective against HIV. Such a regimen commonly includes a combination of two nucleoside mimics and a protease inhibitor, which interferes with an enzyme required for assembly of virus particles. It is also less likely that any mutant strain will overcome all of the inhibitory effects.