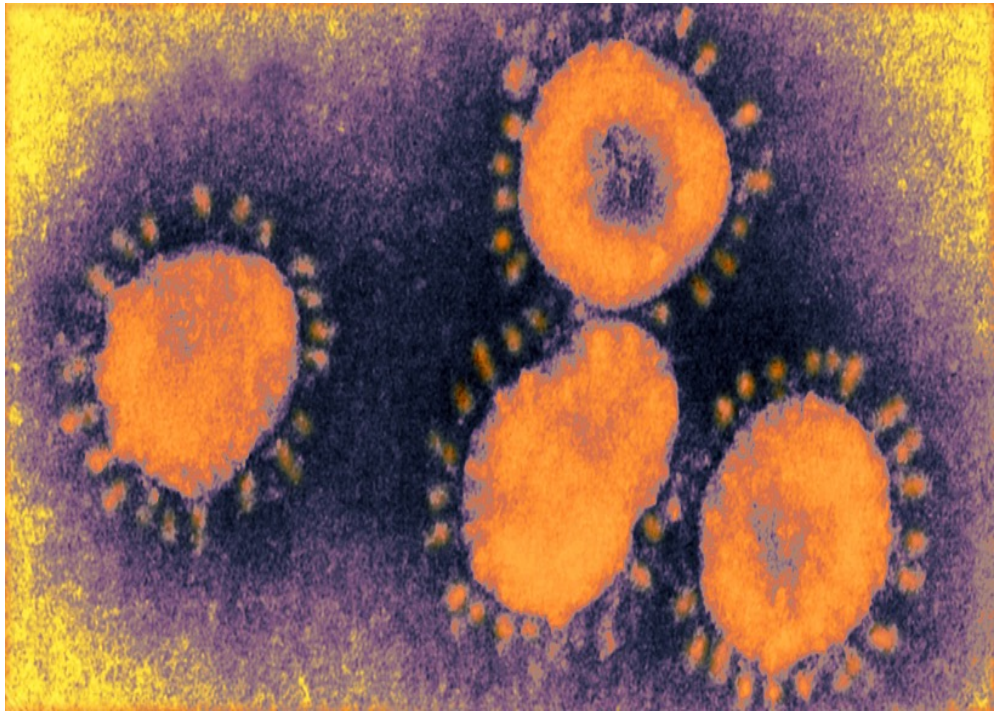
What is a virus?

- Viruses are infectious microscopic obligate parasites, which hijack a host cell for almost all their life-sustaining functions, including energy generation, since they cannot generate or store energy.
- They are the most widespread of all pathogens, capable of infecting all mammals, insects, plants, protozoa and even bacteria. Many viruses are not pathogenic.
- Only the largest and most complex viruses can be seen under a light microscope at the highest resolution; all others require an electron microscope, which is how they were first observ.ed in the 1940s.
- Viruses are some of the oldest micro-organisms, possibly 4 billion years old, and may have a bacterial origin.
- Most viruses vary in diameter from 20-400 nanometres (nm), however giant viruses (the mimiviruses) measure about 500 nm in diameter and can be 700–1,000 nm in length, larger than bacteria. Most viruses are 1% of the size of most bacteria.
- Many animal and plant species have their own specific viruses. Cats have the feline immunodeficiency virus or FIV, a cat version of HIV, which causes AIDS in humans.



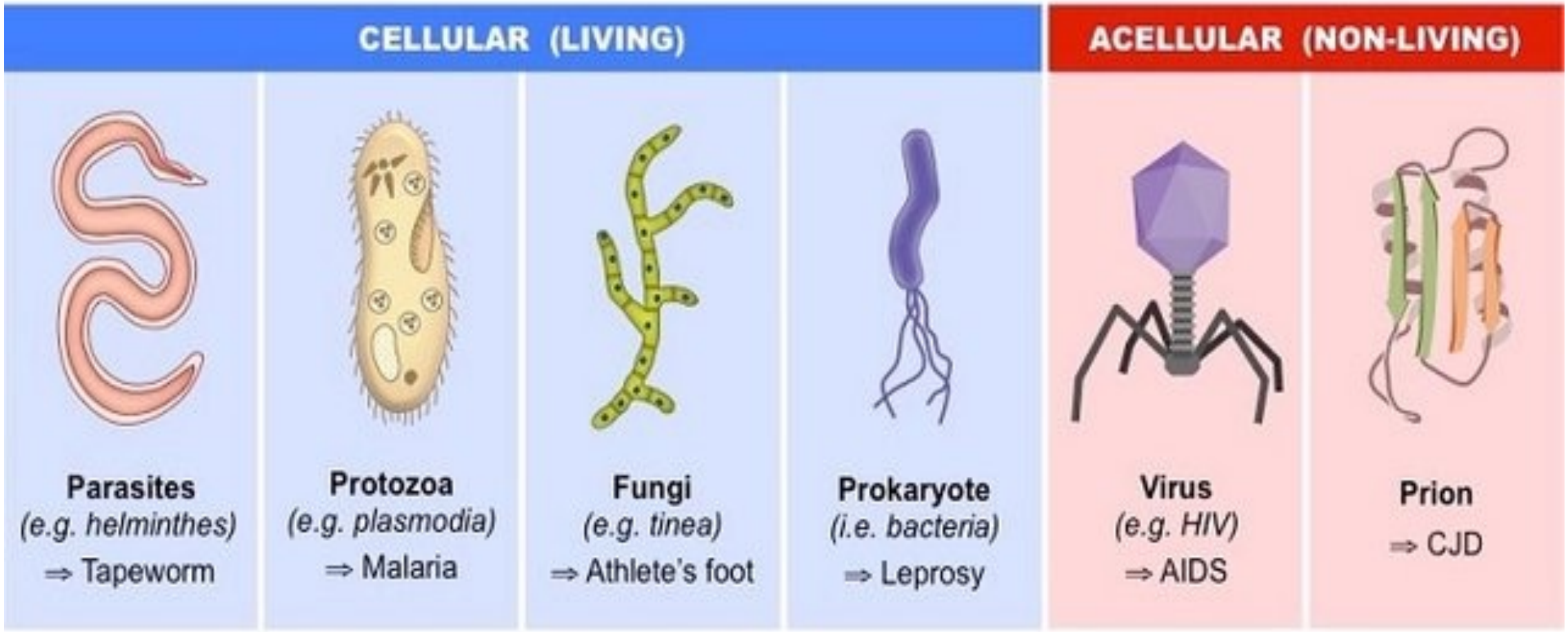
Human coronavirus 229E, magnified to x60,000 via negative contrast electron microscopy

https://www.microscope.com/education-center/articles/coronavirus-under-an-electron-microscope

- P172. Superspreading events during the SARS outbreak in which certain individuals infected unusually large number of secondary cases i.e. greater than R0 which is an average. If superspreaders exist and can be identified and isolated, draconian control measures are not needed for the remaining population.
- P263. Scientific opinion is divided over whether viruses are alive. They have been described as ‘mechanistic shortcuts on the principle of life itself’. Certainly they are parasitic. They compete, attack, evade, struggle to survive and multiply. They mutate and evolve.
- P267. You cannot culture a virus in chemical nutrients because they will only replicate inside a living cell. Its genome is simplified down to the bare necessities for an opportunistic dependent existence (nor more than 1.2 million nucleotides cf a mouse with 3 billion). It doesn’t contain its own reproductive machinery. It steals.
- P268. A virus has been described by Macfarlane Burnet as “ a piece of bad news wrapped up in a protein”. The protein wrap is called the capsid; it protects the virus as a shell and facilitates entry into host cells.
- P290. 2 factors determine whether an epidemic ensues or a more local infection that dies out: transmissibility and virulence.
- Transmissibility is the degree to which the virus can travel from one host to another and depends upon how the virus is expelled from its current host, how long it survives without a host, how easily it is taken up by a new host. SARS-CoV-2 is highly transmissible but is Ebola or HIV-1 were as transmissible we would probably be dead by now.
- Virulence is the severity of the disease.
- P307. Most emerging pathogens are RNA viruses. They are also highly adaptable, replicate faster and mutate faster. They produce acute infections, which are over quickly or they kill you. There is lots of viral shedding with an acute infection (sneezing, coughing, vomiting) which facilitates transmission.
- P391. Retroviruses: Instead of using RNA as a template for translating DNA into proteins, retroviruses convert its RNA into double-stranded DNA within a host cell. This viral DNA then penetrates the host cell nucleus and becomes integrated into the genome of the host. So whenever the host cell replicates, the virus will also replicate at the same time. It cannot be eradicated.
- P503. Seasonal flu causes at least 3 million cases and more than 250,000 fatalities worldwide.
- P506. RNA viruses have a high rate of mutation with minimal quality control and risk of ‘reassortment’. This is the accidental swapping of entire genomic sequences between virions of 2 different subtypes. Sometimes this makes the virus less viable but sometimes it makes it more transmissible and virulent. The continual evolution of a virus is why different flu shots are needed each year.
- P519. The transmission of SARS seems to depend much on superspreaders.

- https://www.bbc.com/future/article/20200617-what-if-all-viruses-disappeared

Viruses and other human microorganisms



Viroids are virus-like infectious organisms that contain only nucleic acid and have no structural proteins.
Prions are composed of misfolded structural proteins with no nucleic acids; prions transmit their misfolded shape onto normal variants of the same protein, making them 'infectious'.

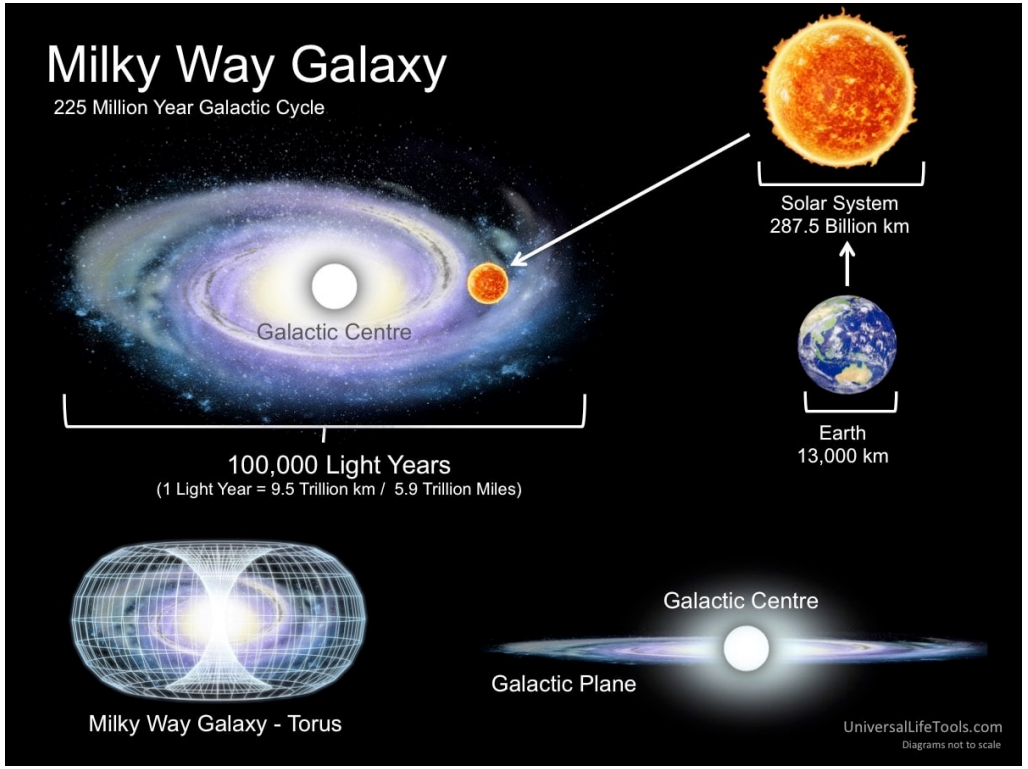
Some differences between viruses and bacteria

- Bacteria are larger than viruses and can replicate independently. Viruses cannot survive or replicate without a host.
- Bacteria can be killed by antibiotics (unless antibiotic resistance develops); antibiotics cannot kill viruses. This can create problems for doctors as viral and bacterial infections can cause similar symptoms.
- There are very few anti-viral drugs and most are highly specific. This is why it appeared to be difficult to treat COVID-19.
- Generally 15% of the human microbiome, principally in the gut, is viral, with the bacteria providing the host cell. These bacterial viruses are called bacteriophages and can infect bacteria in the same way as they infect humans, to survive and replicate. Bacteria cannot infect viruses.
- Interestingly, modified bacteriophages are being studied as a possible replacement for antibiotics since they are capable of inserting themselves inside a bacterium.

(Almand EA, Viruses, 2017)

How many different viruses exist?

- Viruses are the most common biological entities on Earth and also one of the oldest.
- It's impossible to know just how many types of viruses exist in the natural world.
- Rough estimates suggest there could be as many as 100 million types of virus on Earth's surface; if they were all lined up, they would stretch from one side of the galaxy to the other.
- As of January 2021, the NCBI Virus genome database has more than 193,000 complete genome sequences but undoubtedly there are many more to be discovered (https://www.ncbi.nlm.nih.gov/labs/virus/vssi/#/).



Examples of common human viruses

- Viral Respiratory Infections
- Respiratory syncytial virus (RSV)
- Adenovirus
- Rhinovirus (common cold)
- Influenza (the flu)
- Severe acute respiratory syndrome (SARS)
- Coronaviruses e.g SARS-CoV-2 (COVID-19)

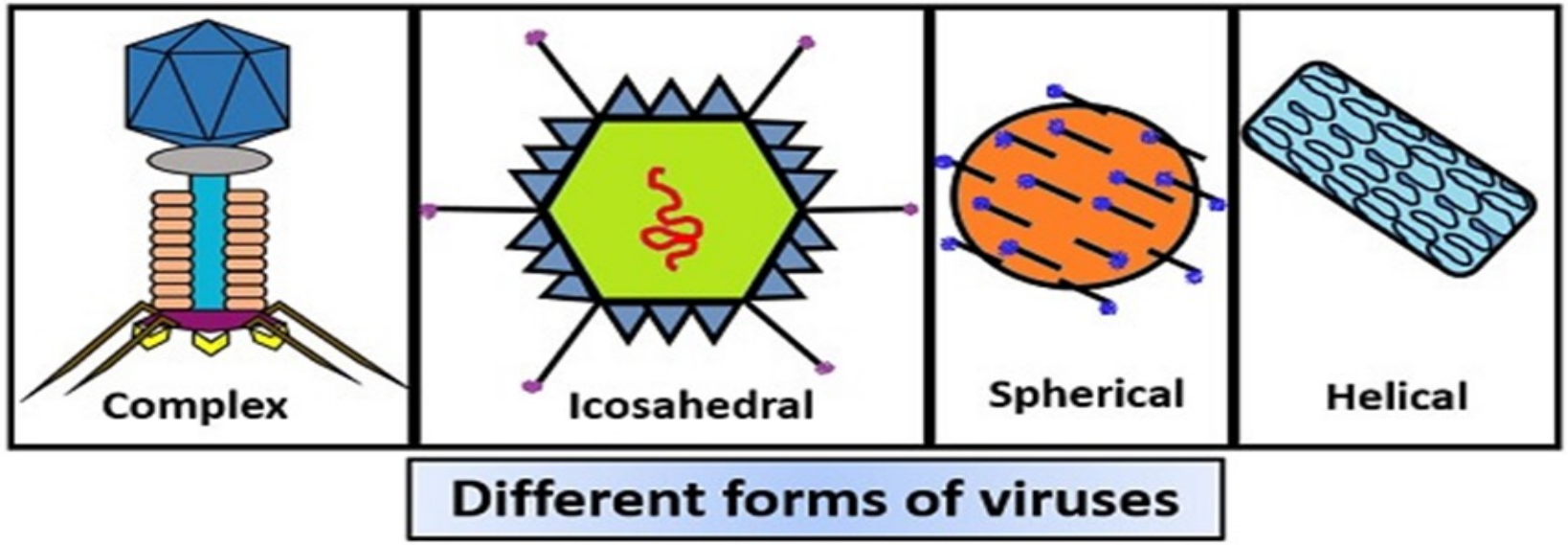
- Viral Infections With Skin Rashes
- Measles
- Rubella
- Varicella (chicken pox and shingles)
- Roseola

- Viral Sexually Transmitted Infections
- Hepatitis B
- Herpes simplex virus
- Human immunodeficiency virus (HIV)
- Human papillomavirus (HPV)

- Other Viral Infections
- Norovirus (stomach flu)6
- Viral hepatitis7

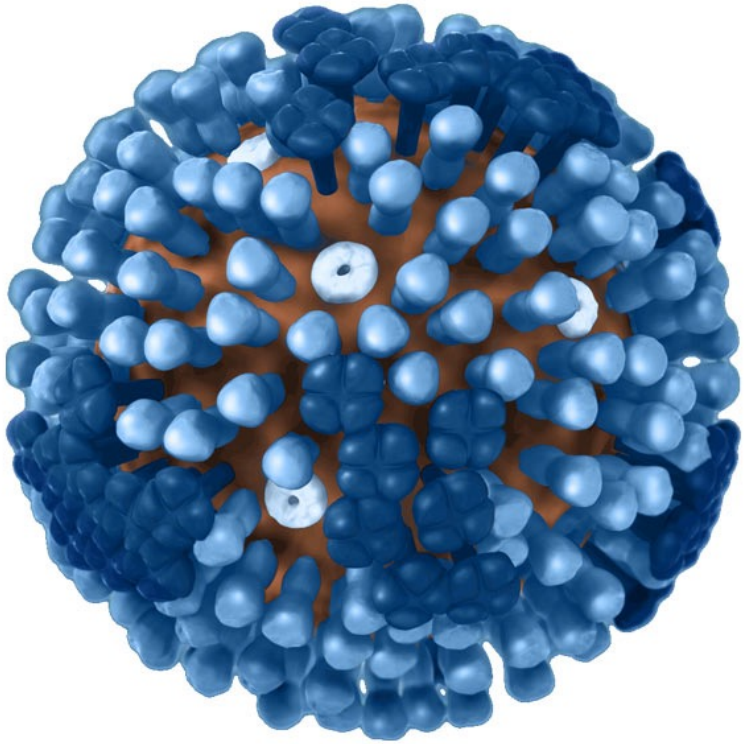
What shape is a virus?

- Virus shapes are usually rods (helical) or filaments (spheres).
- However, bacteriophages (larger and more complex viruses that infect bacteria) have a geometric head and filamentous tail fibers and, uniquely among viruses, contain double-stranded DNA.

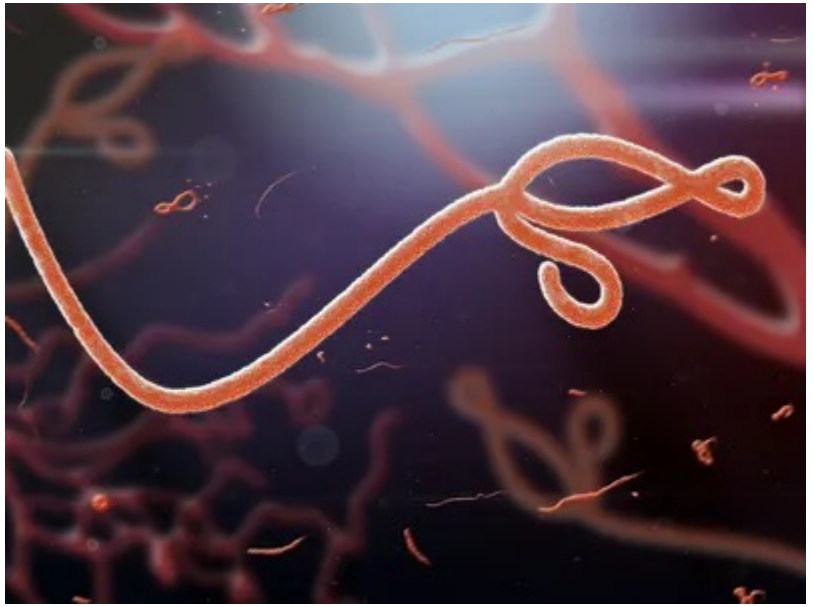


What do viruses look like?

Influenza virus



Ebola virus



Are viruses alive?

- As with mitochondria, which are ‘dependently alive’ (my definition) because they do not have a nucleus and cannot exist outside the host cell, so the same can be said for viruses, which are inert until they infect a living cell.
- Viruses depend upon a host cell for almost all of their life-sustaining functions such as protein synthesis, often used as the marker of ‘life’. Although viruses have genes, they do not have a cellular structure and cannot reproduce or capture or store energy themselves without a host cell. Possible exceptions are the giant bacteria-like viruses (bacteriophages), which contain components for protein synthesis.
- As such, scientists believe it is accurate to think of viruses as part of the continuum between living and non-living. They have been described as being ‘on the edge of life’.
- Philosophers say it is all down to how we define ‘life’. Generally, this is believed to be the condition that distinguishes animals and plants from inorganic matter, including the capacity for growth, reproduction, functional activity and continual change prior to death. But even if not strictly ‘alive’, viruses are certainly not inert or inorganic matter!
- There is a vigorous online debate about this! Opposing views are neatly encapsulated here https://microbiologysociety.org/publication/past-issues/what-is-life/article/are-viruses-alive-what-is-life.html.

(Rybicki EP (1990). "The classification of organisms at the edge of life, or problems with virus systematics". South African Journal of Science. 86: 182–86; Koonin EV, Starokadomskyy P. Are viruses alive? The replicator paradigm sheds decisive light on an old but misguided question. Stud Hist Philos Biol Biomed Sci. 2016 Oct;59:125-34)

Viruses in the human body

- It is estimated that >380 trillion viruses inhabit the healthy human body (https://www.inverse.com/science/gorgeous-galaxy-image-hubble-webb-mashup).
- What determines whether the potentially pathogenic viruses actually become pathogenic?
- The terrain (see Rachel Nicoll article: https://countrysquire.co.uk/2022/09/21/response-to-roger-watsons-article-terrain-theory-terrorists/).

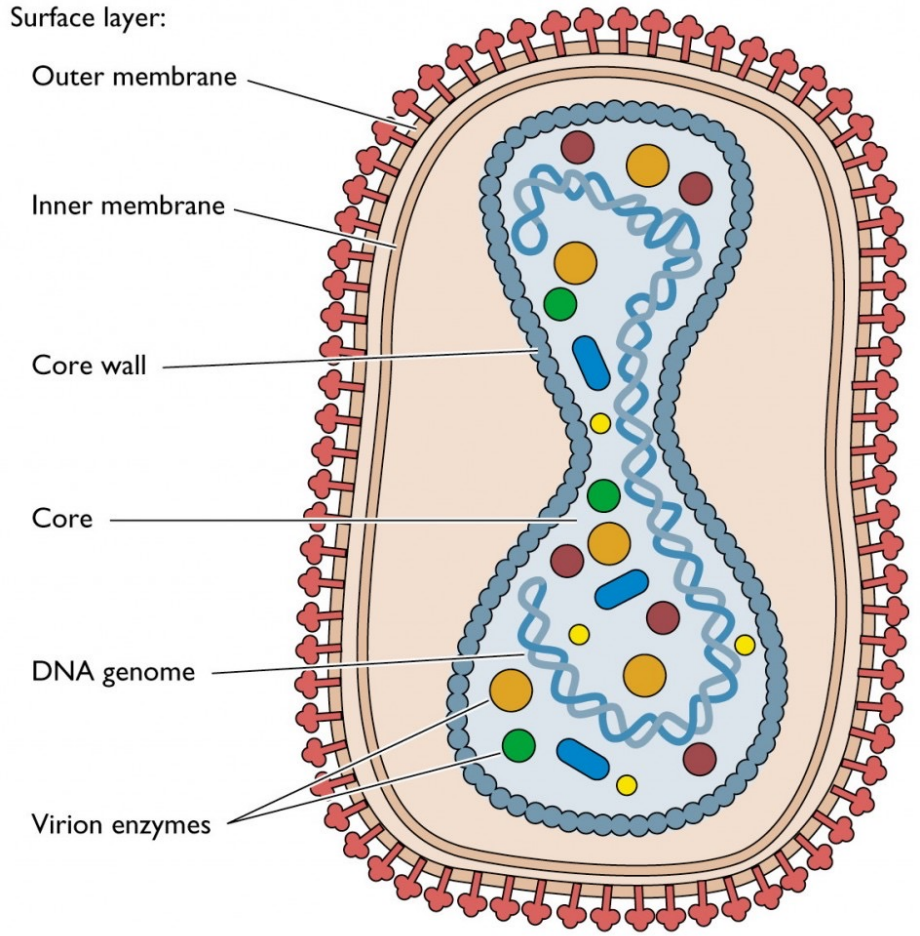
Viruses are ever-present in our body and surroundings

- Respiratory viruses do not need to seek us out; they are there in our nose and throat waiting for a chance to enter a cell. It is the terrain (which includes the power of our immune system) that determines whether we succumb to a virus or not.
- In principal, cold and damp conditions are favourable for respiratory viruses, as is dry heated air. But some viruses are exceptions.
- Influenza viruses strike in the winter and may be a different variant each season. This is why the flu vaccine is unlikely to work well – because it is always priming us with last winter's virus, which may have no bearing on this winter's virus.

Virus structure

- Viruses are made up of either DNA or RNA (never both), the DNA or RNA represents the viral genome, enclosed in a protein coat (capsid). They have been described as ‘mobile genes’.
- Viruses lack the capacity to independently read and act upon the information contained within these nucleic acids. They depend entirely on the host cell to facilitate their metabolism and replication.
- Viruses may also be enclosed by a lipoprotein ‘envelope’, which enables the virus to survive for a short while outside the cell. This means it may not kill its host cell when it leaves but makes the virus harder to kill.
- SARS-CoV-2 is an RNA virus with a lipoprotein envelope.

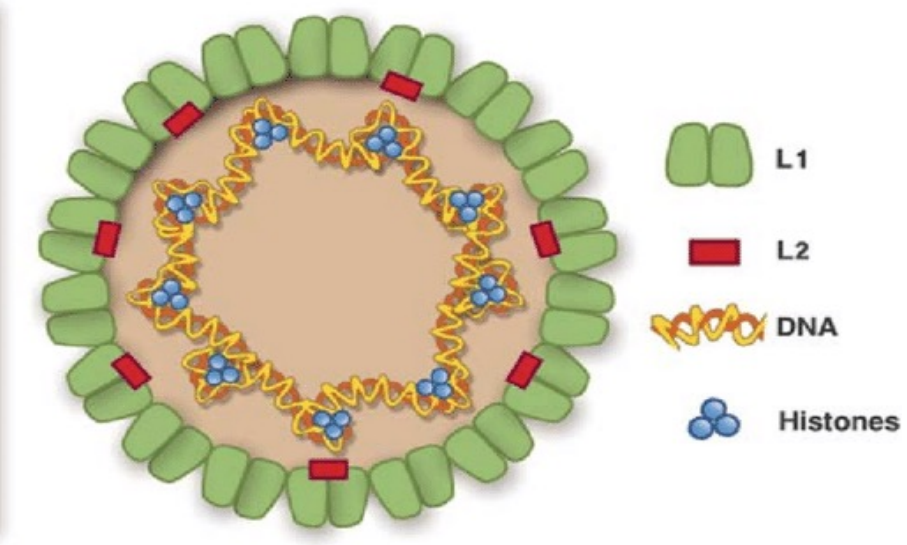
(www.livescience.com)

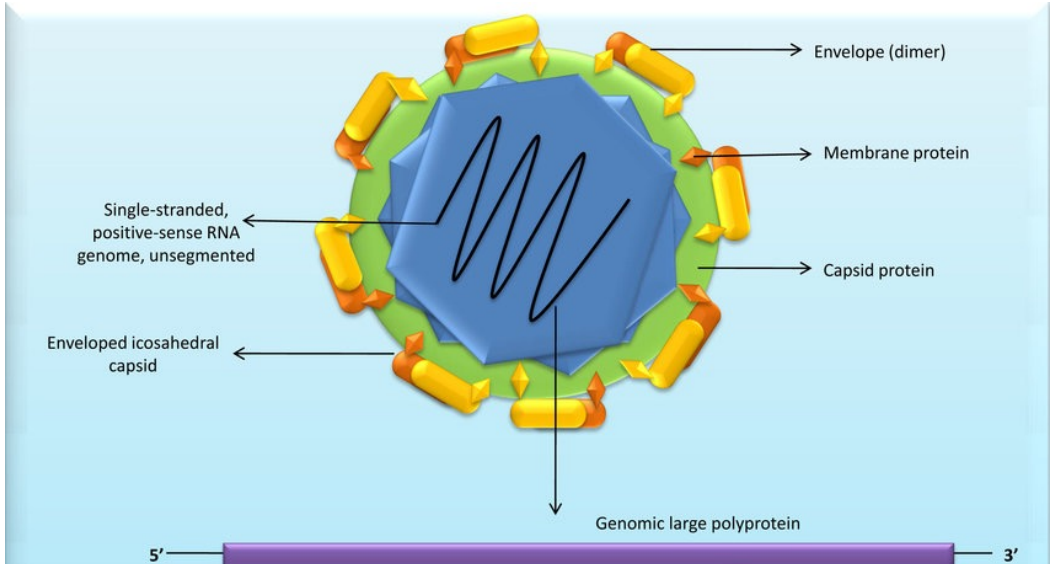


Virus structure – viral genome

- A virus consists of short sequences of nucleic acid, either DNA (deoxyribonucleic acid) or RNA (ribonucleic acid), which form the viral genetic material, encoding the genetic information unique for each virus.
- RNA viruses are more complex than DNA viruses and have a high mutation rate, giving them a unique evolutionary capacity.
- As compared to most other organisms, where DNA is always a double-stranded structure, viruses are unique because their DNA or RNA material can be either single-stranded (ss), double-stranded (ds) or partially ds. Furthermore, ss viruses will also be classified as to whether they are positive ss, negative ss, or negative with ambisense viruses, depending on if they are complementary to the viral messenger RNA (mRNA).
- The vast majority of viruses that infect humans, including SARS-CoV-2 and influenza, have single strand RNA genomes. These include nine negative ssRNA and eight positive ssRNA virus families. Smallpox and herpes are DNA viruses.
- Single stranded RNA viruses can mutate rapidly and are far more flexible than double stranded viruses.
- The amount and arrangement of the viral proteins and nucleic acid determine their size and shape and are unique for each class of virus. The number of genes in each virus can range from 0 – 2,500; by comparison, humans have 20,500 genes, possibly only 8 times more! (https://www.geneticsdigest.com/how-many-genes-do-humans-have/)

Viral genomes may be circular or linear





Human papilloma virus with circular DNA

Zika virus with linear single strand RNA

Note: Bacteria and mitochondria (because they are derived from bacteria) also have circular DNA

Viral genome size

- Genome size varies; some of the largest can be over a million base pairs long, while an RNA virus that infects bacteria (MS2), has barely 3,500 base pairs.
- In general, RNA viruses have smaller genome sizes than DNA viruses because of a higher error-rate when replicating, and have a maximum upper size limit
- Genome size varies greatly between species. The smallest, the ssDNA circoviruses, code for only two proteins and has a genome size of only two kilobases. The largest, the pandoraviruses, have genome sizes of around two megabases which code for about 2500 proteins.
- Some viral genomes have been found to be between 40-50 million years old.

(Belyi VA, Levine AJ, Skalka AM. Sequences from ancestral single-stranded DNA viruses in vertebrate genomes: the parvoviridae and circoviridae are more than 40 to 50 million years old. J Virol. 2010 Dec;84(23):12458-62; Philippe N, Legendre M, Doutre G, Couté Y, Poirot O, Lescot M, Arslan D, Seltzer V, Bertaux L, Bruley C, Garin J, Claverie JM, Abergel C. Pandoraviruses: amoeba viruses with genomes up to 2.5 Mb reaching that of parasitic eukaryotes. Science. 2013 Jul 19;341(6143):281-6)

Who is the smartest of us all (based on number of genes in the genome)?

- The genome of the humble banana has >36,000 genes (c.f. humans with 20,500). (D'Hont A, et al. The banana (Musa acuminata) genome and the evolution of monocotyledonous plants. Nature. 2012 Aug 9;488(7410):213-7)

- And bananas and humans share >60% of their DNA!

Viral structure - capsid

- The protein shell (capsid) surrounds the nucleic acid which protects it from digestion by enzymes (nucleases) and provides sites on its surface that recognise and attach the virion to receptors on the surface of the host cell.
- In some viruses, the capsid provides proteins to enable the virion to penetrate through the cell surface membrane or to inject the infectious nucleic acid into the interior of the host cell.
- Certain viruses also have other proteins internal to the capsid; some of these proteins act as enzymes, often during the synthesis of viral nucleic acids.

Viral structure – the lipoprotein envelope

- Viruses may be enclosed by a lipoprotein membrane known as an envelope, derived from the host cell membrane as it exits the cell, a process known as ‘budding’. This makes the virus more difficult to kill.
- The envelope enables the virus to survive outside the cell, long enough to enter the bloodstream and find a replacement host. This makes the virus potentially far more dangerous. Non-enveloped viruses can only infect neighbouring cells.
- A virus that is located outside a host cell is known as a virion, an independent, inactive particle that moves through the environment, infecting other organisms. Only once they are incorporated into a host cell do viruses take on living characteristics of their own, borrowing the host's biochemistry to reproduce.
- An enveloped virus (unlike a non-enveloped virus) leaves a host cell without destroying it.

Virus classification

- Viruses are classified by whether they are DNA or RNA viruses, the strandedness (double or single) of their genetic material and whether or not they possess a lipoprotein envelope outside their protein coat.
- SARS-CoV-2 and influenza are single-stranded RNA viruses with a lipoprotein envelope, representing the worst of all possible worlds (they are complex, mutate easily, highly adaptable and can survive outside the cell)!
- A virus with single- or double-stranded RNA as its genetic material is known as an RNA virus. RNA viruses use virally encoded RNA-dependent RNA polymerase (RdRp) to reproduce their genomes. The RNA genome serves as a template for the creation of new RNA strands.
- At least three types of RNA must be created during RNA virus replication: the genome, a copy of the genome and messenger RNAs (mRNAs). Rapid environmental changes, such as changes in the pharmacological challenge or immunological pressure, force RNA viruses to have a variety of evolutionary techniques that let them adapt quickly to their surroundings.

Viral strategy

- Although viruses differ considerably, they all have the one objective: to make viral proteins and more copies of the viral genome (DNA or RNA) to perpetuate the viral strain. Consequently, they are continually in search of host cells.
- Once the virus enters the cell, the viral genome is released into the host cell cytoplasm, hijacking the cell replication machinery and mounting a complex program of viral gene expression, which is highly regulated. Effectively, viruses reprogramme the host cell to allow the virus to reproduce many times over.
- The newly made viruses then burst out of the cell, sometimes killing it, and go on to infect neighbouring cells. However, because the virus perpetually needs host cells, it must avoid killing too many in each host. Mutually assured destruction is not in the best interests of the virus!
- At various stages in its journey through the body, the virus is liable to attack by the immune system but in some people, their strong immune defences are enough to prevent symptoms and illness. However, viruses have evolved some clever defences and will select the shortest and fastest means of replication in order to avoid detection and attack by the immune system.
- Viruses have developed means of distributing replicated virus particles or transmission, known as ‘viral shedding’. For example, the rhinovirus (a virus which causes the common cold) infects cells in the nasal cavity, tickling the nerve endings to cause sneezing. Sneezing causes large numbers of viroid-containing mucous droplets to be forcefully ejected, which will float in the air until inhaled by potential hosts.
- Viruses may also carry out lateral (horizontal) gene transfer, whereby genes can be removed from the cell genome and taken out of the cell, or genes can be introduced to the cell genome from outside the cell through infection.

Viral immune system evasion tactics

Viruses have evolved clever defences to trick the immune system into ignoring it or thinking it is a part of ourselves:

- disruption of the interferon signalling pathway,
- pattern recognition receptor evasion,
- nucleic acid shielding,
- remodelling the cellular architecture,
- targeted gene silencing,
- recognition protein cleavage
- repeatedly mutating to change its surface molecules (‘antigenic drift’).

Viral longterm survival

- Viruses are very persistent. They may survive in a ‘latent state’ in viral reservoirs and are kept under control by the immune system. However, in immune deficiency the virus may be reactivated to cause a second infection. These particularly include the herpes viruses but also HIV, hepatitis B and C, Zika virus and Ebola.
- Alternatively, viruses may be integrated into the genome of the host cell (e.g. HIV, hepatitis), so that each time the host cells replicate, the virus’s genetic material is replicated as well, spreading its genetic information throughout the host. Integration into the host genome may take place using the enzyme reverse transcriptase, as with HIV, but there are other mechanisms as well. In the host genome, the virus is known as a ‘provirus’.

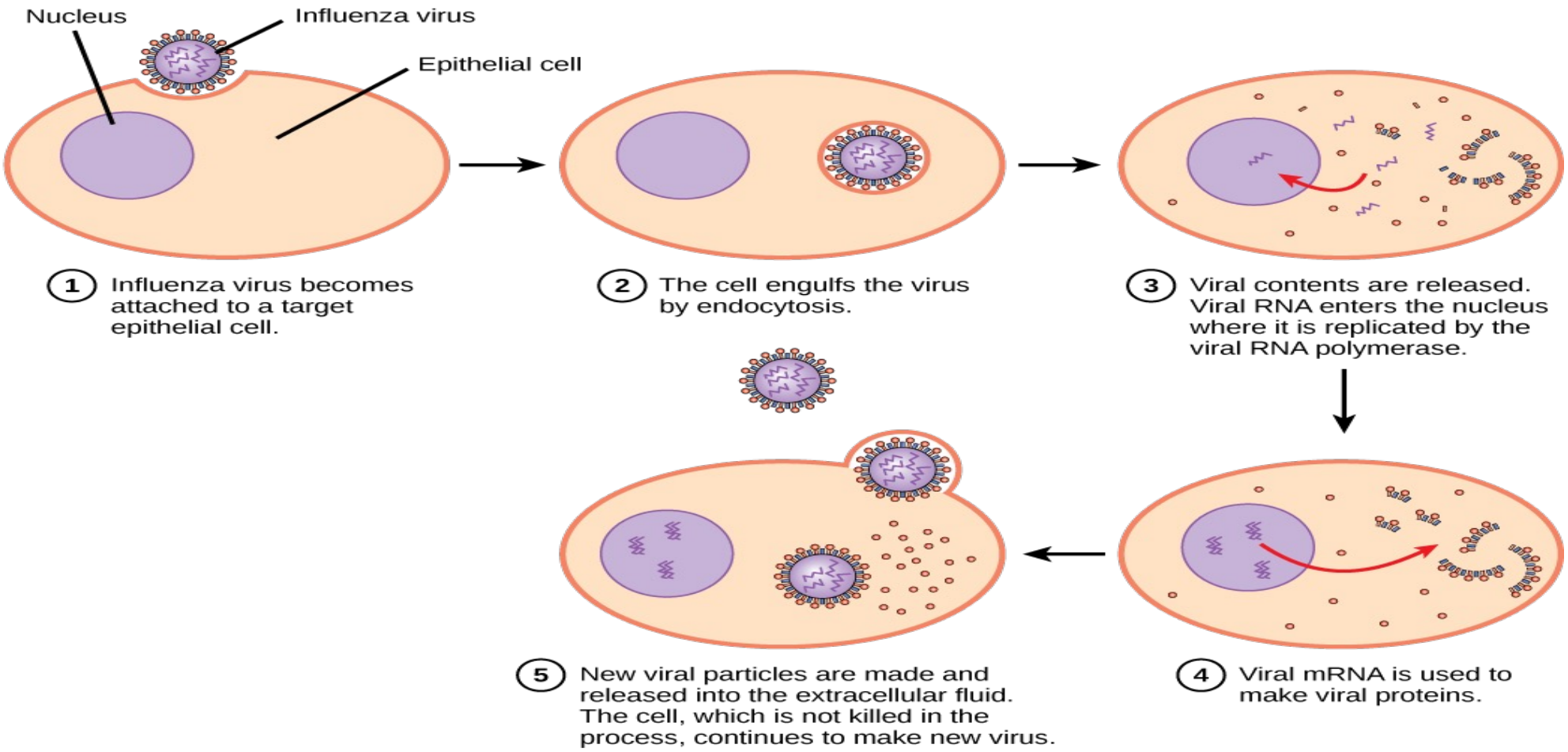
How viruses enter cells

- The outer surface of the virion (invading virus) contains certain proteins that can recognise and bind to cell surface receptors to facilitate attachment to the host cell.
- These are known virus/receptor pairs:
  - Coronaviruses and the angiotensin-converting enzyme 2 (ACE2) receptor
  - Influenza and sialic acid-containing cell-surface receptors which bind with the fusion protein haemagglutinin
  - Human immunodeficiency virus (HIV) and the CD4 molecule on T lymphocytes and macrophages
  - Epstein Barr virus (EBV) and the complement receptor CR2 on B lymphocytes
- Then the virus either:
  - Injects the genetic material of the virus into the interior of the cell while the protein capsid (and envelope, if present) remains at the cell surface, or
  - Penetrates the outer host cell membrane and enters the cell's interior (cytoplasm) through membrane fusion or endocytosis, forming a vesicle which fuses with cytoplasmic endosomes. The enzymes of lysosomes then facilitate release of the viral capsid into the cytoplasm.
- Endocytosis: The material to be taken into the cell is surrounded by an area of cell membrane, which then buds off inside the cell to form a vesicle containing the ingested material. Endocytosis, which includes pinocytosis and phagocytosis, is a form of active transport.
- In the case of whole-virion penetration, the virus will remove its viral capsid ('uncoating') generally through the action of enzymes, thereby releasing its genetic material into the cytoplasm for replication.

Viral replication

- Viruses reprogramme the host cell to allow the virus to reproduce many times over.
- To do this, the viral nucleic acid, whether RNA or DNA, encodes the genetic information for the synthesis of all viral proteins, either directly or through the action of RNA polymerase, and using the nucleotides and amino acids of the host cell. Some viruses also use the lipids and sugar chains of the host cell to form their membranes and glycoproteins (proteins linked to short polymers consisting of several sugars).
- DNA viruses must use the host cell's RNA polymerase to make mRNA, while RNA viruses (such as influenza and SARS-CoV-2) are at an advantage as they can use their own RNA polymerase. RNA retroviruses use their own reverse transcriptase to make their DNA, which is inserted into the host genome.
- But viruses cannot replicate alone as they cannot synthesise proteins because they lack the ribosomes which facilitate the translation of viral messenger RNA (mRNA) into proteins (mRNA is a copy of the nucleic acid which enables ribosomes to directs protein synthesis). Instead, viruses must use the ribosomes of their host cells to translate viral mRNA into viral proteins, a process that may take less than an hour or more than a week.
- Viral replication may take place in the nucleus of the host cell or its cytoplasm.
- The parental virus gives rise to thousands of progeny, usually genetically and structurally identical to the parent virus. These are released by lysis (the cell is killed by bursting its membrane) or budding (the virus acquires its envelope from the cell membrane).

Diagram of influenza virus replication

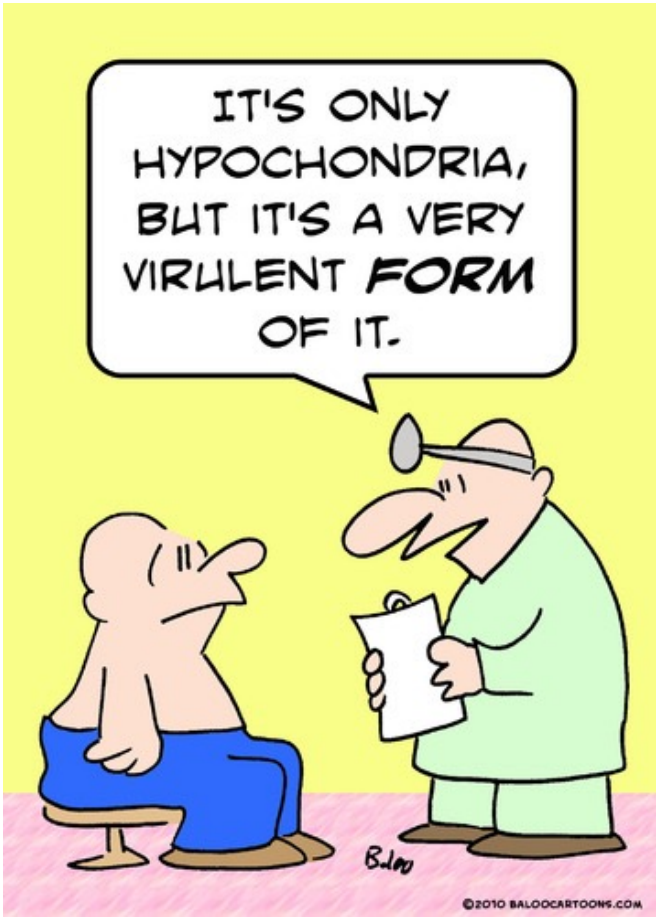


Means of viral transmission

- Direct contact transmission: The direct contact transmission route requires physical contact between an infected and uninfected subject through kissing, biting or sexual intercourse, for example. Some of the most notable sexually transmitted viruses include the human immunodeficiency virus type 1 (HIV-1), human T-lymphotropic virus type 1 (HTLV-1), hepatitis B virus (HBV) and human papillomavirus types 16 and 18 (HPV-16 and HPV18, respectively).
- Indirect transmission: Through indirect transmission, the virus is transmitted through contact with fomites. Fomites are inanimate objects or materials such as medical equipment or shared eating utensils, which can transfer the virus to a new host. Indirect transmission also includes vectors, living messengers that delivers the virus from one host to another such as mosquitos and ticks.
- Common vehicle transmission: Common vehicle transmission refers to when individuals are exposed to the virus from a contaminated source such as food, water, medications or intravenous fluids. Cytomegalovirus is a urine-associated virus and there are several viruses that are transmitted through the faecal-oral route: polioviruses, coxsackieviruses, hepatitis A virus, rotavirus, astrovirus, norovirus.
- Airborne transmission: Airborne transmission refers to the respiratory route of exposure for viruses that can be in the form of droplets, aerosols, and respiratory secretions on the hands and objects. Some of the most notable viruses that are transmitted through this route include influenza virus, coronaviruses, measles, varicella-zoster virus, human rhinovirus, human adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumovirus.

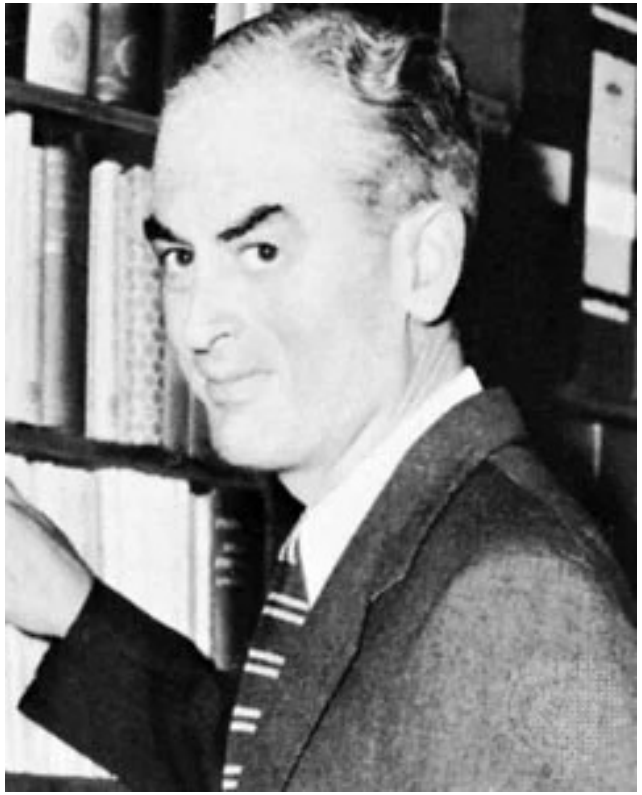
Virulence

- Virulence is defined as the degree of pathogenicity of a pathogen (bacteria, fungi, viruses) and is determined by its ability to invade and multiply within the host, damage host tissues or impact immune responses.
- Virulence may be measured by infectivity rates or case fatality rates. This depends not only on how much harm the virus does to an infected person, but also on how well the virus can avoid the body's defences, replicate itself and spread to other carriers.
- Virulence varies among viruses, even when they are all the same species. This is why flu seasons vary in severity from year to year.



So should we hate and fear viruses?

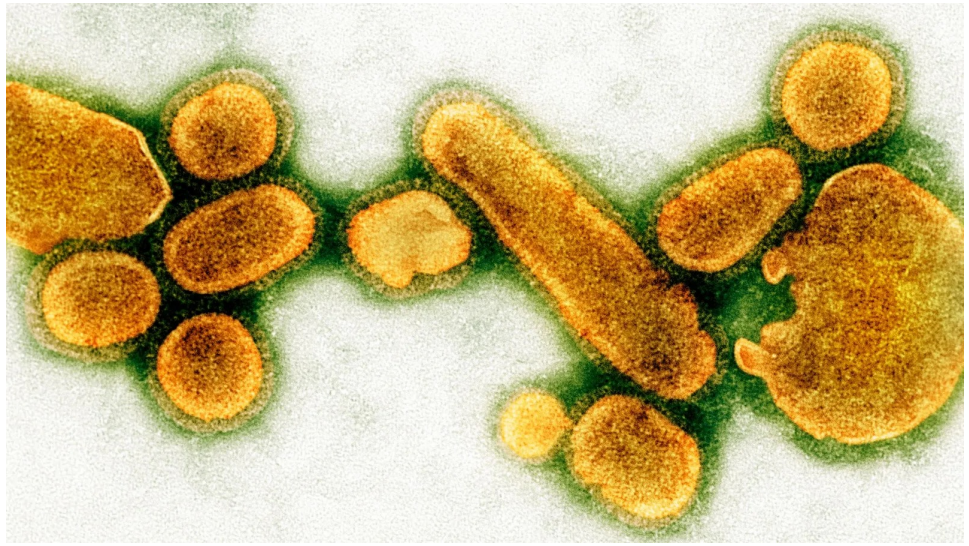
- In the mid-20th century, Professor Peter Madawar famously described a virus as "a piece of bad news wrapped up in protein" (https://www.researchgate.net/publication/351359341_Virus_-Bad_news_wrapped_up_in_protein_Sir_Peter_Medawar).
- But we know better now…..



Only few viruses are pathogens

- Viruses are the most widespread of all micro-organisms, although the vast majority are not pathogenic. Many enter into a quasi-symbiotic relationship with the host.
- Viruses that do not recognise our cellular receptors or otherwise fail to gain entry to our cells will be harmless.
- Some viruses are beneficial and are thought to enter our genomes as protection against more pathogenic *de novo* infections; viruses can make up around 50% of the human genome. Viruses can aid digestion and production of vitamins in the gut and detoxify toxins, while retroviruses are incorporated into the mother's placenta to protect the foetus from the mother's immune response. Adenoviruses which can protect against tumour growth are being developed to fight cancer, while herpes viruses can suppress HIV or bacterial infection.
- There are also 'helper viruses', which can share their components with defective viruses or help repair host cell DNA.
- The true infectious part of any virus is its nucleic acid (DNA or RNA). In many viruses the nucleic acid alone, stripped of its capsid, can infect cells, although considerably less efficiently than can the intact virions.
- Essentially, we humans cannot survive without viruses and other microorganisms, whereas microorganisms can survive perfectly well without humans! They were present on earth before humans and will outlive us after humans become extinct, as they are much more flexible and adaptable than we are.

BBC: “If all viruses disappeared, the world would be very different — and not necessarily for the better”



(https://www.bbc.com/future/article/20200617-what-if-all-viruses-disappeared)

- “If all viruses suddenly disappeared, the world would be a wonderful place for about a day and a half, and then we’d all die” says Tony Goldberg, an epidemiologist at the University of Wisconsin-Madison.
- “All the essential things they do in the world far outweigh the bad things.”
- The vast majority of viruses are not pathogenic to humans, and many play integral roles in propping up ecosystems. Others maintain the health of individual organisms – everything from fungi and plants to insects and humans.

But it’s worth mentioning the viruses that may cause cancer

A number of human viruses are known to be carcinogenic:

- Human T cell leukaemia virus (HTLV-1), a retrovirus, distantly related to HIV.
- Hepatitis B virus (HBV), causing liver cancer.
- Hepatitis C virus (HCV), causing liver cancer.
- Human papilloma viruses (HPV), leading to cervical and other genital cancers.
- Herpes viruses, such as Epstein Barr (EBV), which contributes to Burkitt’s lymphoma in Africa and nasopharyngeal carcinoma in China, and human herpes virus 8 (HHV 8) which contributes to Kaposi’s sarcoma.

Viral mutation

- Errors in viral RNA replication are called mutations. Viruses with these mutations are called variants.
- Although mutations occur due to replication errors in the host cell, much of this drives viral evolution by altering their genetic material to make them more or less virulent and a threat to the human host.
- If the replication error confers an evolutionary advantage (more effective movement from host to host, improved adhesion to cell surface receptors, improved evasion of immune system, treatment or vaccine, faster replication) it will be continued and a new variant will have been created. Evolutionary advantage may also occur where the virus mutates to become less harmful to the host, so that the virus can live in its host without causing illness or death. If the replication error does not confer an evolutionary advantage, the mutation will die off.
- Rates of mutation vary among viruses. RNA viruses mutate faster than DNA viruses, single-stranded viruses mutate faster than double-strand virus and genome size appears to correlate negatively with mutation rate.
- The influenza virus, however, can undergo more radical mutations, such as completely changing its spike protein by swapping spike proteins with another virus that is simultaneously present.
- This sort of mutation is not possible with coronaviruses because they can only undergo point mutations, meaning that only one nucleotide at a time can be changed. Therefore, there will never be any large antigenic changes either for antibodies or for killer T cells.

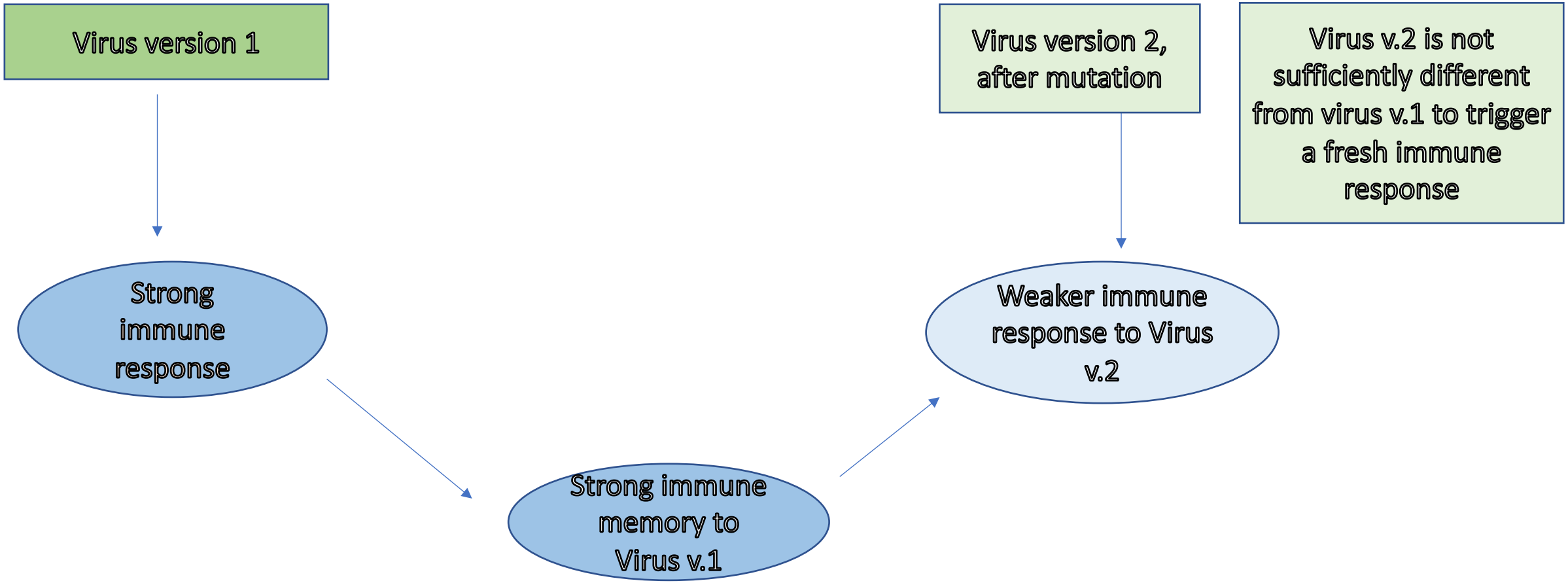
Problems for replication of RNA viruses

- RNA viruses replicate rapidly in ways which make them unstable.
- DNA viruses carry their own nucleic acid and protein folding proof-reading enzymes to minimise mutations and mis-translations during nucleic acid replication and protein production.
- RNA viruses have no proof-reading capability, making them more prone to errors and mutations.
- As a result of this instability, truly pure strains of an RNA virus are rarely found in nature. They tend to exist as mixtures of closely related variants, sometimes referred to as a "quasi-species".

Viral mutation: key terms

- ‘Antigenic drift’ describes a mutation where individual bases in the DNA or RNA mutate to other bases.
- ‘Antigenic shift’ describes a major change in the genome of the virus.
- ‘Original antigenic sin’: suppose an individual is infected with a new virus and is later infected with a variant of the same virus. If ‘original antigenic sin’ is present, the individual’s immune system will respond to the antigens carried by the *original* version of the pathogen, resulting in weaker immunity. It is the first exposure that determines the immune response to variants.
- Unfortunately, this will occur rather than the immune system mounting another primary response to the new antigen, which would allow faster and stronger responses.
- Effectively, the immune system is "trapped" by the first response it has made to each antigen, leaving it unable to mount potentially more effective responses during subsequent infections.
- Original antigenic sin has been demonstrated to occur in several infectious diseases, including COVID-19 and influenza.
- ‘Original antigenic sin’ is also known as antigenic or immunological imprinting.

Diagrammatic explanation of original antigenic sin



Implications of original antigenic sin for the immune system

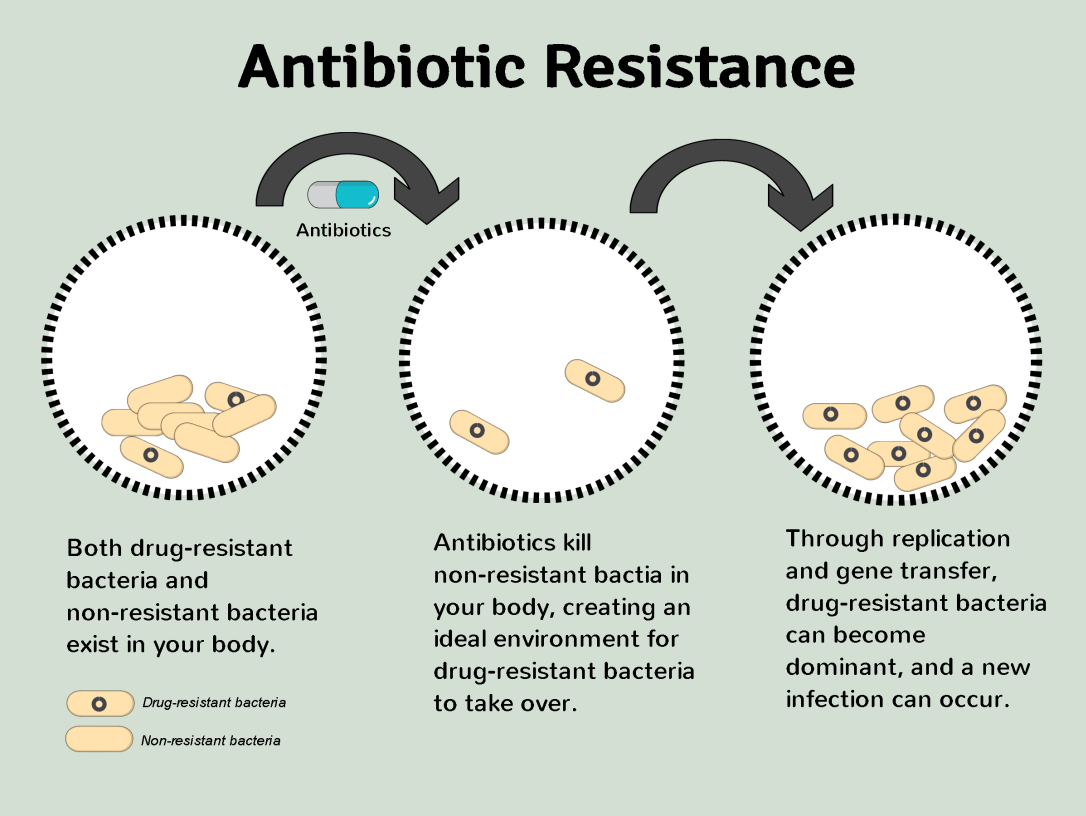
- Original antigenic sin was first described by Thomas Francis in 1960. He noted that, regardless of whatever influenza A strains were in circulation, subjects tended to have dominant antibody responses to the strains that were circulating in their early childhood.
- While we can rely on the immune system to mount an adequate secondary response to protect us from reinfection by the same strain, we can't always rely on it to mount an adequate response to variants because it relies on its memory of the original strain. The immune system takes the path of least effort.
- Although original antigenic sin can weaken immunity, it can sometimes work to advantage. During the 2009 H1N1 'Swine Flu' pandemic, older individuals who had been exposed to the 1918 H1N1 'Spanish Flu' experienced substantially lower relative mortality rates than those usually observed for their age group.
- Other studies have shown cross-reactivity of antibodies, which are often clonally related and remain capable of protecting against challenge from related variants, offering protective benefits during secondary exposures.
- Essentially, the more closely related the variant is to the original strain, the better the protection.

Implications of original antigenic sin for vaccination

- A major reason flu vaccinations don't work is that they are powerless to redirect adult immune systems against other influenza strains. Most people who get flu jabs are adults, with immune systems long since primed by childhood infection.
- Hence this Lancet case study of an influenza outbreaks among boys at Christ's Hospital School in Sussex in the 1970s: 'In each outbreak, the protective effect of inactivated influenza-A vaccine was limited to those boys not already immune, who were vaccinated for the first time with the most up-to-date strain. Revaccination with the same strain did not increase the degree of protection, and revaccination with a later strain did not afford protection against subsequent challenge.'
- So the flu vaccines work well if we are flu virgins but have little effect if we have caught it earlier.

(Hoskins TW, et al. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. Lancet. 1979 Jan 6;1(8106):33-5)

We’ve all heard of antibiotic resistance….



- Does anti-viral resistance also exist?
- Yes.

Anti-viral resistance: it's the mutations again

- Antiviral pharmaceuticals generally block the virus's ability to replicate, so one evasion strategy is to mutate so that the antiviral no longer works against the new variant of the virus. Resistance to HIV anti-virals is well known and it has been observed in COVID-19.
- Antiviral drugs will have the greatest effect (and the greatest potential for resistance to emerge) at the time of maximum viral replication, which in SARS-CoV-2 occurs early in infection.
- Who is particularly at risk for developing antiviral resistance?
  - People who take antivirals for long periods to treat chronic viral infections such as HIV, genital herpes and hepatitis B or hepatitis C.
  - People who have compromised immune systems due to autoimmune disease, organ transplants or cancer treatments.
- Are antiviral-resistant viruses contagious? Yes. This situation is called transmitted drug resistance. People who develop an antiviral-resistant strain of a virus can pass it to others through the exchange of bodily fluids: semen, saliva and blood. Pregnant women can also pass antiviral-resistant viruses to their babies during the birthing process. With transmitted resistance, a virus is already resistant to specific antivirals even if it has never previously encountered the drug.
- Needless to say, increased awareness of anti-viral resistance has triggered the development of yet more anti-viral drugs!

Viral interference (aka viral competition)

- Generally speaking, multiple coinfections are common in respiratory diseases, although the presence of more than one virus at a time does not necessarily mean that there is more than one active infection. Additional viruses may have no effect at all, they can become an active infection making the illness more severe or one virus may suppress the other.
- With respiratory viruses, interference tends to occur in the airway epithelial cells. A likely mechanism is the interferon response which could confer a temporary nonspecific immunity to the host.
- An example is the influenza virus and rhinovirus; when rhinovirus levels in a population tend to be high, levels of flu tend to be low and vice versa.
- When swine flu (H1N1) arrived in the US in 2009, it was delayed in certain populations that were having ongoing outbreaks of rhinoviruses at the time and hospitalized adults had fewer-than-expected instances of co-infection with both viruses. This viral blocking occurred through stimulation of antiviral defences in the airway mucosa.
- There is not enough research in this area to conclude definitively.

How does viral immunity relate to Koch's Postulates?

- Dr Robert Koch, physician and microbiologist, 1843-1910, drew up the first rules for determining the cause of infectious disease and is at the heart of germ theory:
    1. The micro-organism should be found in all cases of the disease and not in healthy individuals.
    2. The organism is capable of being grown in culture
    3. The culture should reproduce the disease when introduced into a susceptible host
    4. The micro-organism can be isolated from this host and re-cultured.
- However, this fails to take into account that we all have any number of potentially pathogenic micro-organisms in us all the time which do not cause disease. Both these and invading organisms can be neutralised by a healthy immune system.
- Additionally, it is not possible to culture a virus unless some of the host cells are also present.

It may seem as if viruses have the upper hand!

- “The stupidest virus is cleverer than the cleverest virologist” (George Klein, virologist, 1925-2016)
- But we have an immune system….
- If we did not, the human race would have become extinct a long time ago.