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The deadly dozen: An overview of the top killer viruses

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Abstract

The present review was inspired by the COVID-19 pandemic that is presently the cause of great concern worldwide. Viruses have been part and parcel of living entities since life existed on earth. Over the centuries there has been records of numerous instances of noticeable viral attacks on humans that resulted in significant number of fatalities. Earliest records of a viral infection was found in Egypt during 1580–1350 BC and amongst the oldest that infect humans are smallpox and measles viruses. Viral epidemics came to prominence when early humans started to live in communities increasing the chances of close contact. As human behavior evolved living in agrarian societies, so did viruses. Included in this review are some of the aspects of what a virus is, how a virus infects and how the viral infection is detected. Finally details of twelve different killer viruses that are the causative agents of some of the fatal diseases in humans are examined.

Keywords: Virus; Pandemic; Epidemic; Polymerase chain reaction; Nucleotide sequencing.

Introduction

A virus is a submicroscopic infectious agent that can only replicate inside living cells of an organism. Viruses cause infections and diseases to all life forms from microorganisms including bacteria and archaea, to plants and animals (Koonin *et al.,* 2006). They have over the centuries resulted in millions of deaths. Epidemics caused by viruses began when human behavior changed during the Neolithic period, around 12,000 years ago, as humans developed more densely populated agricultural communities (McMichael, 2004). Earlier, humans lived in small, isolated communities, and most epidemic diseases did not exist. However, with increasing concentration and localization of people viruses spread rapidly and subsequently became endemic. Viruses of plants and livestock also increased as humans became dependent on agriculture and farming. Humans have been battling viruses since before our species had even evolved into its modern form. Among the earliest records of a viral infection is in Egypt from the 18th dynasty (1580–1350 BC) (Drutz and Ligon, 2000). Smallpox and measles viruses are among the oldest that infect humans. Having evolved from viruses that infected other animals, they first appeared in humans in Europe and North Africa thousands of years ago. The viruses were later carried to the New World by Europeans during the time of the Spanish

Conquests, but the indigenous people had no natural resistance to the viruses and millions of them died during epidemics. Influenza pandemics have been recorded since 1580 (Potter, 2001), and they have occurred with increasing frequency in subsequent centuries. The influenza pandemic (January 1918 – December 1920, known as Spanish flu) was an unusually deadly pandemic, the first of the two pandemics involving H1N1 influenza virus in which 40–50 million died in less than a year, was one of the most devastating in history ((Johnson and Mueller, 2002). The nature of viruses remained unknown until the invention of the electron microscope in the 1930s, when the science of virology gained momentum (Brenner and Jorne, 1959; Oldstone, 2014). For some viral diseases, vaccines and antiviral drugs have allowed us to keep infections at bay, and have helped sick people recover. But we're a long way from winning the fight against viruses. In recent decades, several viruses have jumped from animals to humans and triggered sizable outbreaks, claiming thousands of lives. The Ebola outbreak (2014-2016) in West Africa killed up to 90% of the people it infected, making it the most lethal member of the Ebola family (Ebola Virus disease in West Africa, WHO, 2014). Ebola virus disease (EVD), is a viral haemorrhagic fever of humans and other primates (Ebola Virus disease in West Africa, WHO, 2014; Centre for Disease Control and Prevention Ebola Otbreaks, 2000-2014; Cordelia et al. 2017). The novel coronavirus currently driving the outbreaks around the globe, had lower fatality rates, but still pose a serious threat to public health as it is highly infectious and we don't yet have the means to combat it. In this write-up we present 12 worst killers as well as some known facts about the Covid - 19 virus that has taken the world by storm and yet to be fully understood.

The first question that comes to mind is what a virus is and how does it infect and produce disease conditions. To begin with, a virus isn't "alive" in a typical sense. By definition, viruses are the smallest and simplest entities lacking an energy-generating system and having very limited biosynthetic capabilities (Feischmann, 1996). It is just a collection of genetic material (DNA or RNA) varying in size and complexity and a small toolbox of proteins. The blueprint for the structure and functioning of a virus is contained in its genetic material. The smallest viruses may have only a few genes while the largest viruses have as many as 200 (Gelderblom, 1996; Koonin *et al.* 2015). The proteins are used to perform two selfish tasks: 1. to get inside the cells of its host and 2. to hijack that cell's own genetic machinery in order to produce thousands of copies of itself.. In size, most viruses vary in diameter from 20 - 400 nm; the largest, however, measures about 500 nm in diameter. Only large viruses can be seen under the light microscope at the highest resolution. A virus propagates by infecting a living organism (host) and it does so by "commandeering" the host cell machinery. A virus basically reprograms the host cell to become a virus factory. Since viruses contain genetic material, like cell based living entities viruses have genetic variation and can evolve to newer forms. So, even though they don't meet the definition of life, viruses seem to be in a "questionable" zone. Viruses come in different shapes and structures and are very diverse. It is estimated that there are roughly 10^{31} viruses (Microbiology by numbers, 2011). Does that mean there are 10^{31} viruses just waiting to infect us? Actually, most of these viruses are found in oceans,

where they attack bacteria and other microbes. Every kind of living organism is probably host to at least one virus. Most viruses cause disease, and they are usually quite specific about the area of the body that they attack, for example, the liver, the respiratory tract, or the blood. Common viruses include Influenza, Herpes zoster, HIV, the common cold, and the rabies virus. Although viruses vary in their sizes, shapes, and life cycles, they have a few key features in common (Flint *et al*., 2003). These include: 1. A protective protein shell, or capsid 2. A nucleic acid genome made of DNA or RNA, tucked inside of the capsid 3. A layer of membrane called the envelope (not all viruses). Replication of the viral genome is essential for inheritance and continuity. Gene expression usually involves converting DNA into messenger (what is known as transcription) RNA (mRNA) and translation of mRNA into protein. This information could get altered if the DNA/ RNA undergoes changes. Like all other organisms, viruses are subjected to genetic alterations in two primary ways which determine their infectivity. 1. Errors made during the replication process called mutations (and RNA viruses in particular are known to be bungling replicators as they undergo a lot of mutations). Since viruses reproduce in such massive numbers, eventually a "winning" combination comes up and a new viral strain is born. 2. The second way that viruses can acquire new infective capabilities is known as "reassortment" i.e. when a mammal has the misfortune of being infected with two or more (say respiratory) viruses simultaneously, then as these viruses replicate, their genome parts can be shuffled together and then recombine/exchange (de Silva *et al*., 2012). An example is H1N1 virus which combined the swine, human and an avian influenza (triple reassortment) (Newman *et al.,* 2008). That's how the swine H1N1 pandemic was born.

Thus comes the next question- how does a virus infect? For a typical virus, the lifecycle can be divided into five broad steps (Payne, 2017) (though the details of these steps will be different for each virus): 1. Attachment: The virus recognizes and binds to a host cell *via* a receptor molecule on the cell surface (the corona virus bind to the angiotensin converting enzyme-2 which serves as the receptor). 2. Entry: The virus or its genetic material enters the cell. One typical route for viral entry is fusion with the host cell membrane, which is most common in viruses with envelopes. Viruses may also trick the cell into taking them in by a bulk transport process called endocytosis. 3. Next, the viral genes are expressed to make viral proteins. This step involves copying the viral genome and making more viral proteins, so that new virus particles can be assembled. The materials for these processes (such as nucleotides to make new DNA or RNA) come from the host cell, not the virus. Most of the "machinery" for replication and gene expression is also provided by the host cell. However, certain steps, such as the copying of an RNA virus's genome, cannot be performed by host cell enzymes. In such cases, the viruses must encode their own enzymes. All viruses must encode capsid proteins, and enveloped viruses typically also have to encode envelope proteins (which often aid in host recognition). Viruses may also encode proteins that manipulate the host genome (e.g., by blocking host defenses or driving expression of genes to benefit the virus), help with viral genome replication, or play a role in other parts of the viral lifecycle. 4. Assembly: New viral particles are assembled from the genome copies and viral proteins synthesized.

During assembly, newly synthesized capsid proteins come together to form the full-sized capsid. 5. Release: The last step in the virus lifecycle is the release of newly made viruses from the host cell which then infect other cells. Different types of viruses exit the cells by different routes: some make the host cell burst (a process called lysis), while others exit through the cell's own export pathways (exocytosis), and some bud from the plasma membrane, taking a patch of it with them as they go. In some cases, the release of the new viruses kills the host cell. In other cases, the exiting viruses leave the host cell intact so it can continue turning out more virus particles.

So how are viruses detected? In the diagnostic laboratory virus infections can be confirmed by a multitude of methods. Diagnostic virology has changed rapidly due to the advent of molecular techniques and increased clinical sensitivity of serological assays. Several types of tests may be used to check for viruses (Storch, 2000): 1. Viral culture, 2. Antibody test (Antibodies are substances made by the body's immune system to fight a specific viral infection), and 3. Viral DNA or RNA detection test.

Viral culture

The method first involves virus isolation**.** Viruses are often isolated from the initial patient sample. This allows the virus sample to be grown into higher quantities and allows a larger number to tests to be run on them. This is particularly important for samples that contain new or rare viruses for which diagnostic tests are not yet developed. Many viruses can be grown in cell culture in the laboratory. To do this, the virus sample is mixed with cells (for e.g. Vera cell line), a process called adsorption, after which the cells become infected and produce more copies of the virus. One means of determining whether the cells are successfully replicating the virus is to check for changes in cell morphology or for the presence of cell death using a microscope.

Nucleic acid based methods

Molecular techniques are the most specific and sensitive diagnostic tests. They are capable of detecting either the whole viral genome or parts of the viral genome. The much talked about method of detection is the **Polymerase Chain Reaction** (PCR) based on nucleic acid amplification. This technique basically involves the use of a thermocycler (PCR machine), the genetic material RNA or DNA which is to be amplified, the enzyme and substrates required for building the new viral DNA or RNA and other ingredients like fluorescent dyes (which helps in detection). Variations of PCR such as real time PCR is a qualitative and quantitative method to determine viral loads in patient serum. **Nucleotide sequencing** is another diagnostic method that offers the full sequence of a virus genome. Hence, it provides the most information about very small differences between two viruses that would look the same using other diagnostic tests.

Microscopy based methods

Under this, **i**mmunofluorescence assay is commonly used to detect whether a virus is present in a tissue sample. These tests are based on the principle that if the tissue is infected with a virus, an antibody specific to that virus will be able to bind to it. To do this, antibodies that are specific to different types of viruses are mixed with the tissue sample. After this the tissue is exposed to a specific wavelength of light or a chemical that allows the antibody to be visualized (Cynthia *et al.,* 2009).

Host antibody detection

A person who has recently been infected by a virus will produce antibodies in their bloodstream that specifically recognize that virus. This is called humoral immunity. Two types of antibodies are important. The first called IgM is highly effective at neutralizing viruses but is only produced by the cells of the immune system for a few weeks. The second, called, IgG is produced indefinitely. Therefore, the presence of IgM in the blood of the host is used to test for acute infection, whereas IgG indicates an infection sometime in the past. Both types of antibodies are measured when tests for immunity are carried out. It can be done for individual viruses using a technique called ELISA (abbreviated for enzyme linked immunosorbent assay) but in automated panels that can screen for many viruses at once are becoming increasingly common. Virus detection by culture, PCR and serological studies have their places in the diagnosis of infection. In all instances of acute infection, virus detection using PCR is the method of choice, as antibody responses are much less informative. Indeed, in recurrent episodes, the antibody titre may not vary (Andeotti *et al.,* 2003). There are other tests like the complement fixation test and enzyme immune assays that are also used. The development of macro- and microarrays with several hundreds or thousands of probes allows for identification of viruses with only marginal homology to known taxa. Arrays present a powerful tool, allowing for broad spectrum detection of known and unknown viruses. The use of next -generation sequencing as a tool for virus detection and identification is also very much in use. Today, bioinformatics and structural analyses of putative proteins can lead to the discovery of previously unknown viruses. But this is another topic altogether.

Now that we are somewhat familiar with viruses, let us look into few viruses that are the causative agents of some of the lethal diseases in humans.

1. Marburg virus

Marburg is a highly virulent disease that causes hemorrhagic fever, with a fatality ratio of up to 88% (Brauburger *et al.,* 2012). The virus is a single stranded RNA virus first reported in 1967, when small outbreaks occurred among laboratory workers in Germany who were exposed to infected monkeys imported from Uganda. The viral outbreaks were then reported in the 1998-2000 in the Democratic Republic of Congo, as well as in the 2005 outbreak in Angola, according to the World Health Organization (WHO). Marburgvirus

genomes are approximately 19 kbp long and contain seven genes. Its infection in human was initially reported to be from prolonged exposure to mines or caves inhabited by Rousettus bat colonies. An infected individual can spread the virus by direct contact i.e., through human-to-human interaction (through broken skin or mucous membranes) with blood, secretions or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. The incubation period for the Marburg virus ranges from 2-21 days. The disease begins abruptly, with high fever, severe headache, muscle aches, abdominal pain, cramping and severe watery diarrhea. Nausea, vomiting and a non-itchy rash appear between 2 to 7 days after the onset of symptoms. Many patients develop severe hemorrhagic symptoms with bleeding from nose, gums and vagina. Fresh blood is also lost in vomitus. Death usually occurs due to severe blood loss and shock.

2. Ebola virus

The first known Ebola outbreaks in humans struck simultaneously in the Republic of the Sudan and the Democratic Republic of Congo in 1976 (Ebola Virus Disease in West Africa, WHO, 2014; Singh and Ruzek, 2014; Malvy *et al.,* 2019; Richardson et al. 2019). Ebola is spread through contact with blood or other body fluids, or tissue from infected people or animals. The outbreak also took place in West Africa in early 2014. Ebola virus is similar to Marburg in that both can cause hemorrhagic fever, meaning that infected people develop high fevers and bleeding throughout the body that can lead to shock, organ failure and death. The virus contains one molecule of linear, single-stranded, negative-sense RNA, 18,959 to 18,961 nucleotides in length. This viral genome codes for seven structural proteins and one non-structural protein. The fruit bats of the Pteropodidae family are natural hosts of Ebola virus. Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals such as fruit bats, monkeys, chimpanzees, gorillas, forest antelope or porcupines found ill or dead in the rainforests. The disease causes very similar symptoms to Marburg virus. Its incubation period is 2-21 days. An Ebola infected person cannot spread the disease until they develop symptoms. Symptoms of EVD can be sudden and include: Fever, muscle pain, headache, fatigue and sore throat followed by diarrhoea, vomiting, development of rash and symptoms of kidney and liver failure. In many cases, there is bleeding from gums or blood in the stool.

3. Rabies

Rabies lyssavirus, formerly *Rabies virus*, is a virus that causes rabies in humans and animals (Abraham and Banerjee, 1976). Rabies is a preventable viral disease most often transmitted through the bite of a rabid animal. The rabies virus infects the central nervous system of mammals, ultimately causing disease in the brain and death. The vast majority of rabies cases reported to the Centers for Disease Control and Prevention (CDC) each year occur in wild animals like bats, raccoons, skunks, and foxes, although any mammal can

get rabies. Rabies virus belongs to the order Mononegavirales, are enveloped and carries a non-segmented, negative-stranded RNA genome (Anilionis *et al.,* 1981). The vaccines for pets, which were introduced in the 1920s, have helped make the disease exceedingly rare in the developed world, however the condition remains a serious problem in India and parts of Africa.

4. HIV

Today, HIV (human immunodeficiency virus), also a retrovirus (RNA) remains one of the largest pandemics in the world. HIV is a virus that attacks cells in the human immune system, such as helper T cells (specifically CD^{4+} T cells), macrophages, and dendritic cells that are vital for body to fight infection, making the infected person vulnerable to other infections and diseases. It is composed of two copies of positive-sense single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein (Muesing *et al.,* 1985; Lewis *et al.,* 1992). It is spread by contact with certain bodily fluids of an infected person most commonly during unprotected sex or through sharing injections. HIV is the same virus that can lead to AIDS (acquired immunodeficiency syndrome) which originated in non-human primates in Central and West Africa. While various sub-groups of the virus acquired human infectivity at different times, the global pandemic had its origins in the emergence of one specific strain – HIV-1 subgroup M – in Léopoldville in the Belgian Congo (now Kinshasa in the Democratic Republic of the Congo) in the 1920s (Keele *et al.,* 2006). An estimated 32 million people have died from HIV since the disease was first recognized in the early 1980s. The infectious disease that takes the biggest toll on mankind right now is HIV. Powerful antiviral drugs have made it possible for people to live for years with HIV. But the disease continues to devastate many low and middle-income countries, where 95% of new HIV infections occur. Nearly 1 in every 25 adults within the WHO African region is HIV-positive.

5. Smallpox

Smallpox is a highly contagious and deadly disease that was estimated to have infected 300 million people in the 20th Century before it became the only human infectious disease ever to be completely eradicated. Smallpox is caused by the agent referred to as the *variola* virus (VARV). *Variola* is a large brick-shaped virus, with a single linear double stranded DNA genome (Massung *et al.,* 1994). The two classic varieties of smallpox are *variola* major and *variola* minor. The occurrence of smallpox extends into pre-history, the disease emerged in human populations about 10,000 BC. The earliest credible evidence of smallpox is found in the Egyptian mummies of people who died some 3000 years ago (Barquet and Domingo, 1997). Smallpox has had a major impact on world history.

Viral transmission occurred through inhalation of airborne *Variola* virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. The initial symptoms of the disease included fever and vomiting, followed by formation

of sores in the mouth and a skin rash that turns into characteristic fluid-filled bumps with a dent in the center. The bumps then scabbed over and fell off, leaving scars. The last naturally occurring case of small pox was diagnosed in October 1977 and the WHO certified the global eradication of the disease in 1980 (Fenner *et al.,* 1988).

6. Hantavirus pulmonary syndrome (HPS)

Hantavirus Pulmonary Syndrome (HPS) is a severe, sometimes fatal, respiratory disease in humans caused by infection with hanta viruses (Factsheets, Centre for disease Control and Prevention, 2016). Hantaviruses belong to the bunyavirus family of viruses. They are enveloped viruses with a genome that consists of three single-stranded RNA segments designated S (small), M (medium), and L (large). All hantaviral genes are encoded in the negative (genome complementary) sense. The complete genome is 11800-13800 nucleotides long. The virus can be transmitted to humans by a direct bite or inhalation of aerosolized virus, shed from stool, urine, or saliva from a rodent. Rodent infestation in and around the home remains the primary risk for hanta virus exposure. It first gained wide attention in the U.S. in 1993, when a healthy, young Navajo man and his fiancée living in the United States died within days of developing shortness of breath. A few months later, health authorities isolated hanta virus from a deer mouse living in the home of one of the infected person. HPS has an incubation phase of 2-4 weeks. Patients develop flu-like symptoms including fever, cough, muscle pain, headache, lethargy, shortness of breath, nausea, vomiting and diarrhea. The patient could rapidly deteriorate into acute respiratory failure, characterized by pulmonary edema, as well as cardiac failure, with hypotension, tachycardia and shock.

7. Influenza

Influenza commonly known as “the flu”, is an infectious disease caused by an influenza virus (World Health Statistics, 2018). The most common symptoms are high fever, runny nose, sore throat, muscle and joint pain, headache, coughing, and feeling tired. These symptoms typically begin within two days into exposure to the virus and most last for one to two weeks. Three of the four types of influenza viruses affect humans- Type A, Type B, and Type C (Longo, 2012; Types of Influenza Viruses Seasonal Influenza, 2017). The genome of influenza type A viruses consists of eight single-stranded RNA segments, and the viral particle has two major glycoproteins on its surface: hemagglutinin and neuraminidase. The Influenza B virus genome is 14,548 nucleotides long and consists of eight segments of linear negative-sense, single-stranded RNA. The multipartite genome is encapsulated, each segment in a separate nucleocapsid, and the nucleocapsids are surrounded by one envelope. Although influenza A and B virus genomes both comprise eight negative-sense, single-stranded viral RNA (vRNA) segments, influenza C virus has a seven-segment genome. Influenza spreads around the world in yearly outbreaks, resulting in about three to five million cases of severe illness and about 290,000 to 650,000 deaths according to WHO. Approximately 33% of people

with influenza are asymptomatic. But occasionally, when a new flu strain emerges, a pandemic results with a faster spread of disease and, often, higher mortality rates. The most deadly flu pandemic, called the Spanish flu, began in 1918 and sickened up to 40% of the world's population, killing an estimated 50 million people (Andrews 2016; History.com staff, 2018). It can be difficult to distinguish between the common cold and influenza in the early stages of these infections. Influenza symptoms are a mixture of symptoms of common cold and pneumonia, body ache, headache, and fatigue. The common cold, also known simply as a cold, is a viral infectious disease of the upper respiratory tract that primarily affects the nose. The throat, sinuses, and larynx may also be affected.

8. Dengue

Dengue virus (DENV) is the cause of dengue fever (Izabela *et al*., 2010). It is a mosquito-borne, virus whose genome is about 11000 bases of positive-sense, single stranded RNA (ssRNA) that codes for three structural proteins (capsid protein C, membrane protein M, envelope protein E) and seven nonstructural proteins (Kuhn *et al*., 2002). The first reported epidemics of dengue fever occurred in 1779-1780 in Asia, Africa, and North America; the near simultaneous occurrence of outbreaks on three continents indicates that these viruses and their mosquito vector have had a worldwide distribution in the tropics. The virus appeared in the 1950s in the Philippines and Thailand, and has since spread throughout the tropical and subtropical regions of the globe. The virus has increased dramatically within the last 20 years, becoming one of the worst mosquito-borne human pathogens in tropical countries (Cucunawangsih and Lugito, 2017). Current estimates indicate that as many as 390 million infections occur each year, up to 40% of the world's population now lives in areas where dengue is endemic, and the disease with the mosquitoes that carry it is likely to spread farther as the world warms (global warming). Dengue sickens 50 to 100 million people a year, according to WHO. Although the mortality rate for dengue fever is lower than some other viruses, at 2.5%, the virus can cause an Ebola-like disease called dengue hemorrhagic fever, and that condition has a mortality rate of 20% if left untreated. A vaccine for Dengue was approved in 2019 by the U.S. Food and Drug Administration for use in children between 9-16 years old living in areas where dengue is common according to the CDC (Center for Disease Control) (Centers for Disease Control and Prevention, NCEZID, 2019).

9. Rotavirus

Rotaviruses are the most common cause of diarrheal disease among infants and young children. The virus is transmitted by the fecal-oral route. It infects and damages the cells that line the small intestine and causes gastroenteritis (which is often called "stomach flu". Nausea, vomiting, watery diarrhea and low-grade fever are the characteristic symptoms of rotaviral enteritis. Once a child is infected by the virus, there is an incubation period of about two days before symptoms appear. There are ten species of rotavirus, referred to as A, B, C, D, E, F, G, H, I and J (Suzuki, 2019). Humans are

primarily infected by the species *rotavirus* A. The genome of rotaviruses consists of 11 unique double helix molecules of RNA (dsRNA) which are 18,555 nucleotides in total (Estes and Cohen, 1989). Twelve proteins are encoded by the rotavirus genome that help the virus to infect and reproduce within the host. Although children in the developed world rarely die from rotavirus infection, the disease is a killer in the developing world, where rehydration treatments are not widely available. Two vaccines are now available to protect children from rotavirus. WHO estimated that worldwide, 453,000 children younger than age 5 died from rotavirus infection in 2008. But countries that have introduced the vaccine have reported sharp decline in rotavirus hospitalizations and deaths.

10. Nipah virus

The Nipah virus (NiV) is a type of RNA virus placed in the newly created Henipavirus genus with the closely related Hendra virus and Cedar virus (Barry *et al.,* 2012). The Henipavirus family is pleomorphic, meaning their shape is varied, and traditionally 40 to 600 nm diameter. The core of a virion contains a linear ribonucleprotein (RNP) comprising of negative sense single stranded RNA. Nipah virus was first recognized in 1999 during an outbreak among pig farmers in Malaysia. In May 2018, an outbreak of the disease resulted in 17 deaths in the Indian state of Kerala (Chatterjee, 2018; Nipah Virus Infection, 2018). Nipah virus is a zoonotic virus and the viral transmission happens in humans from animals (such as bats or pigs), or from consuming contaminated foods or directly from human-to-human. The incubation period ranges from 4 to 14 days. Symptoms include fever, headaches, vomiting and sore throat. In severe cases this could be followed by dizziness, drowsiness, altered consciousness, and neurological signs that indicate acute encephalitis.

11. Corona viruses (SARS- CoV and MERS-CoV)

A. SARS- CoV

Among the corona virus infections in recent times **SARS- CoV, MERS-CoV** and **COVID- 19** have been in news due to their sudden appearance, rapid spread and catching us almost unprepared to mitigate the health threats they present. Severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) is a strain of virus that causes severe acute respiratory syndrome (SARS) (Thiel, 2007; Fehr and Perlman, 2015). It infects the lungs. SARS first appeared in 2002 in Guangdong Province, China, and has spread to several countries. The severity of this disease is such that the mortality rate appears to be ~3 to 6%, although a recent report suggests this rate can be as high as 43 to 55% in people older than 60 years. The virus is considered to have come from bats, which then hopped into nocturnal mammals called civets before finally infecting humans. After triggering an outbreak in China, SARS spread to 26 countries around the world, infecting more than 8000 people and killing more than 770 over the course of two years (Little, 2020). It is an enveloped, positive-sense, single-stranded RNA virus which infects the epithelial

cells within the lungs (Macro *et al.,* 2003). The virus enters the host cell by binding to the angiotensin converting enzyme 2 (ACE2) receptor (Li *et al.,* 2005; de Groot *et al.,* 2013). Transmission of SARS-CoV is primarily from person to person. Symptoms of the disease are influenza-like and include fever, malaise, myalgia, headache, diarrhea and often progresses to pneumonia, a severe condition in which the lungs become inflamed and filled with pus. SARS has an estimated mortality rate of 9.6%, and as of yet, has no approved treatment or vaccine. However, no new cases of SARS have been reported since the early 2000s, according to the CDC.

B. **MERS-CoV**

Middle East respiratory syndrome (MERS), also known as camel flu, is a viral respiratory infection caused by the MERS-coronavirus (MERS-CoV) (Wog *et al.,* 2019; Fehr *et al.,* 2015). Typical symptoms include fever, cough, diarrhea and shortness of breath. The disease is typically more severe in those with other health problems and in severe cases kidney failure, disseminated intravascular coagulation (DIC), and pericarditis have also been reported. This virus sparked an outbreak in Saudi Arabia in 2012 and another in South Korea in 2015. The virus belongs to the same family of viruses as SARS-CoV, and likely have originated in bats, as well. MERS-CoV virus is an enveloped positive-sense single-stranded RNA belonging to the genus betacoronavirus which is distinct from SARS coronavirus and the common-cold coronavirus. It enters its host cell by binding to the DPP4 receptor (Fehr *et al*., 2015). The disease infected camels before passing into humans. MERS often progresses to severe pneumonia and has an estimated mortality rate between 30% and 40%, making it the most lethal of the known coronaviruses that jumped from animals to people. As with SARS-CoV, MERS has no approved treatments or vaccine.

12. SARS-CoV-2: the causative agent in the recent pandemic COVID-19

This is the virus that has gripped the world's apprehension towards its journey into future. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus strain that causes the respiratory illness coronavirus disease (COVID-19) (Gorbalenya *et al.,* 2020). It is colloquially known as the coronavirus, and was previously referred to by its provisional name 2019 novel coronavirus (2019-nCoV). The disease has first come into focus in the months of November- December, 2019 in Wuhan province in China. Since then the virus has travels throughout the world at an astonishing speed indicating its highly contagious nature. It is so contagious in humans that the World Health Organization (WHO) has designated the ongoing COVID-19 infection as pandemic and as Public Health Emergency of International Concern (WHO Director-General Opening Remarks at media briefing on COVID-19, 2020). As of 26 April 2020, more than 2.91 million cases of COVID-19 have been reported in 185 countries and territories, resulting in more than 203,000 deaths. SARS-CoV-2 is a positive-sense single-stranded RNA virus with its RNA sequence being ~ 30,000 bases in length. This

virus belongs to the same large family of viruses known as SARS-CoV (corona viruses) and of the subgenus *Sarbecovirus* (beta-CoV lineage B) (Mousavizadeh and Ghasemi, 2020; Sah *et al.,* 2020). The virus likely originated in bats, like SARS-CoV, and passed through an intermediate animal most probably a pangolin before infecting people. Intense research established human-to-human transmission of SARS-CoV-2 on 20 January 2020. The primarily mode of transmission between people is through close contact and via respiratory droplets produced from coughing, sneezing, or talking. Another probable cause of infection is indirect contact via contaminated surfaces. When it infects host cells, it replicates its genomic RNA (gRNA) and produces nine smaller RNAs known as subgenomic RNAs (sgRNAs) that are used for synthesizing various proteins- spike protein (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N), and several accessory proteins. The gRNA is packaged by the structural proteins to assemble progeny virions which burst out of the host cells and repeat the cycles of infection (Chen and Guo, 2020). It mainly enters human cells by binding to the receptor angiotensin converting enzyme 2 (ACE2) (Lan *et al.,* 2020; Verdecchiaa *et al.*, 2020). Further, there is some indication of human-to-animal transmission of SARS-CoV-2, including examples in felids. Researchers have sequenced the viral genome from many infected persons and with sufficient number of sequenced genomes have constructed a phylogenetic tree of the mutation history of a family of viruses. A phylogenetic analysis of those samples showed that these were highly related and as of 27 March 2020, 1,495 SARS-CoV-2 genomes sampled on six continents were publicly available.

On 11 February 2020, the International Committee on Taxonomy of Viruses (ICTV) announced that according to existing rules that compute hierarchical relationships among coronaviruses on the basis of five conserved sequences of nucleic acids, COVID-19 has been placed as a strain of *Severe acute respiratory syndrome-related coronavirus*. Since its appearance, the virus has infected tens of thousands of people in China and thousands of others worldwide (the figure keeps rising). The ongoing outbreak prompted an extensive quarantine in almost all continents, restricting travel to and from affected countries and a worldwide effort to develop diagnostics, treatments and vaccines. The disease COVID-19 has an estimated mortality rate of about 2.3%. COVID-19 affects different people in different ways. People who are older or have underlying health conditions seem to be most at risk. Most infected people will develop mild to moderate symptoms. Common symptoms include fever and tiredness, dry cough and shortness of breath. Some people may experience aches and pains, nasal congestion, runny nose, sore throat and diarrhea. The disease can progress to pneumonia in severe cases. On average it takes 5–6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days.

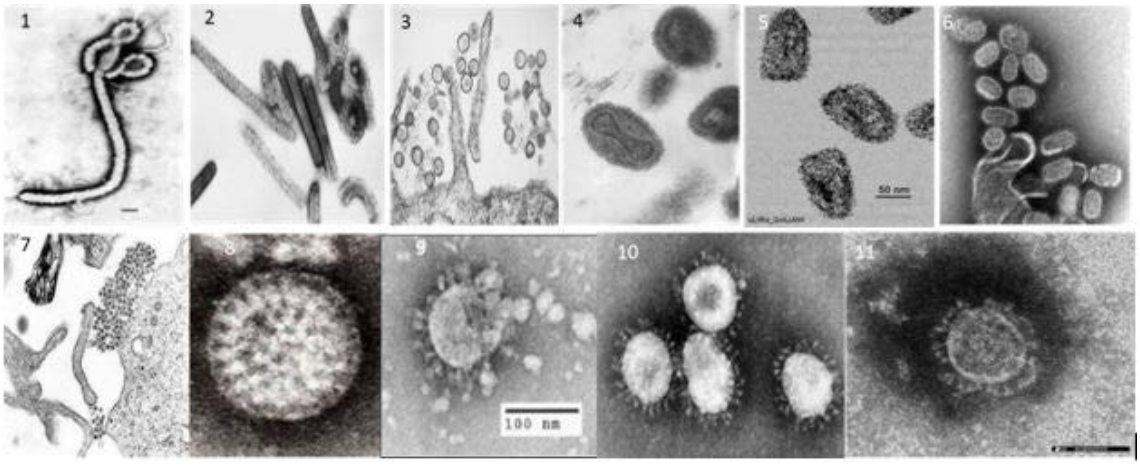

Figure 1: Electron microscopic pictures of different viruses- 1. Ebola 2. Marburg 3. Hantavirus 4. Small pox virus 5. Rabies virus 6. Influenza virus 7. Dengue virus 8. Rotavirus 9. SARS- CoV 10. MERS- CoV 11. SARS- CoV 2. (Micrographs courtesy: Wikipedia).

Mortality of any viral disease is calculated by dividing the number of patients who died by the number who have been infected. Mortality rates tend to range higher early on in an outbreak, because the denominator is falsely low. Without accurate diagnostic testing, the number of patients infected includes only those with obvious symptoms. This seems to be the case with COVID-19. Since symptoms alone make for a sketchy denominator, public health officials rely on laboratory verification of infection, but historically, viruses have been difficult to detect. Because they are hard to grow in a lab, the next best step is to look for antibodies against the virus. Unfortunately that can be inaccurate too as it often misses early infections because the body has yet to mount an antibody response.

In case of Covid-19 uncertainty over whether it is the virus itself or the response of a person's immune system that ultimately overwhelms a patient's organs, is making it difficult for doctors to determine the best way to treat people who are critically ill. There are reports suggesting that the immune system plays a part in the deterioration and death of people infected with the new coronavirus, and this has spurred a push for treatments such as steroids that rein in that immune response. Some of the earliest analyses of people with the coronavirus suggested that it might not be the virus alone that ravages the lungs and kills; rather, an overactive immune response might also contribute (COVID-19: Navigating Uncertainities Together, 2020). High blood levels of proteins called cytokines, which can ramp up immune responses have been reported. They include signaling protein called interleukin-6 (IL-6) which is a call to arms components of the immune system, including macrophages. Macrophage cells fuel inflammation and can damage normal lung cells. The release of cytokines known as a "cytokine storm", also occurs with other viruses. Thus, collateral damage from the immune response may aggravate the illness. There are no specific medicines available to treat COVID-19 as yet, desperate search for a vaccine and hundreds of studies are being carried out (Ledford, 2020). COVID-19

vaccine expected to come out in September may in fact be the most fast-tracked vaccine ever created in all history. For those interested they may look up - What Drugs May Fight Coronavirus COVID-19? Drug Trials, Treatments, Vaccines; reviewed by Charles Patrick Davis,(https://www.onhealth.com/content/1/what_drugs_fight_covid-19_treatments_vaccine_trial).

Conclusion

In conclusion, one can say that we have come a long way in combating various infectious agents. Through scientific pursuit we have learned a lot in terms of understanding the biology of viruses and other pathogens. The more we know the better equipped we are in coming up with therapeutic measures. However, in the virus we have a formidable enemy. Its simple structure probably aids in changing its form frequently which continually poses challenges in developing drugs and vaccines for different strains of the virus. In the end one can only conclude that pandemics of these kinds will continue to appear in the future, how much they kill will depend on the evolution of the strains, how virulent they are, their kill rate, modes of infection, how prepared we are and methods of containment and treatment.

References

Abraham, G. and Banerjee, A.K. 1976. Sequential transcription of the genes of vesicular stomatitis virus. *Proceedings of the National Academy of Sciences of the United States of America*,73: 1504–1508.

Andreotti, P.E., Ludwig, G.V., Peruski, A., Tuite J.J., Morse S.S. and Peruski L.F. Jr. 2003. Immunoassay of infectious agents. *BioTechniques*, 35: 850–859.

Andrews E. 2016. Why was it called the 'spanish flu?' The 1918 influenza pandemic did not, as many people believed, originate in Spain. https://www.history.com/news/why-was-it-called-the-spanish-flu.

Anilionis, A., Wunner, W.H. and Curtis, P.J. 1981. Structure of the glycoprotein gene in rabies virus. *Nature*, London, 294: 275–278.

Barquet, N., Domingo, P. 1997. Smallpox: the triumph over the most terrible of the minister of death. *Annals of Internal Medicine*, 127(8): 635–642.

Barry, R., Winegar, R. and Freiberg, A.N. 2012. Recent Progress in Henipavirus Research: Molecular Biology, Genetic Diversity, Animal Models. *Antiviral Research*, 95: 135-49.

Brauburger, K., Hume, A.J., Mühlberger, E. and Olejnik, J. 2012. Forty-Five Years of Marburg Virus Research. *Viruses*, 4(10): 1878–1927. doi: 10.3390/v4101878.

Brenner, S. and Horne, R.W. 1959. A negative staining method for high resolution electron

microscopy of viruses. *Biochimica et Biophysica Acta*, 34:103-110.

Centers for Disease Control and Prevention Ebola outbreaks 2000-2014. http://www.cdc.gov/vhf/ebola/resources/outbreaks.html.

Centers for disease control and prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD), 2019.

Chatterjee, P. 2018. Nipah virus outbreak in India. *The Lancet, World Report*, 391: (10136), pp. 2200.

Chen, Y., Liu, Q. and Guo, D. 2020. Emerging coronaviruses: Genome structure, replication and pathogenesis. *Journal of Medical Virology*, 92: 418-423. https://doi.org/10.1002/jmv.25681.

Cordelia, E., Coltart, M., Lindsey, B., Ghinai, I., Johnson, A.M. and Heymann, D.L. 2017. The Ebola outbreak, 2013–2016: old lessons for new epidemics. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*, 372(1721): 20160297.

COVID-19: Navigating Uncertainties Together. 2020. *Cell*, 16; 181(2), 209-210. doi: 10.1016/j.cell.2020.03.041.

Cucunawangsih, L., Lugito, N.P.H. 2017. Trends of dengue disease epidemiology. *Virology (Auckl)*, 8. doi: 10.1177/1178122X17695836.

Cynthia, S., Goldsmith, S. and Miller, E. 2009. Modern uses of electron microscopy for detection of viruses. *Clinical Microbiology Reviews*, 22(4): 552–563. doi:10.1128/CMR.00027-09.

de Groot, R.J., Baker, S.C., Baric, R.S., *et al.* 2013. Middle East respiratory syndrome corona virus (MERS-CoV): announcement of the Corona virus study group. *Journal of Virology*, 87(14): 7790–7792. doi:10.1128/JVI.01244-13.

de Silva, U.C., Tanaka, H., Nakamura, S., Goto, N. and Yasunaga, T. 2012. A comprehensive analysis of reassortment in influenza A virus. *Biology Open*, 1: 385-390. doi: 10.1242/bio.2012281.

Drutz, J.E. and Ligon, B.L. 2000. *Seminars in Pediatric Infectious Diseases.* Special article: Polio: Its history and its eradication, 11(4): 280-286.

Estes, M.K. and Cohen, J. 1989. Rotavirus gene structure and function. *Microbiological* Reviews, 53(4): 410–449.

Factsheets: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID). 2016. Division of High-Consequence Pathogens and Pathology (DHCPP).

Fehr, A.R. and Perlman, S. Maier, H.J., Bickerton, E. and Britton, P. 2015. Coronaviruses: an overview of their replication and pathogenesis. *Methods in Molecular Biology*, 1282: 1–23.

Fenner, F., Henderson, D.A., Arita, I., Jezek, Z., Ladnyi, I.D. 1988. Smallpox and its Eradication. Geneva: World Health Organization. ISBN 92-4-156110-6.

Fleischmann, W.R. Jr. 1996. Viral Genetics, In: Baron S, (editor). *Medical Microbiology*, 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; Chapter 43.

Flint, S.J., Enquist, L.W., Racaniello, V.R., Skalka, A.M. 2003. Principles of virology: molecular biology, pathogenesis, and control of animal viruses. 2nd ed. Washington, D.C., ASM Press.

Gelderblom, H.R. 1996. Chapter 41: Structure and classification of viruses http://www.ncbi.nlm.nih.gov/books/NBK8174/.

Gorbalenya, A.E., Baker, S.C., Baric, R.S., *et al.* 2020. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*, 5(4): 536–544.

History.com Staff. 2018. Outbreak of World War I. A&E Television Networks. https://www.history.com/topics/world-war-i/1918-flu-pandemic.

Izabela, A., Zybert, R., Wilschut, J., Smit, J.M. 2010. Dengue virus life cycle: viral and host factors modulating infectivity. *Cellular and Molecular Life Sciences*, 67:2773–2786.

Johnson, P. and Mueller, J. 2002. Updating the accounts: global mortality of the 1918–1920 "Spanish" influenza pandemic. *Bulletin of the History of Medicine,* 76(1): 105-115.

Keele, B.F., Van Heuverswyn, F., Li, Y. et al. 2006. Chimpanzee Reservoirs of Pandemic and Nonpandemic HIV-1. *Science*, 313 (5786): 523–526.

Koonin, E.V., Doljab, V.V., and Krupovic, M. 2015. Origins and evolution of viruses of eukaryotes: The ultimate modularity. *Virology*, 479-480: 2–25 https://doi.org/10.1016/j.virol.2015.02.039.

Koonin, E.V., Senkevich, T.G. and Dolja, V.V. 2006. The ancient Virus World and evolution of cells. *Biology Direct*, 1(1): 29. doi:10.1186/1745-6150-1-29.

Kuhn, R.J., Zhang, W., Rossmann, M.G., Pletnev, S.V., et al. (2002). Structure of Dengue Virus: Implications for Flavivirus organization, maturation, and fusion. *Cell*, 108(5): 717–725.

Lan, J., Ge, J., Yu, J., et al. 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, 581 (7807). doi: 10.1038/s41586-020-2180-5.

Ledford, H. 2020. How does covid-19 kill? Uncertainty hampers doctors' ability to choose treatments. *Nature*, 580, 311-312.

Lewis, P., Hensel, M. and Emerman, M. 1992. Human immunodeficiency virus infection of cells arrested in the cell cycle. *EMBO Journal,* 11: 3053-3058.

Li, F., Li, W., Farzan, M. et al. 2005. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science*, 309: 1864–1868.

Little B. 2020. SARS Pandemic: How the virus spread around the world. https://www.history.com/news/sars-outbreak-china-lessons.

Longo, D.L. 2012. Chapter 187: Influenza. Harrison's principles of internal medicine (18th Edition), New York: McGraw-Hill. ISBN 978-0-07-174889-6.

Malvy, D., McElroy, A.K., de Clerck, H., Gunther, S. and Griensven, J.V. 2019. Ebola virus disease. https://doi.org/10.1016/S0140-6736 (18)33132-5.

Marco, A.M., Steven, J.M., Jones, C.R. et al. 2003. The genome sequence of the SARS-associated coronavirus. *Science*, 300 (5624), 1399-1404. doi: 10.1126/science.1085953.

Massung, R.F., Liu, L., Qi, J., et al. 1994. Analysis of the complete genome of smallpox *variola* major virus strain Bangladesh -1975. *Virology*, 201(2):215-40.

McMichael, A.J. 2004. Environmental and social influences on emerging infectious diseases: past, present and future. *Philosophical Transactions of the Royal Society B*, 359(1447): 1049–1058.

Microbiology by numbers. 2011. *Nature Reviews Microbiology*, 9: 628. https://doi.org/10.1038/nrmicro2644.

Mousavizadeh, L. and Ghasemi, S. 2020. Genotype and phenotype of COVID-19: Their roles in pathogenesis. *Journal of Microbiology Immunology and Infection,* https://doi.org/10.1016/j.jmii.2020.03.022.

Muesing, M.A., Smith, D.H., Cabradilla, C.D., Benton, C.V., Lasky, L.A. and Capon, D.J. 1985. Nucleic acid structure and expression of the human AIDS/ lymphadenopathy retrovirus. *Nature,* 313: 450-458.

Newman, A.P., Reisdorf, E., Beinemann, J., Uyeki, T.M., Balish, A., Shu B., Stephen Lindstrom, S., Achenbach, J., Smith, C. and Davis, J.P. 2008. Human Case of Swine Influenza A (H1N1) Triple Reassortant Virus Infection, Wisconsin. *Emerging*

Infectious Disease, 14(9): 1470–1472. doi: 10.3201/eid1409.080305.

Nipah Virus (NiV) Infection. 2018. WHO Fact sheet, WHO.

Oldstone, M.B.A. 2014. History of Virology, in Encyclopedia of Microbiology (Fourth Edition).

Payne, S. 2017. Viruses: Understanding to Investigation. 1st Edition. Academic Press.

Potter, C.W. 2001. A history of influenza. *Journal of Applied Microbiology*, 91: 572 -579.

Richardson, E.T. and Fallah, M.P. 2019. The genesis of the Ebola virus outbreak in West Africa. The Lancet infectious disease, 19: 348-349. http://dx.doi.org/10.1016/S1473-3099(19)30055-6.

Sah, R., Rodriguez-Morales, A., Jha, R., Chu, D.K.W., Gu H., et al. 2020. Complete genome sequence of a 2019 Novel Coronavirus (SARS-CoV-2) strain isolated in Nepal. *Microbiology Resource Announcements*, 9 (11): e00169-20. DOI: 10.1128/MRA.00169-20.

Singh, S.K. and Ruzek, D. 2014. Viral hemorrhagic fevers. *CRC Press*, Boca Raton, pp 596.

Storch, G.A. 2000. Diagnostic Virology: *Clinical Infectious Diseases*, 31(3): 739–751. https://doi.org/10.1086/314015.

Suzuki, H. 2019. Rotavirus Replication: Gaps of Knowledge on Virus Entry and Morphogenesis. *The Tohoku Journal of Experimental Medicine*, 248 (4): 285–296. doi:10.1620/tjem.248.285.

Thiel, V. 2007. Coronaviruses: Molecular and Cellular Biology. 1st Edition, Caister Academic Press.

Types of Influenza Viruses Seasonal Influenza (Flu). 2017. Centers for Disease Control and Prevention (CDC), 27 September 2017.

Verdecchiaa, P., Cavallinia, C., Spanevellob, A., Angelib, F. 2020. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *European Journal of Internal Medicine*. https://doi.org/10.1016/j.ejim.2020.04.037.

WHO Director-General's opening remarks at the media briefing on COVID-19. 2020. World Health Organization (WHO) (Press release).

WHO Ebola Response Team Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections. *New England Journal of Medicine,* 2014 Oct 16; 371(16): 1481–1495.

Wong, A.C.P., Xin, L., Lau, S.K., Woo, P., Patrick, C.Y. 2019. Global epidemiology of Bat Corona viruses. *Viruses*, 11(2): 174. doi:10.3390/v11020174.

World Health Organization, Regional Office for Africa, Disease Surveillance and Response Programme, Disease Prevention and Control Cluster. [2014]. Ebola Virus Disease in West Africa ([Situation as of 23 November 2014)]. https://apps.who.int/iris/handle/10665/144505.

World health statistics. 2018. Monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization.