

The Covid Crisis: Return of Fear and Uncertainty

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ABSTRACT

Covid-19 is the news once again making headlines and announcing its comeback. It has had a profound impact since its December 2019 emergence in Wuhan, China. The 2019 outbreak was a turning point affecting nearly every country with varying degrees of severity, has led to significant worldwide mortality and morbidity, causing millions of deaths and long lasting health complications for many. The rapid spread worldwide, led to the World Health Organization calling it a “global pandemic” on March 11, 2020. Covid-19 is a viral zoonotic disease which spreads from animals-to-humans and humans-to-humans. It is caused by the novel SARS-CoV-2 coronavirus. Covid-19 is an enveloped, positive-sense single stranded RNA virus that attaches to the host cell through its spike protein that facilitates entry into the host cell via the ACE2 receptors. The virus primarily spreads through respiratory droplets of an infected person when coughing, sneezing or talking. Asymptomatic or pre-symptomatic individuals can also spread the disease. Covid-19 has caused major social, economic, business and lifestyle disruptions. Covid-19 symptoms range from mild to severe and appear between 2-14 days after exposure. The most common symptoms include fever, cough, shortness of breath, fatigue, muscle or body aches, loss of taste or smell, headache, nausea or vomiting and diarrhea. In more severe cases, it can cause pneumonia, ARDS, organ failure and even death. Covid-19 diagnosis is mainly done by polymerase chain reaction (PCR) - the gold standard of testing. Histologically, Covid-19 is responsible for many changes to the lungs, heart, kidneys, liver and GI tract. Symptoms lasting beyond the primary infection (“long-covid”) have shown to have a significant impact on an individual’s daily life. There are several factors that increase the risk of infection - individuals who are over 60 are at a higher risk versus younger individuals. Individuals with comorbidities, those who are immunocompromised, those who smoke, use alcohol, lack exercise or are unvaccinated have a higher risk of infection. Infected individuals with underlying health conditions can experience a host of complications such as mild to severe organ impairment (heart, liver, kidney, brain), diabetes, dementia, neurological, GI, hematological or muscular pain. The risk also increases for individuals who are lower on the socio-economic spectrum. The Centers for Disease Control and Prevention (CDC) recommends the use of vaccines, masks, social distancing, hygiene protocols, quarantine and isolation to reduce the transmission risk, prevent hospitalization, severe illness or death. The advent of highly efficacious vaccines using novel mRNA technology has seen the effects of the disease wane. Covid-19 infection rates are slowing and the pandemic is giving way to an endemic. However, one question remains - how well prepared are we for the next major outbreak?.

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1. Introduction

Over the course of world history, human-kind has witnessed numerous endemics, epidemics and pandemics that have affected millions with devastating consequences [1-3].

To the layman, epidemiologists use the term “endemic”, “epidemic” and “pandemic” seemingly interchangeably. Although these descriptions can be confusing, they have three very different meanings and more importantly, three very different implications. An endemic refers to the constant presence of a disease in a population within a geographic area. An epidemic is used to describe an incidence of a disease or virus that is actively spreading but remains contained in one or more areas and is generally isolated from the rest of the world. A pandemic however, refers to the same viral or disease incidence, but it is actively spreading across borders and putting large numbers of the world’s population at risk of infection.

In 2019, the world witnessed the beginnings of a global pandemic in the form of a new respiratory illness. Covid-19 is a highly

contagious infectious disease caused by the novel coronavirus “SARS-CoV-2”. With its highly transmissible nature, a new global health crisis threatening millions around the world suddenly emerged. The rapid spread of this virus induced respiratory illness in patients with symptoms similar to that of pneumonia, the flu or the common cold. As we now know, with more than seven hundred million cases and more than seven million deaths globally, Covid-19 was anything but benign [4-21].

The exact cause of Covid-19 is unknown, but evidence suggests it likely originated in bats. The viruses live in, but do not infect the animals. At times the virus jumps from one animal species to another. The virus may mutate or change as they infect other animals. These zoonotic viruses have the ability to jump from an intermediate animal host to humans. The coronavirus is often found in bats, cats and camels.

Covid-19 (SARS-CoV-2) first emerged in December 2019 in the Hubei Province in the city of Wuhan (China). Its original name “Coronavirus-19” is abbreviated as “Covid-19”. The “CO” stands for Corona, “VI” for virus, “D” for disease and “19” is the year of its origin. The disease was formerly referred to as “2019 novel Corona” or “2019-nCoV”.

It is thought the first people infected either worked or visited the Huanan Seafood Market - markets that sold meat, fish and live animals. The World Health Organization (WHO) was informed of an outbreak of “viral pneumonia” on December 31, 2019 in a cluster of patients. The WHO declared Covid-19 a “Public Health Emergency of International Concern” on January 30, 2020 and a “Pandemic” on March 11, 2020. With porous borders and the ease of global travel, this declaration set the stage for the ravages this disease would inflict on nearly every country in the world.

Since its initial vice-like grip on the world, clinical and experimental studies have been conducted to identify the virus and its ever-evolving nature. Scientists now have a better depth and breadth of knowledge to identify effective means of prevention and treatment.

The coronavirus name is defined by its “corona” or “crown-like” spikes that appear on the surface of the virus. Some examples of the coronavirus in humans are: Severe Acute Respiratory Syndrome (SARS), Mild East Respiratory Syndrome (MERS) and the common cold.

2. Viral Endemics, Epidemics & Pandemics

Endemics, epidemics and pandemics are a centuries-old phenomena that have scarred our history books from the earliest of times. The voracity of these has left civilizations shell-shocked, bringing nations to their knees and leaving economies in ruins.

Some of the most significant infectious diseases in human history have been characterized by making the jump from animals to humans and from humans to humans. Regardless of their characteristics, the social, cultural, religious, political and economic fallout of these outbreaks is profound. Some of the more life altering pandemics are detailed below [22-41].

Antonine Plague (165-180 AD): The Roman Empire was inflicted with what was likely smallpox or measles killing between 5-10 million people.

The Justinian Plague (541-542 AD): The Byzantine Empire during the reign of Emperor Justinian was subject to a pandemic that is considered to be one of the first recorded in history. It killed between 25-50 million people.

Black Death / Bubonic Plague (1347-1351): This famous outbreak appeared in the mid-14th century and spread across Europe, Asia and Africa. An estimated 75-200 million succumbed to its devastating grip. This outbreak was caused by the *Yersinia pestis* bacterium and spread through infected fleas and rats.

The Great Pestilence (Cocoliztli Epidemics of the 16th Century): This mysterious outbreak which affected Mexico and Central America displayed symptoms such as high fever and bleeding. It is said that between 5-15 million indigenous people succumbed to it over its multi-year recurrence.

Cholera (1817- Present): The first cholera pandemic originated in India and spread across Asia and Europe between 1817 and 1824. The second cholera pandemic spread from Asia to Europe and America between 1829 and 1851 and most recently to South Asia (1961). Cholera is characterized as an acute diarrheal illness caused by the ingestion of food or water contaminated with the *Vibrio cholerae* bacteria usually found in shellfish and plankton.

The Third Plague Pandemic (1855-1959): This incidence of the bubonic plague impacted all five continents. Major cities like Hong Kong (1894), Bombay (1896), Sydney (1900), Cape Town (1901) and Los Angeles (1924) were all affected.

Spanish Flu (1918-1920): The Great Influenza was exceptionally deadly, affecting an estimated 500 million people and killing

upwards of 50 million. It was caused by the H1N1 subtype of the influenza A virus.

Asian Flu (1957-1958): Originating in Guizhou, China, it is caused by the influenza A virus subtype H2N2. It is estimated that between 1- 4 million deaths globally were caused by the Asian flu.

Hong Kong Flu (1968-1969): A decade after the Asian flu, the emergence of the Hong Kong flu resulted in one million deaths. It was caused by the H3N2 strain.

Ebola Virus (1976-Present): First detected in South Sudan and the Democratic Republic of Congo, it kills between 25% and 90% of those infected. Sporadic outbreaks between 1976-2016 have claimed close to 12,000 lives.

HIV/AIDS (1980-Present): Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the immune system. HIV made the jump from primates to humans during the early-to-mid 20th century in west-central Africa. There is no vaccine or cure for HIV and it has been attributed to 40 million deaths and counting.

Swine Flu (2009-2010): First detected in La Gloria, Mexico. This H1N1 virus is characterized by a reassortment of bird, swine, human and Eurasian pig flu virus. It mainly affected younger populations and pregnant women.

Zika Virus (2015-2016): The Zika virus outbreak of 2015 caused only mild symptoms like fever, headache, vomiting, muscle pain and skin rash - more alarmingly, it caused birth defects like microcephaly and neurological disorders in newborns. It comes from the Flaviviridae family of viruses and is spread through mosquitoes.

SARS (2002-2004): Severe Acute Respiratory Syndrome outbreak resulted in over 8,000 cases and approximately 800 deaths. It is a viral respiratory disease of zoonotic origin caused by the SARS-CoV-1 virus.

MERS (2012): Middle East Respiratory Syndrome originated in the Middle East and was attributed to over 2,500 cases and 870 deaths.

Covid-19 (2019-Present): Perhaps the most well-known respiratory ailment in modern age emerged in the latter part of 2019. COVID-19 is a highly contagious disease caused by the SARS-CoV-2 coronavirus. To date more than 700 million cases and more than 7 million deaths have been noted. The following serves as a brief timeline of events and activities related to Covid-19:

2019

December	The first cases of a novel pneumonia-like disease are detected in Wuhan, China
December 31	Chinese authorities inform the World Health Organization (WHO) of multiple cases of an unknown disease

2020

January	SARS-CoV-2 is identified as the causative virus
January 11	The first death from the novel respiratory disease COVID-19 is reported in Wuhan
January 13	Thailand, Japan and South Korea start reporting cases
January 30	The WHO declares Covid-19 a Public Health Emergency of International Concern (PHEIC)
February 11	The WHO designate “Covid-19” (coronavirus disease 2019) as the official name

March 11	The WHO declares COVID-19 a global pandemic as a declaration the virus has spread to nearly every country in the world. Global lockdowns and travel restrictions are implemented. Early virus mutations (D614G) appear; increasing transmissibility
April - June	Global case count surpasses 10 million with hundreds of thousands of deaths. Healthcare systems face immense pressure (Italy, US, and Spain)
July - December	Second and third waves of infection appear in parts of the world Vaccine development progresses rapidly with early emergency use authorizations granted for vaccines from Pfizer (Pfizer-BioNTech) and Moderna. Highly transmissible variants Alpha (B.1.1.7) emerge in the UK.
October	Delta (B.1.617.2) is first seen in India
	Beta (B.1.351) is identified in South Africa in late 2020

2021

January - March	Mass vaccination campaigns commence worldwide targeting high-risk groups first. Gamma (P.1) discovered in Brazil known for immune evasion
April - June	Highly transmissible Delta (B.1.617.2) is globally dominant
July - December	Omicron (B.1.1.529) first reported in South Africa in November becomes the dominant strain - spawning off numerous sub-variants like BA.2, BA.4, BA.5 and XBB. Delta becomes the dominant global strain globally causing infection surges even in highly vaccinated regions. Vaccine boosters are introduced to counter waning immunity and variant resistance

2022

January - March	Highly transmissible Omicron (B.1.1.529) is spreading rapidly but causing milder illnesses. Global case counts reach their highest level
April - December	Restrictions ease globally - a focus on vaccination counts Omicron (B.1.1.529) sub variant - BA.2, BA.4, BA.5 and XBB are localized concerns

2023

January - June	Global case counts and deaths start significant decline WHO declares an end to COVID-19 PHEIC in May Omicron (XBB.1.5) causing up to 25% of new infections
July - December	Surveillance and vaccination efforts continue with focus on high-risk populations and new variants

2024

January - Present	COVID-19 remains a circulating pathogen with localized outbreaks. Vaccine updates released periodically to target emerging variants. Omicron (KP.3.1.1, EG.5 and BA.2.86) variant and its sub-variants have been the dominant strain in the U.S.A. Flirt Variant: As of early May, KP.2 makes up about 28% of infections
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3. Epidemiology

The epidemiology of Covid-19 involves understanding many factors and characteristics that make up the disease. Studying its transmission patterns and influencing factors on its progress is paramount to understanding the disease. Understanding incubation and infection periods are critical. Understanding how a population is impacted by an emerging disease and its variants. How an effective and dynamic public health response administered hand-in-hand with an effective clinical response (i.e. vaccinations) is used to establish preventive measures, attenuated severity, declining infection rates and finally disease containment [42-55].

Global Spread

Covid-19 was first identified in Wuhan, China in December of 2019. Due to its highly transmissible nature and its rapid global spread, the WHO declared Covid-19 a pandemic in March of 2020. From a micro perspective, infected individuals can spread the disease to 2-3 other individuals, which directly impacts public health and herd immunity parameters. From a macro perspective, Covid-19 has produced several waves, phases, variants and severities worldwide. This is mainly due to a multitude of country-specific factors like public health policy, local healthcare infrastructure, healthcare intervention and vaccine availability.

Incubation and Infection

Covid-19 has an incubation period of between 2-14 days with an average of 5-6 days. The onset of symptoms usually appear between 1-2 days after exposure.

Transmission

Covid-19 primarily spreads through the aerosolized droplets of an infected person when they cough, sneeze, talk or breathe. Asymptomatic or pre-symptomatic individuals also have the ability to spread the virus. It is advisable to avoid close personal contact with infected persons and to remain in well-ventilated areas. Although rare, contact with contaminated surfaces or objects has been known to transmit the disease.

Demographics

Covid-19 affects all demographics. Three major categories are: age, environment and socio-economic factors. Age related factors expose vulnerabilities in adults over the age of 65; as they are at higher risk for severe illness and death. This demographic are usually immuno-compromised and have underlying health conditions (i.e. cardiovascular disease, respiratory ailments, diabetes, kidney disease). Environmental factors impact individuals who live in close settings, those with prolonged exposure to infected person(s), those who live in densely populated areas or environments with inadequate airflow. Socio-economic factors such as ethnicity, living conditions, occupation, access to healthcare impact Covid-19 risk.

Clinical Outcomes

Individuals can experience Covid-19 symptoms that range from mild to severe. In severe cases, hospitalization, ICU care (i.e. intubation) and death are all possible outcomes. In addition to this, long covid symptoms like fatigue, joint pain, cognitive impairment and the like linger on even after recovery. Covid-19 death rates range in the 1-3% Case Fatality Rate (CFR) - factors such as age, comorbidities, healthcare capacities are all contributing factors.

Covid-19 Variants

After the appearance of the initial virus, variants and sub-variants emerged. SAR-CoV-2 mutated over time into the Delta, Omicron and their sub-variants. These variants caused new waves of infection globally. Each variant has a unique mutation in the spike protein which alters its characteristics. These characteristics can include an increase in transmissibility, altered severity and vaccine efficacy - all contributing factors to varying epidemiological patterns. In the case of Omicron, this variant spread with greater ease and speed than earlier strains, thus leading to larger and far-reaching waves of infection. In other cases, certain variants demonstrated reduced vulnerabilities to immunity from prior infections or vaccinations.

Public Health Administration & Response

Public health administration and response is only as good as the governments that run them. Accurate data collection and reporting, widespread testing and effective contact tracing, establishing social protocols and public awareness campaigns, vaccination development and administration - are all essential in containing the viral spread.

Vaccinations & Social Protocols

Two drivers of crucial importance in mitigating the fallout of these viral events are mass vaccinations and establishing social protocols. Mass scale vaccination is important for reducing the spread, severity and mortality of the virus. Modern day Covid-19 vaccines have proven very effective in preventing severe disease, hospitalization and death - even in the face of newly emerging variants. Establishing and following strict social protocols such as social distancing, wearing masks, frequent washing of the hands, quarantine/isolation when called for - further enhance the goal of containing the viral spread.

4. Etiology

The etiology of Covid-19 focuses on the cause(s) of the disease, the pathogen(s) responsible for the disease and the biological mechanisms behind the disease. All of these determine how a disease infects and affects the body. Only after this, can downstream activities used to contain and control the disease be addressed. Crucial milestones such as vaccine development, crafting and administering public health policy, mass vaccination campaigns and global health impact risks are an extension of a disease's etiology [56-61].

Pathogen

The pathogen for Covid-19 is SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). Covid-19 is a novel coronavirus which belongs to the Coronaviridae family and the Betacoronavirus genus. It shares genetic similarities to SAR-CoV and MERS-CoV; coronaviruses that caused the outbreak of 2003 and 2012 respectively.

Origins

In December of 2019, SARS-CoV-2 was first detected in humans. The place of origin was Wuhan, China, more specifically, the live

animal and fish markets there. It is believed that bats were the primary hosts, as they harbor many coronaviruses genetically similar to SARS-CoV-2. Zoonotic transmission through an intermediate animal host, most likely pangolins or some other wild animal, appear to be responsible for the jump to humans. However, an exact pathway remains unclear.

Viral Structure

The genetic information of Covid-19 is encoded on a 30,000 single strand nucleotide of positive-sense RNA, making it one of the largest genomes among RNA viruses. The genetic material encodes structural and nonstructural proteins: Spike (S), Envelope (E), Nucleocapsid (N) and Membrane (M). The club-shaped S Protein on the envelope gives the coronavirus its characteristic crown-like appearance.

Pathogenesis

SARS-CoV-2 enters the host cell by binding its spike protein to the ACE2 receptor on the human cell. The ACE2 receptor cells are found in abundance in respiratory tract tissue, as well as tissues of the heart, kidney and GI tract.

Viral Mutation

The Covid-19 virus is in a constant state of mutation. These mutations, especially in the spike protein, result in viral variants. Viral variants allow for a faster spread either through higher transmissibility rates or in most cases, evasion of the immune system.

Risk Factors

Different demographics are at a higher risk of infection. The elderly are classified as high risk candidates due to having compromised immune systems and underlying age-related conditions such as cardiovascular disease, diabetes, kidney disease and respiratory ailments. Other demographic profiles also pose higher risk; these include smokers, those who have sedentary lifestyles and those who are obese.

5. The Virus Structure

The structure of the SARS-CoV-2 is complex and consists of important moieties. It is an enveloped, positive-sense (can be directly translated by host ribosome into viral protein), single stranded RNA virus approximately 29.9 kilobases in length, with encoded structural and non-structural accessory proteins belonging to the Coronaviridae family. Understanding the structure of SARS-CoV-2 is crucial in developing diagnostic tools, vaccines and antiviral therapies (Figure 1) [62-69].

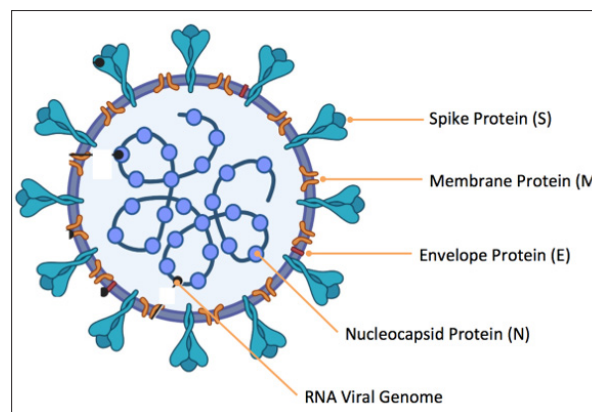


Figure 1: Coronavirus Structure - Showing Proteins and Virus RNA

There are four primary structural proteins encoded by the viral genome.

- Spike (S) Protein: A trimeric glycoprotein that forms spikes on

the surface giving it a crown-like appearance. This protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell to gain entry. It contains two subunits S1 and S2. S1 contains the receptor-binding domain (RBD) for ACE2 and S2 facilitates membrane fusion for viral entry.

- Envelope (E) Protein: A small structural protein that plays a crucial role in the viral assembly, contributing to the virus' ability to manipulate the host cell membrane.
- Membrane (M) Protein: It is the most abundant structural protein. It maintains the shape of the viral envelope and organizes the virus' assembly.
- Nucleocapsid (N) Protein: It encapsulates the viral RNA genome protecting it in replication and transcription. It plays a role in modulating the host's immune response.

In addition the virus has a lipid envelope and accessory/nonstructural proteins.

- Lipid Envelope: A lipid bi-layer derived from the host cell during viral budding. It embeds the spike, envelope, membrane proteins and makes the virus susceptible to disinfectants and detergents.
- Accessory and Non Structural Proteins (NSPs): NSPs are encoded regions of the genome which are necessary for replication, immune evasion and host response modulation.

The entry of SARS-CoV-2 into host cells is a multi-step process that involves receptor bindings, membrane fusion and a viral genome release (Figure 2). It then proceeds to affect the body at the molecular level and then at the systemic level (organs). Understanding the mechanism behind the invasion and replication assists in developing effective vaccines and other treatment protocols to control and contain the impact of the disease. The first step is the viral entry or invasion into the host cell. SARS-CoV-2 enters the host cell through the angiotensin-converting enzyme 2 (ACE2) receptor. The spike protein binds to the ACE2 receptor on the surface of human cells thereby facilitating the entry. The next step is fusion. After the attachment, the virus undergoes an adaptational change that allows it to fuse with the host cell's membrane. This process is facilitated by cellular proteases such as serine. Once this step is complete, it undergoes the replication phase. Once the virus is inside the host cell, it releases its RNA genome. This is then translated and replicated within the host cell leading to the production of new viral particles. The next phase of this process is where systemic failures occur. The virus causes direct damage to cells, particularly the respiratory system where cell apoptosis occurs followed by cellular dysfunctions. The body's response includes both innate and adaptive mechanisms - recruiting immune cells, the production of interone and other cytokines causing "cytokines storms"; which result in massive tissue damage and organ failure.

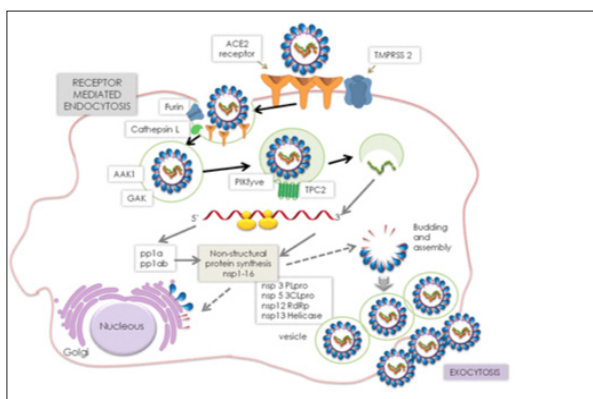


Figure 2: Mechanism of Covid-19 Entry into the Cell

Adapted from the Journal of Medicinal Chemistry Vol 63 / Issue 21. June 2020.

6. Covid-19 Variants

Covid-19 variants reference the mutation in the genetic material (RNA) of the SARS-CoV-2 virus over time. These mutations occur as the virus replicates and spreads. There are approximately 12 recorded variants of Covid-19, and that figure is likely to increase as the virus continues to mutate. Variants differ in their transmissibility, severity and their ability to evade immunity. While most mutations are harmless, others significantly impact how the virus behaves. Some variants may thwart the effectiveness of vaccines, diagnosis or treatment protocols [70-74].

The WHO and other health agencies classify variants of the SARS-CoV-2 virus based on their potential impact to the public. By identifying and understanding the impact each variant has, public health officials can devise virus control and containment strategies. Each variant has unique characteristics that define it - here are some of the more salient ones. Mutation: is a change in the virus' genetic material (RNA) sequencing during replication. Some mutations are benign while others are not. Variants: are defined by the number of mutations they undergo which differentiate them from the original virus. Lineage: is used to describe a variant which shares a common ancestor. Variants of Interest: is used to reference a specific genetic change in the variant that may affect its transmissibility, immune response or severity. Variants of Concern: is used to describe a variant with evidence of increased transmissibility, increased severity and reduced effectiveness of vaccines or treatment (Delta, Omicron). Variants of Consequence: is used to describe a variant with evidence that current preventive measures (diagnosis, treatment protocol, vaccines) are significantly less effective.

Key Variants of SARS-CoV-2:

- Alpha Variant (B.1.1.7): First identified in the UK (September 2020). This variant possesses higher transmissibility, increased severity and increased binding capacity to human cells through a mutation in the spike protein.
- Beta Variant (B.1.351): First identified in South Africa (May 2020). It contains mutations that may affect vaccine efficacy (resistance).
- Gamma Variant (P.I.): First identified in Brazil (November 2020). It contains mutations associated with higher transmissibility and lower vaccine efficacy.
- Delta Variant (B.1.617.2): First identified in India (October 2020). It has shown a significantly higher transmissibility with a higher risk of severity.
- Omicron Variant (B.1.1.529): First identified in South Africa (November 2021). It is characterized by numerous mutations in the spike protein leading to higher transmissibility but with weaker severity.
- XBB Variant: First identified in November 2022. It is from the Omicron lineage and exhibits increased transmissibility and a partial immune response with lower vaccine and treatment effectiveness.
- The Flirt Variant: First identified in 2024. It is highly contagious and its lineage hails from the Omicron strain (evolving from JN.1 and KP.2).
- The KP.3.1.1 Variant: This is the latest and most predominant strain found in several regions and responsible for an increase in cases amongst both older and younger populations.

The impact that variants have are multi-faceted. Some variants affect the transmissibility and spread more easily than the original strain

(Delta, Omicron). Some result in greater severity of illness. Others modify the immune response in that they evade immunity from prior infections or vaccinations. Changes in the genetic sequence of Covid-19 variants may affect testing accuracy, resistance to antiviral drugs or monoclonal antibodies and attenuated immune response.

7. Statistics

Statistics, especially in the case of a viral outbreak and spread are crucial in determining important aspects of the disease. Understanding the initial point of origin, case counts, the rate of spread, death rates, recovery rates, the effectiveness of public health policy and vaccination campaigns. All this information gathering and analysis leads to better control and containment of current and future viral outbreaks. Case data is regularly collected, updated and analyzed as new information is made available [75-80].

Covid-19 by the Numbers

Since the beginning of the Covid-19 pandemic up until the end of 2024, there have been over 800 million globally confirmed cases. During the same period, the global death rate is at just over 7 million. 13 billion Covid-19 vaccinations have been administered globally. In countries that are resource-advantaged, greater than 70% of the population has been covered; conversely, in countries that are resource-constrained, less than 20% of the population has been covered. Global case fatality rates (CFR) range from 1-3% - higher mortality rates are attributed to older populations and in individuals with comorbidities. The CFR was high during the initial outbreak but has since decreased due to improved treatment and vaccinations (variant coverage, availability).

Regional Differences

Even though the majority of infected individuals recover from Covid-19, recovery rates are largely dependent on region, the caliber of national healthcare, testing/vaccination availability and vaccination/treatment effectiveness amongst others. In North America, the United States witnessed the highest number of cases and deaths. Canada and Mexico saw a significant number of outbreaks occur during this period as well. In South America, Brazil and Argentina experienced a substantial number of cases, with Brazil being hit particularly hard with a higher than normal mortality rate. In Europe, multiple waves of infection hit the UK, France, Germany, Italy and Spain. In Africa, several countries and more notably, South Africa have seen a fair amount of infection. Asia fared the worst of all - China, Southeast Asia and especially India had a significant number of cases and faced a very deadly second wave mid-2021. Mortality rates will continue to ebb and flow per newly emerging variants and the access to the vaccines that guard against them.

Socio-Economic, Age & Gender Differences

Covid-19 and its grip on the world, brought to light how socio-economic, age & gender play a significant role in patient outcomes. From an age perspective, the elderly have demonstrated higher mortality rates than their younger cohorts. Younger populations have greater infection rates, yet lower death rates. Males have shown to have higher death rates compared to females. The economically disadvantaged and minorities have demonstrated higher infection rates and poorer patient outcomes than their more favorably advantaged opposites.

Healthcare Infrastructure

In general, the healthcare infrastructure of every country has, in one way or another, been impacted by Covid-19. Patient hospitalizations and ICU rates are largely influenced by age groups. Covid-19 variants like Alpha, Delta, Omicron and Flirt have driven infection surges -

sometimes in recurring waves. Each variant and wave has its own unique characteristic of severity and mortality. As such, depending on the country and its resources, Covid-19 hospitalizations/ICU care puts a significant strain on the healthcare infrastructure. Some richer countries fare better than resource constrained ones. High infection rates significantly impact healthcare workers - workforce shortages, limited resources and an overworked workforce all shape patient care and patient outcomes.

Vaccine Availability & Efficacy

Another stark reality of the Covid-19 pandemic was the general availability and efficacy of vaccines worldwide. Not all vaccines are created equally and not all vaccines are distributed democratically. Looking back, resource rich countries with higher caliber healthcare infrastructures and advanced public health policy in place, fared much better in patient care and patient outcomes. From a micro perspective, individuals who were unvaccinated or those with underlying conditions were more likely to require hospitalization and/or ICU care. Covid-19 variants also impacted ICU admission rates. Approximately 10-30% of those who recovered from Covid-19 experienced what is known as "long covid". Long-covid typically lasts from a few weeks to a few months. Patients complained about lingering symptoms such as fatigue, joint pain, brain fog, respiratory and cardiac ailments.

The net result of all these statistics demonstrate how Covid-19 disrupted the world order. Sickness, death, job losses, business disruptions that impacted all sectors of the economy (manufacturing, healthcare, agriculture, education, travel & hospitality, supply chain, etc.) resulted in GDP contractions estimated in the trillions. Not to mention increased rates in individual anxiety, stress, depression, mental health and lifestyle disruptions.

8. Medical Professionals

Medical doctors and support teams play a vital role in the treatment of Covid-19 cases. Each team is responsible for a very targeted and specialized focus that addresses diagnosis, treatment, management, recovery and support services [81-90].

Medical Doctors: Responsible for diagnosing and treating Covid-19 patients. This includes managing symptoms, coordinating care; and in critical cases, overseeing intensive care, intubation/ventilation services and other as-needed specialized care.

Primary Care Physicians: Responsible for the treatment, care, management, follow up and ongoing monitoring of mild to moderate Covid-19 cases. Also responsible for the treatment and management of long Covid-19 (fatigue, pain management, reduced cognitive abilities, reduced physical abilities).

Pulmonologists: Responsible for managing all areas of critical respiratory care for Covid-19 cases. This includes addressing complications like pneumonia and acute respiratory distress syndrome (ARDS). It also includes the management of mechanical intubation/ventilation, other advanced respiratory support services and pulmonary rehabilitation care to improve overall respiratory health.

Infectious Disease Specialist: Responsible for providing guidance on infection control measures and antiviral treatment for infectious diseases (Covid-19, others).

Nurses (ICU): Responsible for providing specialized care services for patients that include monitoring vital signs, administering medicines and respiratory support care.

Respiratory Therapists: Responsible for managing and administering mechanical ventilation, oxygen therapy and other specialized care in the event of severe cases.

Pharmacists: Responsible for managing, dispensing and providing guidance (drug interaction and side effects) for medications and antiviral drugs for Covid-19 cases.

Psychologists and Psychiatrists: Responsible for mental health therapy and support for Covid-19 patients and healthcare workers alike. They address any psychological stresses, anxieties and depression that Covid-19 can bring about.

Physical Therapists: Responsible for helping Covid-19 patients recover physical function, strength and mobility. This service can also be administered at home as part of a home health services support program.

Occupational Therapists: Responsible for helping Covid-19 patients regain the ability to perform self-care tasks and daily activities. This service can also be administered at home as part of a home health services support program.

Speech Pathologists: Responsible for helping Covid-19 patients experiencing difficulties swallowing or communicating.

Social Workers: Responsible for helping Covid-19 patients with the social and emotional challenges associated with illness and recovery. They offer emotional support, counseling and any other supportive assistance needed.

The care teams involved in the comprehensive management of treatment, recovery, rehabilitation and support, address a wide variety of very specialized services for a wide variety of special needs. The goal is to bring about the best possible patient outcome and return the patient to a pre-illness state.

9. Luminaries & Institutions

The following scientists have made significant contributions in our understanding, managing and mitigating the effects of the Covid-19 pandemic. They have touched everything from vaccine development, public health policy, epidemiology to researching treatments [91-95].

Dr. Anthony Fauci: Affiliated with the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Fauci played a preeminent role in leading the U.S. response to COVID-19. He was responsible for providing multi-faceted guidance on public health policy, vaccine research & development, treatment strategies and public communication. In addition, he has been a global ambassador in his advisory role to international health organizations, global vaccine distribution and promoting international collaboration. His efforts in crafting a response to the pandemic and advancing public health measures worldwide is unmatched.

Dr. Tedros Adhanom Ghebreyesus: Affiliated with the World Health Organization (WHO). Dr. Ghebreyesus served as the Director-General of the WHO. He was instrumental in coordinating the global response to the COVID-19 pandemic which included public health guidance and vaccine distribution.

Dr. Katalin Karikó: Affiliated with BioNTech/Pfizer. Dr. Karikó spearheaded the development of the Pfizer-BioNTech vaccine for use against Covid-19. Her pioneering work using mRNA technology proved to be a major breakthrough in vaccine development.

Dr. Ugur Sahin: Affiliated with BioNTech. Dr. Sahin served as co-founder of BioNTech and was instrumental in the development of the Pfizer-BioNTech Covid-19 vaccine. This vaccine was granted EUA (Emergency Use Authorization) status during the Covid-19 pandemic.

Dr. Drew Weissman: Affiliated with the University of Pennsylvania. Dr. Weissman along with Dr. Karikó, developed the mRNA vaccine technology. This technology was used in the development of Pfizer's BioNTech and Moderna's COVID-19 vaccines.

Dr. Robert Redfield: Affiliated with the Centers for Disease Control and Prevention (CDC). Dr. Redfield served as Director of the CDC and played a guiding role in public health measures and disease prevention for the CDC's response to the COVID-19 pandemic.

Dr. Maria Van Kerkhove: Affiliated with the World Health Organization (WHO). Dr. Van Kerkhove's deep understanding of Covid-19's epidemiology contributed to the response and guidance by the WHO on managing the pandemic.

Dr. David Ho: Affiliated with Columbia University. Dr. Ho's previous research on HIV/AIDS brought to bear a deep understanding on viral evolution and developing effective viral treatments.

Dr. John I. Gallin: Affiliated with the National Institutes of Health (NIH). Dr. Gallin's research on Covid-19 led to crafting an effective treatment approach.

Dr. Adar Poonawalla: Affiliated with the Serum Institute of India. Dr. Poonawalla leads the Serum Institute, which is a major producer of Covid-19 vaccine, Covishield. He has played a significant role in global vaccine distribution.

10. Public Health Agencies

10.1 US Based Agencies

There are several public health agencies worldwide that provide a guiding light in times of crisis. A public crisis usually rears its ugly head during pandemics, times of war or during natural disasters. The role of any public health agency is to provide guidance, craft policy, mass communication, research, development, testing and distribution of vaccine/medicines relevant to the situation and communicate with other such global agencies to warn and inform. Here are a few examples and their individual charters during the Covid-19 pandemic:

Centers for Disease Control and Prevention (CDC): The CDC is a federal agency that ensures public health protection and disease control. Responsible for developing Covid-19 testing protocols and monitoring systems. Responsible for publishing social protocol guidelines (use of masks, quarantine parameters, preventive measures and social distancing) to control and contain the viral spread. Responsible for providing real-time data on cases, hospitalizations and mortality rates. Responsible for coordinating with state and local health departments for public health response.

National Institute of Health (NIH): The NIH is one of the world's foremost medical research agencies. They are responsible for conducting research on SARS-CoV-2, including its pathogenesis and immune response. Responsible for supporting the development of Moderna's mRNA vaccine. Responsible for funding clinical trials for Covid-19 treatments (monoclonal antibodies, antiviral drugs). Responsible for launching the Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) program.

Food and Drug Administration (FDA): The FDA ensures the safety, efficacy and security of drugs, vaccines and medical devices. They are responsible for granting the Emergency Use Authorizations (EUAs) for Pfizer, Moderna and Johnson & Johnson's Covid-19 vaccines. Responsible for reviewing and approving diagnostic tests for Covid-19. Responsible for monitoring post-authorization therapeutic safety of vaccines.

Department of Health and Human Services (HHS): The HHS oversees public health and emergency response at the federal level. Responsible for managing vaccine distribution through "Operation Warp Speed". Responsible for funding support of healthcare systems and public health agencies.

Biomedical Advanced Research and Development Authority (BARDA): The BARDA develops countermeasures against medical threats to the public's health. Responsible for playing a pivotal role in the development and production of COVID-19 vaccines and therapeutics. Responsible for partnering with private companies to accelerate vaccine manufacturing. Responsible for funding innovations in diagnostic tools and treatments.

Federal Emergency Management Agency (FEMA): The FEMA provides disaster relief and emergency management. Responsible for supporting the logistics of vaccine and PPE distribution and delivery. Responsible for establishing vaccination sites across the country. Responsible for coordinating emergency response efforts with state and local governments.

Assistant Secretary for Preparedness and Response (ASPR): The office of the ASPR strengthens the nation's preparedness for public health emergencies. Responsible for managing the Strategic National Stockpile (SNS) for critical supplies (ventilators, PPE). Responsible for supporting the distribution of Covid-19 therapeutics and vaccines.

Occupational Safety and Health Administration (OSHA): OSHA Ensures workplace safety. Responsible for publishing workplace safety guidelines to reduce viral transmission rates. Responsible for monitoring compliance with health standards for industries such as healthcare, manufacturing, etc.

U.S. Public Health Service (USPHS): The USPHS supports federal public health initiatives. Responsible for deploying healthcare professionals to assist with vaccination campaigns. Responsible for direct care in underserved areas.

National Guard and Department of Defense (DOD): Agencies that support public health, logistics and emergency response. Responsible for assisting in vaccine distribution and administration. Responsible for providing logistical support for testing and PPE supply chains. Responsible for staffing temporary hospitals during viral surges.

It is clear to see this Herculean wall of service and support brought about a collaborative and multi-faceted response to the Covid-19 pandemic. The collective efforts across federal, state and local government delivered solid results including: advancing science, protecting the public's health, ensuring vaccine availability for all and maintaining a resilient healthcare infrastructure. It should not be lost that a well funded and well coordinated show of force can achieve anything.

10.2 Globally Based Agencies

Public health agencies outside the United States played a critical role during the Covid-19 pandemic. The roles and charters of these organizations were very similar to those in the US, in that they too contributed to the research, public health policy, case management, vaccination distribution/administration and response strategies. Below is a list of some of the more prominent global player and their contributions:

World Health Organization (WHO)

The WHO coordinated the global response to Covid-19. Responsible for announcing Covid-19 a Public Health Emergency of International Concern (PHEIC). Responsible for publishing global guidelines for testing, treatment and prevention. Responsible for managing the COVAX initiative which ensures equitable vaccine distribution. Providing risk assessments for the emergence of SARS-CoV-2 and its variants.

Health Canada

Health Canada coordinates national health policy. Responsible for approving and monitoring Covid-19 vaccines and treatments. Responsible for providing public health guidelines on masking, vaccination and quarantine. Responsible for coordinating with all provinces for equitable vaccine distribution.

Pan American Health Organization (PAHO)

The PAHO works with the countries of the Americas to improve the health and quality of life of their populations. Responsible for coordinating the COVID-19 response for Latin America and the Caribbean. Responsible for supporting vaccine procurement and distribution through COVAX. Responsible for providing guidance on strengthening the healthcare system.

Instituto Butantan and Fiocruz

A public institution affiliated with the São Paulo State Secretariat of Health. Responsible for developing and producing vaccines (CoronaVac). Responsible for conducting research on Covid-19 treatments and diagnostics. Responsible for providing technical support to Brazil's public health response.

Public Health England (PHE) / UK Health Security Agency (UKHSA)

The PHE protects and improves health and wellbeing and reduces health inequalities. The UKHSA prevents, prepares for and responds to infectious diseases and environmental hazards to keep all communities safe. Responsible for testing, contact tracing and public health campaigns in the UK. Responsible for supporting the AstraZeneca-Oxford vaccine development. Responsible for publishing vaccine efficacy data on SARS-CoV-2 and its variants.

European Centre for Disease Prevention and Control (ECDC)

The ECDC's mission is to strengthen Europe's defences against infectious diseases - it covers the European Union (EU) and the European Economic Area (EEA). Responsible for providing scientific advice and epidemiological analysis to member states. Responsible for coordinating monitoring and reporting Covid-19 cases in Europe. Responsible for publishing guidance on vaccination, public health measures and testing.

Robert Koch Institute (RKI)

The RKI is the public health institute of Germany. Responsible for coordinating Germany's monitoring and reporting of COVID-19 cases. Responsible for providing recommendations on public health measures and vaccination. Responsible for supporting genomic sequencing to monitor SARS-CoV-2 variants.

Africa Centres for Disease Control and Prevention (Africa CDC)
The Africa CDC strengthens the capacity and capability of Africa's public health institutions as well as partnerships to detect and respond quickly and effectively. Responsible for coordinating the continental response and vaccine distribution during the Covid-19 pandemic. Responsible for vaccine procurement by launching the African Vaccine Acquisition Task Team (AVATT). Responsible for strengthening testing capacity and public health infrastructure across the nation.

National Institute for Communicable Diseases (NICD)
The NICD is the national public health institute of South Africa providing reference to microbiology, virology, epidemiology, monitoring and public health research to support the government's response to communicable disease threats. Responsible for conducting genome sequencing to identify and monitor Covid-19 variants. Responsible for providing public health guidance and supported testing infrastructure in Africa. Responsible for coordinating vaccine distribution and public health campaigns.

Chinese Center for Disease Control and Prevention (China CDC)
The China CDC works to protect public health and safety by providing information to enhance health decisions and to promote health through partnerships with provincial health departments and other organizations. Responsible for conducting early studies on SARS-CoV-2 during the Wuhan outbreak. Responsible for aiding global research efforts by publishing the first genome sequence of the virus. Responsible for implementing strict containment measures (mass testing, lockdowns).

Indian Council of Medical Research (ICMR)
The ICMR is the apex body in India for the formulation, coordination and promotion of biomedical research. Responsible for developing indigenous testing kits and vaccines like Covaxin. Responsible for conducting studies on Covid-19 transmission and immunity. Responsible for providing guidelines for testing, treatment and containment in India.

National Institute of Virology (NIV)
The NIV is an Indian institute serving the area of virology. Responsible for playing a critical role in SARS-CoV-2 genomic sequencing. Responsible for supporting vaccine research and development. Responsible for conducting studies on virus behavior and immune response.

Australian Department of Health and Aged Care (DHAC)
The DHAC is responsible for health research, funding, promotion and regulation in Australia. Responsible for implementing strict border control measures to limit virus spread. Responsible for coordinated vaccination campaigns and public health messaging. Responsible for supporting genome research on SARS-CoV-2 variants.

Ministry of Health, Labour and Welfare (MHLW)
The MHLW is a cabinet level ministry of the Japanese government which provides services on health, labour and welfare. Responsible for leading Japan's response to Covid-19 - focusing on testing and healthcare system support. Responsible for monitoring variants and coordinating vaccine distribution. Responsible for promoting public health campaigns, including the "Three Cs": Avoiding Closed spaces - Crowded places - Close-contact settings.

In the above cases, the charter of these agencies is to work individually and collaboratively to address the challenges presented by the Covid-19 pandemic. Their roles encompassed research, public health planning, vaccination administration, healthcare system support,

shaping the global response to the pandemic and ultimately controlling and containing the virus.

11. Signs & Symptoms

Covid-19 is caused by the SARS-CoV-2 virus. It presents a wide range of morbidity symptoms from mild (80% of all cases) to severe (15% of all cases). In certain cases, the virus has led to prolonged health challenges known as "long covid". The signs and symptoms usually appear anywhere from 2 to 14 days. In many cases, mild to moderate symptoms are noted - in other cases, severe symptoms, including death, are observed. The prevention of Covid-19 is the result of a well developed, well funded healthcare system and an effective public vaccination campaign. With early detection of symptoms and other clinical presentations; prompt and accurate diagnosis and treatment can be administered to preserve positive patient outcomes (Figure 3) [96-109].

Asymptomatic Cases

Asymptomatic cases are described as those individuals that test positive for Covid-19, yet show no outward symptoms of the virus. Individuals who go on to show symptoms are called presymptomatic. In both cases, individuals who are asymptomatic and those who are presymptomatic can both spread the virus and infect other individuals. Most individuals that are infected with Covid-19 generally display mild to moderate symptoms, however, an increase in symptom severity can occur.

Mild Cases

For individuals who are infected with Covid-19 and show mild symptoms - their symptoms are not unlike the common cold or the flu. Mild cases consist of mild to moderate headaches, a persistent fever or chill and the constant feeling of being tired or exhausted. Other symptoms include body aches and pains, dry coughs and a sore throat.

Moderate Cases

For infected individuals that have shortness of breath, persistent high fever, extreme fatigue and tiredness, intense body pain, loss of taste/smell, nausea, vomiting and diarrhea; can be characterized as having moderate symptoms (Figure 3).

Severe Cases

In severe cases, symptoms of infected individuals are amplified to a greater degree. Severe respiratory distress, significant shortness of breath, severe chest pain/pressure, mental confusion, acute respiratory distress syndrome (ARDS), pneumonia, hypoxia and even death are all hallmarks. Of particular note, individuals who are above 65 years old, those that are immuno-compromised, those who suffer from chronic conditions (heart disease, kidney disease, obesity, respiratory disease) are also at greater risk of becoming severely infected (Figure 3).

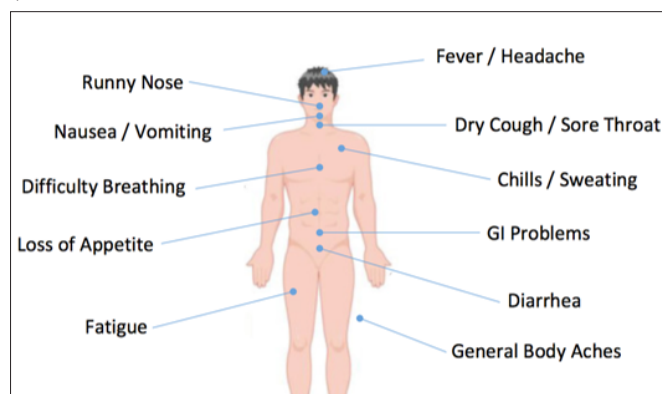


Figure 3: Signs & Symptoms Caused by Covid-19

Critical Cases

For critical-case infected individuals, symptoms include multiple organ failures (lung, kidney, heart), septic shock (sudden drop in blood pressure) and an increased risk of blood clots (pulmonary embolism).

Special Cases

Children and pregnant women comprise special cases. Infected children often show signs of fever, GI symptoms and cardiovascular issues. Pregnant women are no different than their non-pregnant counterparts, but additional care during pregnancy and delivery is required.

Long Covid-19 or Post Covid -19 Syndromes

One of the more interesting phenomena that has emerged from the multi-year onslaught of Covid-19 is the lingering illness known as “Long COVID”, or “Post Covid-19 Syndrome”. It describes a situation where certain individuals experience covid-like symptoms or develop new covid-like symptoms for many weeks or even months after their initial infection has subsided. It is thought to be related to immune dysregulation, chronic inflammation or lingering viral fragments. These ongoing symptoms can be described as:

- Neurological - symptoms that are described as having “brain fog”, memory retention issues, difficulty concentrating and mental fatigue. Sleep disorders or insomnia. Headaches, dizziness, loss of smell or taste, neuropathy or tingling sensations. Depression, anxiety and other mental health issues.
- Physiological - symptoms that can be described as ongoing tiredness, persistent fatigue, fever and continuous pain or discomfort in the chest, joints or muscles.
- Systemic - symptoms that impair cardiovascular (chest pain, palpitations, POTS) respiratory (persistent cough, shortness of breath), muscular-skeletal (muscle or joint pain) psychological (anxiety, depression, insomnia), GI (nausea, abdominal pain, loss of appetite and diarrhea) and endocrine functions.

Covid-19 typically lasts for 4 weeks and is acute respiratory and systemic phase illness demonstrating a full recovery in most cases, whereas Long Covid is a post infection, multi-system chronically fluctuating illness with a prolonged and uncertain recovery.

12. Risk Factors

Studies have shown that Covid-19 affects each individual differently based on their risk profile. In other words, some individuals are at higher risk for being infected with Covid-19 and more susceptible to its severity and complications. An individual’s risk factor is made up of several variables like age, general health, demographics and lifestyle. Effective public health policy is crafted based on understanding the mechanics of the virus or disease and how the general public will be affected by it. Once this is understood, defining disease treatment, disease management and disease prevention protocols embody a comprehensive public health response. The goal of any public health response is to control and contain a disease or viral outbreak [110-114].

Vaccination Status

Individuals who have not taken the Covid-19 vaccination (initial dose or variant boosters) remain at high risk of infection.

Age

Covid-19 has shown to affect the elderly more than any other group as they have a higher risk of contracting the virus. The reason is quite simple, the elderly are considered a group where the probability of having compromised immune systems, underlying

conditions and chronic ailments is far greater than their younger cohorts. The proceeding factors along with hospitalization rates, intensive care treatment and the probability of death increase in those over 65. Generally speaking, advanced age exposes one to greater risk that is associated with poorer prognosis and death.

Conversely, younger cohorts are less likely to contract Covid-19 due to their robust immune systems and the absence of comorbidities. Of note, both cohorts can get infected and spread infection.

Immunity

Having a compromised immune system increases the risk of infection. Immunocompromised individuals are those individuals with weakened immune systems. Becoming immunocompromised can result from a variety of factors such as: organ transplants, bone marrow transplants, chemotherapy treatments and autoimmune disorders (HIV/AIDS, etc.).

Comorbidities

Comorbidities is defined as any individual that is concurrently inflicted with one or more serious medical conditions. Individuals are at a higher risk of infection due to their weakened bodies fighting multiple ailments. These comorbidities can be any of: cancer (vulnerable due to immunosuppression from malignancy treatment), cardiovascular disease (hypertension, ischemic heart disease, heart failure), respiratory disease (COPD, asthma) cystic fibrosis, sickle cell anemia, obesity (linked to chronic low grade inflammation, impaired lung functions), diabetes (hyperglycemia, thromboembolism), neurological disorders (parkinsons, alzheimer’s), lung, kidney (impaired immune response, acute kidney injury) or liver disease (hepatic dysfunction, cirrhosis).

Gender

Studies and observational data suggest that males have a higher rate of infection than females. Pregnant women also have a higher risk of infection.

Socio-Economic Factors

Timely access to high calibre healthcare and effective treatment are factors that determine infection risk and consequences. Disadvantaged countries with less developed healthcare systems are limited in what assistance they may be able to provide. Other socio-economic factors like crowded living conditions and certain employment sectors come with higher risk of infection.

Lifestyle

Smoking, excessive alcohol use, sedentary lifestyles and genetic predisposition also contribute to a higher risk of infection.

13. Complications & Organ Adaptation

Being infected with Covid-19 may lead to a wide variety of complications. These complications can be far reaching in scope, severity and duration. Covid-19 can affect multiple organs and systems (Figure 4). Its symptoms can range from non-existent (asymptomatic) to very severe. Its duration can be a short acute phase to a prolonged phase, lasting several weeks to several months. Blood tests and imaging (X-ray, CT Scans, MRI) are performed on a regular basis to determine the status of vital organs, assess inflammatory markers and to evaluate any damage [115-121, 204-228].

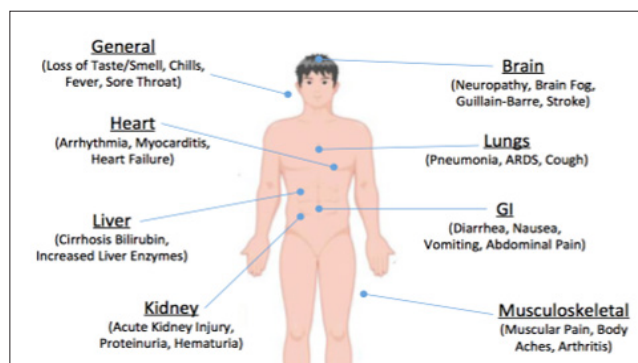


Figure 4: Effect of Covid-19 on Various Organs

Lungs / Respiratory: Covid-19 primarily affects the lungs, resulting in inflammation of the alveoli (air sacs). Acute Respiratory Syndrome (ARS) is a condition when the lungs do not get enough oxygen resulting in widespread accumulation of fluid and inflammation. In severe cases, scarring and lung function impairment occurs. The preceding make it difficult to breathe and may lead to a host of other physiological complications like: respiratory failure, lung fibrosis, and pneumonia.

Heart: Damage to the heart has been noted in infected individuals. Conditions such as inflammation of the heart muscle (Myocarditis), inflammation of the lining around the heart, postural orthostatic tachycardia syndromes (POTS), irregular heart beat (Arrhythmias), chest pains (Pericarditis), weakened heart muscles (Cardiomyopathy), palpitations and even heart failure.

Blood: Issues with abnormal clotting (Coagulation) is a noted complication that affects blood flow and oxygen levels. Abnormal blood clotting can result in very serious conditions like deep vein thrombosis (DVT), thromboembolism, thrombocytopenia, hemorrhaging, disseminated intravascular coagulation (DIC) and strokes. In some instances, pulmonary embolisms occur when blood clots travel to the lungs leading to life threatening situations.

Immune System: Covid-19 can have a profound effect on the immune system causing “cytokine storms” which result in tissue damage, multi-organ damage, inflammation, fever, fatigue, muscle pain and developing autoimmune diseases.

Neurological: Strokes, swelling of the brain (Encephalitis), Guillain-Barre syndrome, “brain fog”, headaches, dizziness, loss of taste and smell, fatigue and long-term memory issues are also notable complications that may stem from being infected with Covid-19.

Gastrointestinal: Covid-19 affects the GI tract by altering ACE2 receptors in the intestine for the entry of the virus. A variety of GI complications such as nausea, diarrhea, vomiting, abdominal pains, loss of appetite and hepatitis have been seen in Covid-19 cases.

Liver: Covid-19 can indirectly cause liver damage through inflammation resulting in abdominal pain, jaundice, elevated liver enzymes (AST, ALT, bilirubin).

Kidney: Covid-19 can cause kidney inflammation resulting in kidney dysfunction. Some patients exhibit symptoms like swelling, decreased urine output or electrolytes imbalances. Covid-19 may increase the risk of chronic kidney disease.

Endocrine: Impairment of thyroid functions have been reported in Covid-19 cases.

Musculoskeletal: Muscle pain (Myalgia) and joint pain are common occurrences with individuals who are infected with Covid-19.

Epidermal: Skin rashes of various types (red or purple discoloration) and other skin diseases are commonly seen in infected individuals.

Prolonged Symptoms

Long term or prolonged Covid-19 symptoms are known as “Long Covid-19” or Post-Acute Sequelae of SARS-CoV-2 (PASC). This particular phenomenon has shown to have a demonstrable impact on quality of life considerations. In essence the symptoms experienced with the acute phase of Covid-19, are prolonged for several weeks or months. Individuals frequently experience shortness of breath, difficulty breathing, constant fatigue, joint and muscle pain. Mental health issues like increased anxiety and depression are also noted. A loss of taste and smell, possible damage to vital organs (lung, heart, kidney) are not uncommon either.

14. Spread and Prevention

The virus spreads primarily through the inhalation of aerosolized respiratory droplets when an infected individual talks, breathes, coughs or sneezes. Direct contact by hugging, kissing or shaking hands can lead to infection. Because these droplets can remain airborne for a long time, especially in poorly ventilated areas. touching a contaminated surface then touching the face, eyes, nose or mouth also carries a risk of getting infected. Certain Covid-19 variants are highly transmissible and individuals with higher viral loads are more likely to transmit it [122-159].

There is a pecking order as to who is more susceptible to getting infected. The elderly population (65 and older), individuals with comorbidities, immunocompromised individuals undergoing cancer treatments, organ transplant patients and those with autoimmune diseases are all at greater risk. Men and pregnant women also seem to be at a higher risk of infection. Vaccination status is also a determinant in getting infection. Those who are unvaccinated or those who have not completed the full vaccination or booster regimen have a higher risk of infection. Other factors include socio-economic factors (access to healthcare, employment sector, crowded poorly ventilated dwellings) and lifestyle factors (alcohol use, smoking, sedentary lifestyle, obesity).

The best way to mitigate the risk of infection involves a multifactorial approach which encompasses vaccination status, personal protective equipment, personal hygiene regimens and social protocols.

Vaccination

The most effective way to prevent infection is getting vaccinated and keeping up with vaccine boosters as they become available. The CDC recommends vaccines for everyone aged 6 months and older. The vaccine protects and lowers the risk of serious illness and even death. Of note, Covid-19 vaccine boosters are available on a regular basis. They address variants of the virus which in many cases are highly transmissible. Since vaccine efficacy usually wanes after 4-6 months, it is of critical importance that strict adherence to a vaccine regimen be followed so as to prolong the effect of immunity and to avoid hospitalization, ICU or death. This is especially true in the case of the elderly, individuals with comorbidities, those who are immunocompromised and healthcare workers. In the US, the FDA has approved for emergency use, mRNA vaccines by Pfizer and Moderna, viral vector vaccines by Johnson & Johnson and AstraZeneca, and protein subunit vaccines by Novavax. Other organizations based in Europe, China, Russia and India have also developed their own vaccines.

Personal Protective Equipment

It is always encouraged to wear a mask when out in public. The mask should be multi-layered and it should cover the mouth and nose from spreading or inhaling respiratory droplets.

Personal Hygiene: A regime of washing the hands frequently with soap and warm water should be adhered to. The use of hand sanitizer when out in public is recommended. Always cover the mouth and nose with tissue when coughing or sneezing. Never cough or sneeze into your hands and avoid close contact with those who have a cough or cold. Disinfect high use surfaces around the house (tables, doorknobs, light switches).

Healthy Living: It is recommended to strengthen and maintain a robust immune system. Enough sleep along with a healthy diet, good hydration and exercise help the immune system to fight off infection.

Regular Testing & Quarantine: Regularly test for Covid-19. In many cases being asymptomatic or coming in close contact with an individual who is asymptomatic carries the risk of spreading infection or getting infection. If one tests positive for Covid-19, quarantine and isolation for 5-10 days is mandatory.

Social Protocols: Maintain social distancing (6 feet or more) in crowded, indoor or poorly ventilated areas. Avoid touching the eyes, mouth or nose. Try to avoid travel (i.e. covid "hot spots") if at all and obey government and public health guidelines. Keep informed of new or updated information from the WHO and CDC.

15. Detection and Diagnosis

With any disease, the first step is to determine what it is and what symptoms it manifests. Detection and diagnosis typically involve a combination of clinical assessment, diagnostic testing and in some cases imaging. All these steps and techniques are required to ensure an accurate identification of the disease and the appropriate treatment protocols to administer. A variety of detection techniques are employed to assess the disease. Some of these are [160-162].

Polymerase Chain Reaction (PCR): This is the gold standard for detecting the SAR-Cov-2 virus. The PCR test uses a saliva swab or a swab sample taken from the nose to test the presence of the virus's genetic material or fragments.

Antigen Test: This test detects specific proteins from the virus. This test is less sensitive than the PCR test, but provides faster results. It is used for rapid screening.

Nucleic Acid Amplification Test (NAATS): This test includes PCR tests and other techniques that amplify the virus' genetic material to detectable levels.

Imaging: X-rays and CT scans are used to identify abnormalities that are typically related to Covid-19, such as pneumonia. CT scans are not used for the initial diagnoses due to radiation exposure and cost.

Contact Tracing: This diagnostic technique determines where the individual has been and who the individual has come into contact with - an individual may have traveled to a "hot spot" or come into contact with an infected person.

Antibody Test: This test was used in the past, it is not currently used.

Differential diagnosis for Covid-19 is another method in determining infection. It involves a clinical assessment for other conditions with similar symptoms - this is to rule out symptoms of other respiratory conditions such as common cold or influenza. Some of which include:

Clinical Assessment: To evaluate common symptoms such as cough, fever, shortness of breath, fatigue and the loss of taste or smell. These symptoms can vary.

Influenza: Influenza (Flu) symptoms such as fever, cough, sore throat, body ache, nasal congestion, chills and tiredness. These symptoms can last between 1-2 weeks.

Common Cold: Symptoms are generally characterized by mild

cold, runny or congested nose, sore throat and rarely feverish.

Pneumonia: Is caused by various pathogens like bacteria and viruses. Symptoms manifest themselves in the form of fever, cough and shortness of breath. Imaging and sputum tests are able to differentiate it from Covid-19.

Bronchitis: This typically causes a persistent cough with wheezing mucus production.

Allergies: Usually result in sneezing, itching, running nose or watery eyes. It typically does not cause a fever or any severe respiratory conditions like shortness of breath.

Asthma: Asthma is a chronic condition with symptoms such as wheezing, shortness of breath, cough and tightness in the chest. These symptoms are generally triggered by specific allergens or irritants as opposed to Covid-19, where a more sudden onset of symptoms occurs.

Gastrointestinal Issues: Symptoms like nausea, vomiting and diarrhea are common to Covid-19 symptoms but with attenuated respiratory distress.

16. Histopathology, Immunohistochemistry and Electron Microscopy

Understanding the effects of Covid-19 on the body's tissue and organs requires an in-depth analysis from a multi-disciplinary perspective. Histopathology, immunohistochemistry and electron microscopy are the techniques used to provide deep insight to pathologists and researchers in better understanding in the inner workings of Covid-19. This deep insight ultimately results in developing treatment therapies that target and manage Covid-19. The following techniques help correlate clinical severity with tissue pathology [163-166].

Histopathology

Histopathology involves the examination of tissue samples under a microscope to study the changes and side effects caused by the virus.

- **Lung Changes:** These changes are characterized by diffuse alveolar damage (DAD) to the epithelium and endothelium. It typically causes inflammation and pulmonary edemas. Very often seen in Covid-19 cases, fibrin rich deposits on the alveolar surface of hyaline membranes is noted in severe cases of acute respiratory distress syndrome (ARDS). Also very common is a type of pneumonia (interstitial pneumonia) affecting the interstitial spaces between alveoli (Figure 5).
- **Vascular Changes:** Another common phenomenon is the Inflammation of endothelial cell lining of blood vessels and small blood clots within the pulmonary capillaries.
- **Other Organs:** Acute tubular injury in the kidney and inflammation of the heart muscle (myocarditis) are typically seen. Inflammation and toxicity cause mild steatosis and necrosis of the liver.

Immunohistochemistry (IHC)

Immunohistochemistry uses antibodies to detect specific protein changes of a virus and the host's response.

- **Viral Protein Detection:** This is able to detect the SARS-CoV-2 nucleocapsid and spike proteins in infected tissue samples thus confirming the presence of the virus.
- **Host Cellular Response:** Detecting inflammatory markers (IL-6, TNF-alpha) confirms inflammatory response. Identifying T-cell and macrophages immune cell types confirms immune response. Markers (CD3, CD8, CD68, CD20) are used to confirm immune cells infiltration in affected organs. IHC can be used to profile cytokines in cytokine storms to determine

damage done by inflammation.

- **Coagulopathy Markers:** Fibrin, Factor V111 and complementary component staining highlight prothrombotic conditions in Covid-19 patients.

Electron Microscopy (EM)

This is a technique used for obtaining high resolution images of biological and non-biological specimens through an electron microscope

- **Viral identity:** Viral identity of SARS-CoV-2 virions with their characteristic spike. Proteins have been observed in type II alveolar cells, endothelial cells and renal tubular epithelium.
- **Ultrastructural Damage:** Alveolar cell apoptosis and necrosis, endothelial injury and multivesicular bodies are common features in infected viral cells.

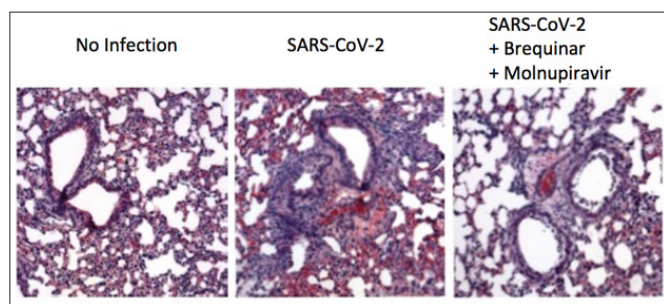


Figure 5: Effect of Antiviral Drugs on the Lung

Adopted from Penn Medicine News, Philadelphia, PA. February 2022

17. Clinical Chemistry / Laboratory Findings

Clinical chemistry or in layman's terms "lab tests" seek to uncover the state and severity of an individual afflicted with Covid-19. Each laboratory test seeks to poll the vital organ in question and reveal if the organ is involved or affected by Covid-19. It also seeks to determine the severity and degree of complexity involved. These findings are crucial for not only reaching a correct diagnosis, but also important in determining an appropriate treatment protocol. Clinical tests are used for ongoing therapeutic monitoring of organs and mortality parameters. Monitoring is done in multiple ways [167-172].

Biochemical Profile

- **Liver Function:** High or elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) usually indicate some form of liver damage. Mild to increased levels of bilirubin usually indicate impaired liver function.
- **Kidney Function:** Elevated levels of blood urea nitrogen (BUN), creatinine, uric acid are an indication of acute or severe kidney damage. Protein in the urine (proteinuria) or blood in the urine (hematuria) are indicators of kidney dysfunction.
- **Electrolyte imbalance:** Hyponatremia and hyperkalemia are often seen or observed.
- **Cardiac Biomarkers:** In severe cases, elevated levels of troponin, CK-MB and creatine kinase indicate cardiac injury or stress.

Metabolic Markers

- **Lactate Dehydrogenase (LDH):** Elevated levels are seen in most severe diseases.
- **Creatine Kinase (CPK):** Increased levels in myositis or rhabdomyolysis.
- **Blood Gasses:** Respiratory disorders like hypoxemia and hypercapnia.

Hematological Markers

- **Lymphopenia:** Is a hallmark of Covid-19, especially in severe cases that indicates a malfunction of T-cells depletion.
- **Leukopenia or Leukocytosis:** Leukopenia is noticed in early stages of the disease, whereas mild leukocytosis is seen in some cases.
- **Neutrophilia:** Seen in severe cases and systemic inflammation is found.
- **Thrombocytopenia:** Is often seen in severe cases due to the direct effect on the immune system.
- **Neutrophil-to-Lymphocyte Ratio:** An elevated ratio indicates systemic inflammation and poor prognosis.

Coagulation Markers

- **D-dimer:** Elevated in most cases especially in severe diseases indicating hypercoagulation risk for thromboembolism.
- **Prothrombin Time (PT) and activated partial thromboplastin time (aPTT):** Prolongation of time indicates coagulopathy.
- **Fibrinogen:** High in the initial stages but may decrease later in advance of disseminated intravascular coagulation (DIC).
- **Platelet count:** Decrease in severe cases resulting in bleeding risk.

Inflammatory Markers

- **C-Reactive Protein:** Elevated in most cases, especially in severe cases.
- **Procalcitonin:** Elevated in bacterial coinfection cases but normal in mild to moderate cases.
- **Ferritin:** Elevated due to hyper inflammation and macrophage activation syndrome.
- **Erythrocyte Sedimentation Rate (ESR):** Mostly elevated.
- **Cytokines:** Elevated levels (IL-6, TNF-alpha, IL-10) in cytokines storm syndrome and in severe viral infection disease.

Viral Detection and Immune Response:

- **RT-PCR:** This is the gold standard for COVID-19 testing and detection.
- **Antibody Test:** IgM appears in the first week of the infection, while IgG is persistent and long lasting.
- **Viral Load:** A high load indicates severe disease and poor prognosis.

18. Cytokine Storm

A Cytokine storm is a hyperinflammatory response triggered by SARS-CoV2 in COVID-19 patients with severe infections. An excessive production of proinflammatory cytokines and chemokines leads to tissue and multi-organ damage (173-177). Pathophysiological effects of this include systemic inflammation, capillary leak - resulting in pulmonary edema, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and multi-organ failure (heart, kidney liver). The biomarkers linked to cytokine storms include high levels of CRP, ferritin, D-dimer, LDH and macrophage activation (hyperferritinemia). To treat these hyperinflammatory responses, the use of IL-6 inhibitors (tocilizumab and sarilumab), corticosteroids (dexamethasone), JAK inhibitors (baricitinib) and supportive care (ventilation/intubation, management of organ dysfunction) are all employed.

Cytokines: IL-6 levels strongly correlate with infection severity. TNF-alpha promotes systemic inflammation, interleukin-1 beta (IL-1 beta) contributes to fever and acute-phase response. Other elevated cytokines are IL-2 and protein-10 (IP-10).
Chemokines: Monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1).

19. Treatment and Management

Although there are no medicines or specific cures available for Covid-19 cases, the infection can be held at bay through a complement of treatment and management protocols. These protocols are based on several patient-dependent and infection-dependent variables, namely the severity of the disease, the patient's health profile and stage of infection. Because there are many moving parts to each individual case, the primary treatment modalities include a combination of supportive care, antiviral medication, antibody therapy and immunomodulators to effectively manage the infection. Hospitalization and vaccines are essential for managing symptoms, preventing complications and improving patient outcomes [178-183].

Mild Cases

Individuals experiencing mild symptoms such as fever, cough, fatigue, loss of taste or smell, sore throat but no evidence of either pneumonia or hypoxia should take an adequate amount of fluids and nutrients and get plenty of rest. In the case of coughs, cough suppressants or expectorants can be used depending on the type of cough. In the case of fever, antipyretic (acetaminophen, tylenol) can be used. For body, joint or muscle pain, many over-the-counter analgesics (ibuprofen, advil, motrin) are available. No antiviral therapy is required for mild cases. The use of oximeters for monitoring oxygen saturation levels is always recommended. Individuals with higher risk profiles (the elderly, comorbidities, immunocompromised) will need vigilant monitoring.

Severe Cases

Individuals experiencing severe symptoms such as respiratory distress or signs of pneumonia require immediate hospitalization for close monitoring and oxygen therapy. A variety of oxygen support and tracking protocols are available on a case by case basis - nasal cannula (high flow oxygen) is used for hypoxemic patients, non-invasive ventilation or mechanical ventilation is used for acute respiratory distress syndrome (ARDS) cases. External fluid, electrolyte and nutrient support are used for hemodynamic stability and critical care. In certain cases, secondary bacterial infections, ulcers, deep vein thrombosis or bedsores require close surveillance to prevent any further complications. Antiviral (Remdesivir) and anti-inflammatory (dexamethasone, hydrocortisone) therapy are effective serious cases.

Critical Cases

Individuals experiencing ARDS, septic shock or multiple organ failures, a variety of treatment therapies may be used in conjunction with each other. For respiratory failure, mechanical ventilation or extracorporeal oxygenation (ECMO) is utilized. For shock or intensive fluid resuscitation cases, intravenous fluids or vasopressors are used. The use of dialysis for acute kidney dysfunction. IL-6 inhibitors (tocilizumab) or Jak inhibitors (baricitinib), broad spectrum antibiotics are used for secondary bacterial infection.

20. Antiviral Drugs

Antiviral drugs come in a variety of shapes, sizes and formats (pills, liquids, inhaler powder, intravenous) and play a crucial role in the treatment and management of Covid-19 cases. These drugs target at various stages of the viral infection life-cycle and are strategically used to inhibit the SARS-CoV-2 virus. They do this by either disrupting its replication machinery or by inhibiting crucial enzymes involved in the life cycle process. The chemical structure of these antivirals mimics or interferes with natural biological molecules of the virus, making them an effective treatment and management defense mechanism against

Covid-19. The following are some key antiviral drugs authorized for emergency use approved by the FDA (Figure 6a). These drugs differ significantly from other anti-parasite drugs like Ivermectin which does not target the SARS-CoV-2 relocation.

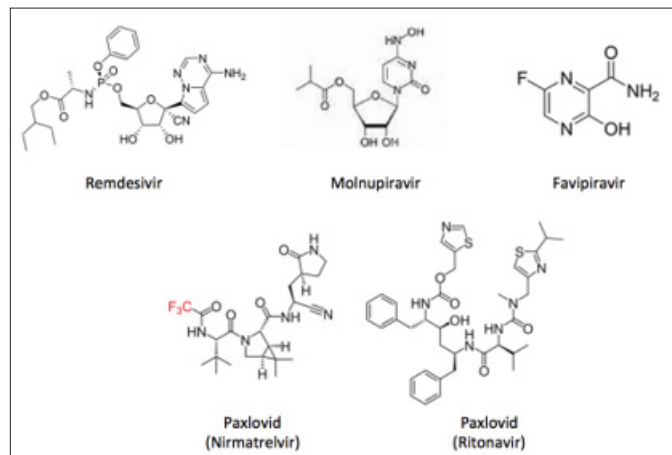


Figure 6a: Structure of Antiviral Drugs

Remdesivir

This is an FDA approved drug that has shown to reduce the severity and duration of illness, especially for hospitalized individuals who require oxygen. It is administered intravenously and its molecular formula is C₂₇H₃₅N₆O₈P. It contains a nucleoside resembling adenosine triphosphate (ATP), analog moiety with a phosphoramidate. It acts by inhibiting the RNA polymerase that is critical for viral replication resulting in a reduced recovery time and lower risk of progression.

Paxlovid

This is an orally ingested medication given to high risk patients with mild to moderate Covid-19 infection. Paxlovid consists of two components - nirmatrelvir and ritonavir. Nirmatrelvir is a protease inhibitor that targets the replication mechanism of SARS-CoV-2; and ritonavir acts as a pharmacokinetic booster that increases the concentration of nirmatrelvir in the blood.

Molnupiravir

This is an orally ingested antiviral used for high risk patients within five days of symptom onset. It is used for non-hospitalized patients and is less commonly used than Paxlovid. It is a nucleoside analog that induces viral mutagenesis by incorporating erroneous nucleotides into the viral RNA - leading to an accumulation of mutations that inhibit viral replication. Its molecular formula is C₁₃H₁₉N₃O₇.

Favipiravir

This is a less efficacious alternative approved in some countries for mild to moderate cases. It is a purine nucleoside analog that inhibits RNA polymerase by incorporating into viral RNA leading to chain termination. It contains a pyridine ring with fluorine and a carboxamide group. Its molecular formula is C₅H₄FN₃O₂.

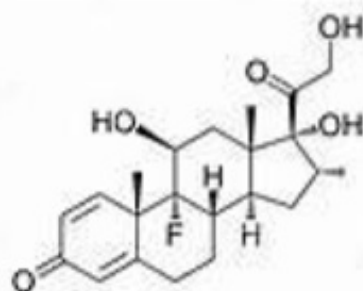
Immunomodulator Drugs

Immune modulators are drugs that either boost or suppress the immune system which may become hyperactive thus resulting in worsening infection symptoms. These drugs have shown to suppress hyperinflammation in situations like cytokine storm syndromes.

Dexamethasone

This is a corticosteroid used in severe cases and reduces inflammation by suppressing cytokines (IL-1-6, TNF-alpha, IFN-

gamma). In addition, for individuals requiring oxygen or ventilation, alternative agents like hydrocortisone or methylprednisolone are used to improve patient outcomes for hospitalized individuals with mild symptoms. They are particularly of use during the latter “hyperinflammatory” stage of Covid-19 (Figure 6b).



Dexamethasone

Figure 6b: Structure of Immuno-Modulators

Cytokine Inhibitors

Tocilizumab and sarilumab target certain cytokines (Il-1, Il-6 inhibitors) to reduce pain for critically ill patients. Tocilizumab for Il-6 inhibitors and sarilumab for Il-1 inhibitors are used to manage cytokine storm syndromes and are most effective in severe cases (Figure 6c).

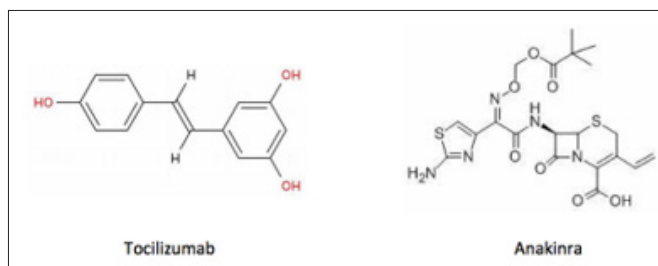


Figure 6c: Structure of Cytokine Inhibitors

Janus Kinase Inhibitors

Both Baricitinib and Tofacitinib, a Janus Kinase (JAK) inhibitor, is used in combination with dexamethasone for moderate to severe cases. This was approved for emergency use by the FDA to treat Covid-19 cases. It has shown to reduce the need for ventilators and has demonstrated improved recovery times in patients (Figure 6d).

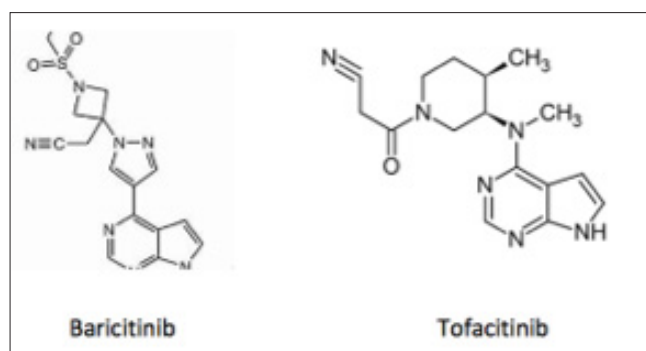


Figure 6d: Structure of Janus Kinase Inhibitors

Monoclonal Antibodies

Are used in certain high risk patients (immunocompromised, comorbidities) as a preventive measure to help neutralize the virus

in the early stages of Covid-19 infection. They work by mimicking the immune system’s ability to fight the virus by binding to the spike protein of SARS-CoV-2, thereby blocking the virus from entering human cells. These antibody therapies are administered through IV infusion and are most effective when given early on in the treatment.

Bamlanivimab and Etesevimab: These are also used together to block SARS-CoV-2 entry into human cells. However, newer variants of Covid-19 have reduced their effectiveness.

Sotrovimab: Target spike protein. This is used to treat high risk patients ages 12 and older against the Omicron variant. It is best used where oxygen supplements are not required and within 10 days of symptom onset.

Evoshield: A combination of two monoclonal antibodies (tixagevimab, ciljivima) are used as a pre-exposure prophylaxis for high risk patients.

Pergarda: This is a new monoclonal antibody used as a pre-exposure prophylaxis for immunocompromised patients who may not produce sufficient antibodies for vaccination. It works by attaching to the spike protein of SARS-CoV-2 thereby blocking its entry into human cells.

Convalescent Plasma Therapy: These antibodies are harvested from the plasma of recovered Covid-19 individuals and are most effective for immunocompromised patients.

Anticoagulation: Low Molecular Weight Heparin (LMWH) used to prevent blood clots or thromboembolism events in hospitalized patients.

21. Vaccines

The chaos and destruction witnessed by Covid-19 was eventually reigned in through the introduction of vaccines. Many countries conducted their own research and development efforts which resulted in vaccines with varying efficacies. The use of mRNA technology used to develop an effective Covid-19 vaccine demonstrated its superiority in its fight against this scourge [184-187].

Vaccines available in the USA

The following vaccines are available and authorized by the Food and Drug Administration (FDA) for use under Emergency Use Authorization (EUA).

mRNA Vaccines: A paradigm shift in vaccine development where mRNA created in a laboratory is used to teach cells how to make a protein (or part of one) that triggers an immune response.

- Pfizer-BioNTech (Comirnaty): Use of mRNA technology approved for individuals 6 months and older with ~95% efficacy against severe disease and hospitalization with variant-adapted efficacy over time. Omicron-adapted monovalent booster available for ages 5+.
- Moderna (Spikevax): Use of mRNA technology approved for individuals 6 months and older with ~95% efficacy against severe disease. Omicron-adapted monovalent booster available for ages 7+.

Protein Subunit Vaccines: This approach uses fragments of a disease-causing virus to trigger the body’s immune response.

- Novavax: Use of protein subunit with Matrix-M adjuvant technology approved for individuals 12 years and older with ~90% against severe disease in initial trials. Available for those who prefer a non-mRNA booster option

Vaccines available Globally

The following vaccines are available globally with several that are approved by regulatory agencies or included in the WHO Emergency Use Listing (EUL):

MRNA Vaccines: As above

- Pfizer-BioNTech (Comirnaty): As above.
- Moderna (Spikevax): As above.

Protein Subunit Vaccines: As above

- Novavax: Approved in multiple countries as a primary series or booster.
- Clover Biopharmaceuticals (SCB-2019): WHO listed for emergency use.
- Covovax: A version of Novavax produced by the Serum Institute of India.
- Zifi Vax: Protein subunit vaccine developed in China

Viral Vector Vaccines: The use of a harmless virus to deliver genetic material that produces a protein or antigen in the body, which in turn triggers an immune response.

- AstraZeneca (Vaxzevria): Widely used in Europe, Asia, Africa and South America with ~70-80% efficacy against symptomatic COVID-19, higher against severe outcomes
- Johnson & Johnson (Janssen): Single-dose regimen initially; boosters now recommended with ~66% efficacy against moderate to severe disease
- Sputnik V: Developed by Russia's Gamaleya Institute, widely distributed in Eastern Europe, Latin America and Africa with ~91% efficacy against symptomatic COVID-19

Others

- CanSinoBIO (Convidecia): Single-dose viral vector vaccine developed in China.
- Inactivated Vaccines:
- Sinopharm (BIBP-CorV): Developed in China; widely used in Asia, Africa, and Latin America with ~79% efficacy in clinical trials, slightly lower for older adults.
- Sinovac (CoronaVac): Developed in China and used in over 50 countries with ~51% against symptomatic disease, higher against severe disease.
- Covaxin: Developed in India by Bharat Biotech with ~78% efficacy in interim analyses

22. Alternate Treatments

Alternative treatments for Covid-19 refer to therapies that are not part of standard medical treatment protocol (antiviral, anti-inflammatory, supportive care). Some individuals explore these alternatives in hopes of modulating their immune response to reduce inflammation. The effectiveness of these alternates vary from case to case and some have shown promise in supportive care. It should be noted these alternative therapies should never replace conventional medical treatment especially for moderate or severe cases. If alternatives are to be employed, they should be done under the strict supervision of a medical professional. The following is an overview of alternate treatments, these however are not sanctioned by any regulatory bodies [188-198].

Vitamins and Supplements

- Vitamin C: Has immune boosting properties and the ability to reduce oxidative stress. It is known as an adjunct therapy especially in patients with vitamin C deficiency.
- Vitamin D: It plays an essential role in reducing respiratory infection and infection severity due to immunomodulatory effects.
- Vitamin E: It protects cells from oxidative damage and supports the immune system.

- Zinc: It inhibits viral replication and is believed to have antiviral properties. It has shown to reduce the severity and duration of respiratory illness.
- Probiotics: They modulate gut micro bacteria and increase immune response.
- Antioxidants: Mucolytic and antioxidant properties that reduce oxidative stress and cytokine storms.
- Glutathione: Has antioxidant properties and reduces inflammation.
- Melatonin: It is known as a sleep aid, but has antioxidant and anti-inflammatory properties.

Herbal and Natural Remedies

Herbal and natural remedies have been shown to support the immune system. Some herbs may exhibit immune modulating effects, however their efficacy in Covid-19 cases is unknown.

- Curcumin: Sourced from turmeric, it has potent anti-inflammatory and antioxidant properties.
- Green Tea: Epigallocatechin Gallate (EGCG) is a potent antioxidant found in green tea that offers general immune support. It inhibits viral entry and replication as well.
- Elderberry: Sambucus Nigra is immune boosting with antioxidant and antiviral properties. It has shown to reduce the severity of infection.
- Quercetin: It is a flavonoid found in many fruits and vegetables that exhibits some anti-oxidant and anti-inflammatory properties. Evidence exists that quercetin may inhibit replication of SARS-CoV-2 and modulate the immune response, but there is no clinical evidence to support this.
- Echinacea: It may reduce the severity of colds by boosting the immune system.
- Ginger: It has anti-oxidant and anti-inflammatory properties and is used to boost the immune system.

Repurposed Drugs

- Ivermectin: Used for parasitic infections but lacks evidence for inhibiting viral replication. It is not recommended by the WHO or FDA for Covid-19 cases.
- Hydroxychloroquine: Initially proposed for Covid-19 treatment, clinical trials have failed to show any beneficial effects. It is not recommended for Covid-19 cases

23. Mortality and Morbidity

Since the beginning of the COVID-19 pandemic a significant increase in global mortality and morbidity rates has been seen. Mortality and morbidity describe the rate of death and rate of illness caused by the disease. Efforts have been made to reduce the rate of mortality and morbidity through vaccinations and improved treatment protocols. There is still a long way to go as ongoing healthcare efforts will be crucial for managing the challenges going forward [199-203].

Mortality

Mortality rates or death rates from the disease vary by country and region. Marco factors such as access to high calibre healthcare, vaccinations status, testing availability and vaccination availability, largely determine mortality rates. From a micro perspective, the elderly, individuals with comorbidities or those who are immunocompromised have a higher risk of infection, and by extrapolation, a higher mortality rate. The global case fatality rate (CFR) varies between 1-2%, initially high during the early phase of the outbreak, the CFR has decreased due to improved vaccines and treatment. Of note, mortality rates will continue to ebb and flow due to the introduction of new variants.

Morbidity

Morbidity rates can range from mild (80% of cases) to severe (15% of cases) illness. Milder cases entail symptoms like cough, sore throat and fatigue - which can be treated at home with over the counter medication, isolation, rest, fluid intake and a proper nutrient intake. Severe cases may lead to pneumonia, ARDS, chest pain, palpitations and multi-organ failure which often requires intensive care hospitalization or mechanical ventilation. Longer term, severe cases may lead to damage to vital organs, impact on quality of life, loss of productivity and the development of other health problems (cardiovascular, mental health, long term disability)

24. Pathogenesis and Disease

The physiological effects of Covid-19 have proved to be very far reaching in nature with varying severity. Covid-19 is a respiratory disease and the virus (SARS-CoV-2) is spread through respiratory droplets when an infected person coughs, sneezes or talks. It has the potential of spreading through contaminated surfaces as well. The virus infects type 11 alveolar cells of the lung and causes damage to the respiratory epithelium cells. This results in symptoms such as cough, fever, fatigue and difficulty in breathing. Infection leads to inflammation (cytokine storms), vascular leakage, tissue damage and fluid accumulation in the alveoli of the lungs. This leads to pneumonia and ARDS followed by respiratory failure. Blood clotting issues are also a symptom of the infection causing serious emergent conditions such as thromboembolism. Other stressors to the body come in the form of excessive ROS production. This oxidative stress influences cellular components resulting in inflammation and tissue damage. Once this process is set in motion, multi-organ dysfunction is noted. The heart (myocarditis, arrhythmias, heart failure), kidney failure (infection, hypoxia), liver injury (elevated liver enzymes), brain injury (anosmia, encephalopathy, stroke) and GI issues (nausea, vomiting, diarrhea) are just some of the severe effects of Covid-19. Apart from the immediate symptoms, some individuals experience persistent symptoms and complications known as "Long-Covid" or post-acute sequels of SARS-CoV-2 (PASC) [229-232].

25. Molecular Pathology

The spike protein is crucial for viral entry into the host cell. Mutations in the spike protein can affect transmissibility and vaccine efficacy. ACE2 are the primary receptors for SARS-CoV-2 entry. Variations in AEC2 expression influence susceptibility and disease severity. Mutations or variants (Alpha, Beta, Gamma, Delta Omicron) in the virus affect transmission rates, immune response (vaccine efficacy) and disease severity. Continuous viral replication and mutations result in the emergence of new variants. These events are to be closely followed for effective vaccine development and public health strategy.

26. Covid-19 and Cancer

The Covid-19 pandemic has demonstrated a considerable impact on patients undergoing cancer treatment. Treatment protocols employed for cancer therapy and their effects on the body expose the already fragile state of an individual to an even greater risk of infection. Individuals with lung cancer sometimes undergo surgery that may lead to infection and other complications. Compromised lung health with the threat of a Covid-19 infection is particularly foreboding. Chemotherapy, radiation and immunotherapy leave the body with an already compromised Immune system. This results in making it harder to fight infection. Individuals undergoing chemotherapy, stem cell transplant or those who have leukemia, lymphoma and multiple myeloma may display increases or decreases in white blood cell counts. Varying levels of white blood

cells in turn lead to conditions such as Neutrophils, Eosinophils, Basophils and Lymphocytes. Older individuals, individuals with advanced stage cancer or individuals with comorbidities (heart disease, kidney disease, liver disease, etc.) also face an elevated risk of infection.

The risks of Covid-19 infection for patients not undergoing cancer treatment is not that much better - Older adults, adults with comorbidities, pregnant women, individuals with respiratory conditions, immunocompromised individuals, individuals with hypertensive conditions and those placed in high risk environments (nursing homes, long term care facilities, crowded living conditions) all face the same risk if infection.

27. Pandemic to Endemic

Prior to the SARS-CoV-2 virus, four coronaviruses emerged which were associated with mild common cold symptoms:

- 229E (HCoV-229E): An alpha variant associated with mild respiratory illness.
- NL63 (HCoV-NL63): An alpha variant which causes mild respiratory infection in children.
- OC43 (HCoV-OC43): A beta variant which causes mild to moderate respiratory infections.
- HKU1(HCoV-HKU1): A beta variant which causes mild to severe respiratory tract infections.

During the last 20 years, two other previously identified coronaviruses were responsible for major epidemics. In 2002, SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavirus) emerged from China and in 2012, MERS-CoV (Middle Eastern Respiratory Syndrome) emerged (Figure 7). In 2019, SARS-CoV-2 is the seventh coronavirus to date that is known to infect humans. They all belong to the coronavirus family (genus Betacoronavirus) that infect animals and jump from animals-to-humans and eventually, humans-to-humans. The origin of all three are linked to zoonotic transmissions carried in animal reservoirs. Bats are the known primary carriers of the disease. It is speculated that human infections came from intermediate hosts most likely civets and pangolins. SARS-CoV-1 and MERS-CoV were quickly controlled due to their lower transmissibility characteristics, while SARS-CoV-2 quickly became a global pandemic due to its highly transmissible nature. The symptoms are characterized as a very severe, highly infectious respiratory illness (Figure 7). Having said that, experts, experience and research indicate the next CoV epidemic will likely follow the same pattern seen with SARS, MERS and COVID-19, with a significant probability of appearing within the next decade.

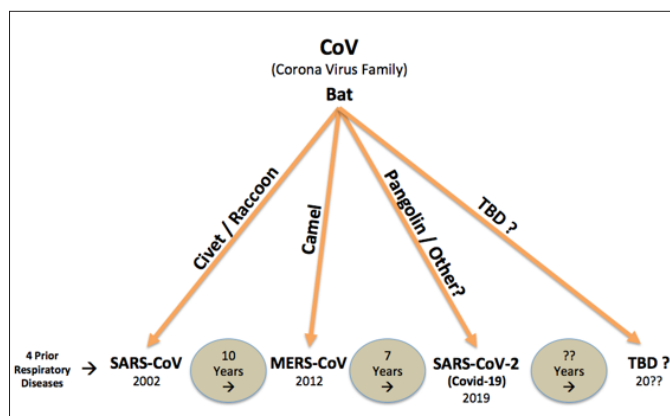


Figure 7: History of Covid

As of late, global Covid-19 cases are on the decline due to the widespread use of vaccines, herd immunity, variant booster shots, social distancing, social awareness and the like. Occasionally localized outbreaks in certain areas may still occur. All signs indicate that the pandemic is entering a new stage. Through repeated localized epidemics in specific populations in certain seasons, it is slowly giving way to becoming endemic (Figure 8).

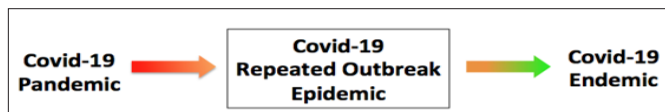


Figure 8: Potential Pandemic Threats

Predicting the exact nature and timing of the next pandemic is not trivial. Ongoing research provides some insight of several potential threats based on historical trends (Figure 9). The threat risk increases due to globalization, climate change, urbanization and close human-to-animal contact. Any of the following pathogens can lead the charge:

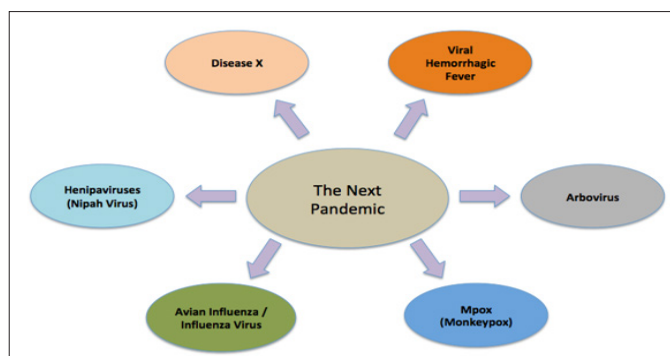


Figure 9: Covid-19 Pandemic Transitions to an Endemic

- Henipaviruses (Nipah Virus): Zoonotic virus spread by bats causing neurological symptoms and high mortality rates.
- Avian Influenza/Influenza Virus: Influenza virus mutates rapidly and can jump between animals and humans: Spanish Flu (H1N1), Avian Influenza (H5N1, H7N9) commonly known as the bird flu has a high potential to mutate and infect humans.
- Mpox (Monkeypox): The WHO declared mpox an international health emergency. Deadlier variants may emerge.
- Arboviruses: Zika, Dengue and Chikungunya pose serious threats due to climate change.
- Viral Hemorrhagic Fever: Ebola and Marburg virus
- Disease X: The WHO uses this as a placeholder for unknown pathogens that could cause future epidemics.

28. Conclusions and Take Home Message

Having gone through the worst part of the Covid-19 pandemic - the world finds itself at a crossroads. The debilitating scourge of this pandemic is now in the rear view mirror, but the ever-present threat of a newer and deadlier disease looms. The scar left by Covid-19 is witnessed on the face of every individual and every sector of the economy. Life as we know it has been touched in one way or another.

The fundamental basis for all the effort spent battling this comes down to “Contain and Control”. Covid-19 first appeared in what is believed to be the open air live animal market in Wuhan, China. It was described as a “pneumonia-like” respiratory illness that resulted in deadly outcomes. Soon after, a rapid, uncontrolled

global spread brought it to the doorstep of every country, putting all at risk. The Covid-19 virus affected individuals very differently - the divide is characterized by three factors: first world economies, patient health profiles and socio-economic standing. Individuals who live in resource-rich countries versus those who do not, have access to better healthcare infrastructure, better vaccine availability/efficacy (mRNA technology), better patient support services and superior public health policy; and as such, generally fare better in patient outcomes. An individual’s health profile also determines infection risk. Individuals who are elderly or those with comorbidities face a higher risk of infection than their younger, healthier cohorts. Finally, an individual’s socio-economic standing is a big determinant in infection risk. Minorities, individuals who work in certain sectors, individuals who face housing scarcity or food scarcity generally carry higher risk of infection and poorer patient outcomes.

That notwithstanding, Covid-19 has proved to be quite a wily foe, and will continue to be so in the foreseeable future. It is zoonotic in nature. Global “hot-spots” where close human-to-animal contact in unsanitary conditions continue to thrive with no regulatory oversight. Hard-to-eradicate animal reservoirs continue to exist. New and ever-evolving viral mutations remain one step ahead of our ability to develop vaccines. These coupled with global vaccine status/hesitancy, public fatigue and misinformation campaigns - continue to provide a fertile breeding environment for this virus to thrive.

The ongoing fight against this pandemic has led to one thing. The Covid-19 virus, like those before it, has now shifted from “pandemic” status to “endemic” status. Valiant efforts by the scientific community and public health agencies have transformed the nature of the virus to one behaving like a seasonal flu. Largely defanged, Covid-19 is circulating among the population with mutations and fluctuations in spread, causing attenuated severity, lower infection rates and geographically localized outbreaks.

One fundamental question remains - how well are we prepared for the next major outbreak?

To answer this, public health officials need to understand their “span of influence”. Meaning, what factors they can influence versus what factors they cannot.

The Covid-19 outbreak brought to light some very stark realities. It is abundantly clear there is no influence over animal biology, their disease reservoirs, the host type (bats, mosquitoes, etc.), virus mutation, etc. From a societal standpoint, there is no influence over social behavior (collective, individual), socio-economic disparities, age, gender, comorbidities or national resources. Looking at these factors alone, one can see the insurmountable task at controlling another outbreak.

All hope is not lost however. In the very darkest of times, pieces of the puzzle have come together to shape a formidable arsenal for humankind. This was developed by public health administrators and the scientific community working hand in hand towards a common goal. First and foremost, the scientific community developed a highly efficacious vaccine using novel mRNA technology. This major paradigm shift in vaccine development allowed traditional research, testing, manufacturing and distribution times to come down significantly. Influential public health administrators and powerful national agencies developed infrastructure to support testing, vaccine availability and public policy (social distancing,

masking, isolation, etc) all in the hopes of preventing transmission. These are areas in which influence can be exerted.

Anytime a viral outbreak has the potential to take hold, a containment strategy must be followed in order to keep it from becoming a pandemic. Covid-19 had devastating global consequences, both from a health and economic standpoint. A containment strategy is one that constantly monitors known and emerging “hotspots” (testing, surveillance, regulatory oversight, information sharing, PPE availability, rapid vaccine development and distribution, etc.). A containment strategy can be very expensive and the cost will most likely be shouldered by nations that are resource rich. All nations must fully be invested in this process, as this is the only way to minimize and contain damage.

The span of influence leaders have, comes down to one question, “Do we want to be one step ahead of the next pandemic?”. Being one step ahead of the next pandemic has serious resource and financial implications. The cost of being one step ahead of the next pandemic is far less costly to humanity than being one step behind. To answer this question will determine how we fare during the next major pandemic.

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