May 2020

SARS-CoV-2 Research Report

MARIANOPOLIS RESEARCH TEAM

Contributors

Negin Amini, Jumanah Baig, Anthony Bay, James Jing, Maggie Jung, Hyerin Kim, Hyeonjeong Kwon, Joyce Li, Linda Li, Laurence Liang, Roger Pang, Bhromor Rahman, Emma Rodriguez, Tejeshwer Singh, Kevin Xu, Etsub Yifru, Michael Zhang, Shi Tao Zhang, Emma Zlatanovska

Executive Team

Tejeshwer Singh, Laurence Liang, Joyce Li, Roger Pang, Michael Zhang

COVID-19 LITERARY REVIEW MAY 2020: INTRODUCTION TO COVID-19

Origin **-Emma Zlatanovska**

Theories on the Origins of COVID-19

With COVID-19 having such a devastating impact worldwide, many have been conjuring up theories about just where this virus may have originated. It was quickly determined that the virus was first identified in Wuhan, China, but its exact origin remains a mystery. The most popular theory up to date is the possibility of the virus being transmitted from one wild animal to another in the Huanan Wet Market in Wuhan, before infecting humans who would have purchased the affected meats to consume. However, only 27 out of the first 41 patients had been in the market, which raises many eyebrows (Ellis, 2020). While everyone has agreed upon the fact that the virus most likely originated in bats, scientists and researchers have yet to determine whether an intermediate host (another animal) contracted the virus to then pass it onto humans. Some believe that the cause of the outbreak may have been farmers who use bat feces to fertilize their soil, while others are exploring the theory that it may have been an accidental leak from a Chinese lab in Wuhan (Kuznia & Griffin, 2020). While one exact source has not yet been identified, scientists and researchers are hard at work to narrow it down to possible causes in order to prevent a similar event in the future.

Laboratory Outbreak Theory

One of the prevalent theories being passed around about the origin of COVID-19 is that there could have possibly been an accidental leak from a lab that works with bats near the Hunan Wet Market in Wuhan (Kuznia & Griffin, 2020). Although the likeliness of this theory holding water is low, the events following this claim remain suspicious. The Wuhan Institute of Virology were quick to issue statements on February 19th that strongly rejected that the "virus was man-made", that "patient zero came from the Institute" and that the "Chinese military took control of the Institute" (Kuznia & Griffin, 2020). However, when CNN attempted to contact the main author of the study that first pointed its finger at a possible lab outbreak, Botao Xiao, he did not respond to their emails nor to their phone calls (Kuznia & Griffin, 2020). Although the genome sequence of the virus does not show any signs of human manipulation, the unfolding of the previous events occurred suspiciously, which is causing many to continue to hold onto this potential theory (Kuznia & Griffin, 2020). Even as this theory is still considered by some, a considerable amount of evidence has surfaced against it. In fact, if this coronavirus had been fabricated by humans, it would have been done using the backbone of previous coronaviruses as templates (Bryner, 2020). This, however, was most likely not the case. In fact, the overall molecular structure of COVID-19 was found to be very distinct from other known coronaviruses such as MERS-CoV and SARS-CoV (Bryner, 2020). Supporting this claim is Kristian Andersen, a PhD and associate professor of Immunology and Microbiology at Scripps Research, who made the following claim: “By comparing the available genome sequence data for known coronavirus strains, we can firmly determine that SARS-CoV-2 originated through natural processes” (Bryner, 2020). He stated that this was the case mainly due to two important features of the spike protein contained within the molecular structure of COVID-19 : the receptor binding domain (RBD)—the portion of the virus cells that allows them to hook themselves onto host cells—and the cleavage site—the portion of the virus cells that allows them to “open and enter” the host cells (Bryner, 2020). In fact, the RBD portion of the virus is so effective at binding to host cells, that Anderson came to the conclusion that it must be the product of natural selection and not of human engineering (Bryner, 2020).

Farming Mishap Theory

Presented by Microbiology professor at Colombia University Vincent Racaniello, this theory suggests that the coronavirus may be a result of farming techniques used in certain countries, including China (Kuznia & Griffin, 2020). In bats, coronaviruses are intestinal viruses, making it so that the virus can be transmitted through their feces, called guano (Kuznia & Griffin, 2020). Farmers in many countries use this guano to fertilize their land, which gives possibility and reason to the theory that COVID-19 may have emerged due to a farmer or an associate who visited Wuhan, China using guano in their farming practices (Kuznia & Griffin, 2020).

History of Chinese Wet Markets

Wet markets are particularly known for offering a diverse selection of wild animals. These wild animals can all be placed in one same market due to a decision made by the Chinese government decades ago. As Vox explains in their short documentary, in the 1970's, China's communist regime was failing to feed more than 900,000,000 of its citizens, which resulted into the death of approximately 36 million people (Ellis, 2020). This forced the Chinese government to allow private farming in 1978. However, private farming dominated the farming of major animals (such as cows, chickens, pigs, etc.), which pushed smaller farmers to begin raising wild animals. The farming of wild animals turned out to sustain people and feed considerable amounts of the Chinese population, which caused the Chinese government to support it. They did so by introducing the Wildlife Protection Law in 1988, which was counterintuitively dangerous for the wildlife that was being farmed. This law designated animals as resources owned by the state and protected the farmers of such animals, which consequently grandly encouraged the farming of wildlife and rendering these animals resources that can be exploited for human benefit. Thus, the wildlife wet market industry in China was booming until 2003, when the SARS-CoV outbreak was traced back to a wet market in Foshan, Guangdong Province in China. Following this event, the Chinese government was quick to shut down wet markets and ban wildlife farming in China. This, however, did not last long. A few short months after the SARS-CoV outbreak, Chinese officials declared 54 species of wildlife animals legal to farm once again. By 2004, the wildlife farming industry was thriving and worth approximately 100 billion yuan, which amounts to approximately 200 million CAD. This increase in value of wildlife farming even pushed the Chinese government to allow the farming of endangered species such as pangolins and tigers. By 2008, the industry was worth 148 billion yuan and the Chinese government was promoting the consummation of wild animals more than ever. Peter Li, associate professor at the University of Houston-Downtown and expert on animal trade in China, states that "[t]he industry has been promoting these wildlife animals as tonic products, as body-building, as sex-enhancing and, of course, as disease-fighting. None of these claims can hold water" (Ellis, 2020). Despite the vast promotion of wildlife farming, Peter Li clarifies that "[t]he majority of people in China do not eat wildlife animals. [The] people who consume these wildlife animals are the rich and the powerful. A small minority" (Ellis, 2020). What's disappointing is that the Chinese government chose to prioritize that small minority over the safety of the rest of its population. This, however, was not done without consequences. COVID-19 is vastly suspected of originating in a Chinese wet market, which forced the Chinese government to shut down several wet markets and ban the farming of wildlife once again. Many organizations are pushing for the Chinese government to place a definite ban over the farming of wildlife and wet markets, but China is instead responding by amending the Wildlife Protection Law that encouraged wildlife farming decades ago.

Hunan Wet Market Theory

As mentioned above, the Hunan Wet Market in Wuhan, China is highly suspected of being the origin of COVID-19. Firstly, the Huanan Market is defined as a Wet Market due to the fact that many diverse wild animals are all slaughtered in one same location and placed in cages stacked one on top of the other (Ellis, 2020). Peter Li, associate professor at the University of Houston-Downtown and expert on animal trade in China, explains that this makes it so that "[a]nimals at the bottom are often soaked with all kinds of liquid" such as "[a]nimal excrement, pus, blood" (Ellis, 2020). This arrangement of animals in wet markets is dangerous seeing as animals that are captured from the wild and brought into locations such as the Huanan Wet Market tend to be very stressed. This stress and diversity in origin regarding these wild animals renders them "virus factories", making it so their close contact with humans and on-site slaughter is directly linked to the transmission of various diseases to humans (Kuznia & Griffin, 2020). In fact, CNN claimed that wet markets are a prime candidate for causing zoonotic spillover (Kuznia & Griffin, 2020). Zoonotic spillover is the "transmission of a pathogen from a vertebrate animal to a human", which is essentially the phenomenon that was observed regarding the primary transmission of COVID-19 (National Institutes of Health, 2017). What has yet to be determined is whether there had been an intermediate host that would place between bats and humans in the transmission process. Researchers are suspecting pangolins, known as scaly anteaters, as possible intermediate hosts (Bryner, 2020). Pangolins are suspected seeing as some coronaviruses that

originated in pangolins have a similar hook structure (the previously discussed RBD) as the one observed in COVID-19. It is thus theorized that COVID-19 either entered humans in its non-pathogenic version to then evolve into its pathogenic state within humans, or that it evolved to its current pathogenic state by natural selection in a non-human host and then was transmitted to humans (Bryner, 2020). Knowing which of the two scenarios occurred would contribute to forecasting the future of the novel coronavirus; if it entered human cells in an already pathogenic form, the probability of future outbreaks is much higher because the virus would most likely still be circulating in the animal population (Bryner, 2020). However, if the virus only evolved to its pathogenic form within humans, the chance of future outbreaks would be lower (Bryner, 2020).

Although the Huanan Wet Market theory seems to be favored amongst the science and media communities, there exists one piece of evidence that suggests otherwise: many of the first known patients had no direct exposure to the Huanan Wet Market and "no epidemiological link was found between the first patient and later cases" (Kuznia & Griffin, 2020). This compromises the Hunan Wet Market theory's chances of being true and pushes many to reconsider whether this could truly be the origin of COVID-19.

Past Coronaviruses

Seeing as COVID-19 is but one of millions of coronaviruses, it resembles two past coronaviruses by the names SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome).

SARS-CoV Outbreak

March 12th of 2003, the WHO issued a global alert about cases of atypical pneumonia in Guangdong and Hong Kong (National Institutes of Health, 2013). Similar to COVID-19, SARS-CoV was an airborne virus, meaning it spread like a cold or like a flu—through small droplets of saliva or through indirect contact (National Health Service, 2019). SARS-CoV was the first severe illness caused by a coronavirus with a mortality rate of 10% and no reported cases since 2004 (National Foundation for Infectious Diseases, 2020).

Origins of SARS-CoV

The origins of SARS are, to this day, unconfirmed. Some sources claim that the virus was transmitted from bats to masked palm civets, which then transmitted it to humans (National Institutes of Health, 2013). Others claim that masked palm civets have been wrongfully accused of hosting the SARS-CoV virus (National Institutes of Health, 2013). What was, however, confirmed by the professor Kwok Yung Yuen of HKU Li Ka Shing Faculty of Medicine, is that the natural host of SARS-CoV was the Chinese Rufous Horseshoe Bat (National Institutes of Health, 2013). These findings were then backed up by other Chinese sources as well as some Australian researchers in 2005 (National Institutes of Health, 2013). Although supported by many scientific sources, these claims are still somewhat controversial due to lack of evidence (National Institutes of Health, 2013). In fact, the SARS virus found in bats is considerably different from that found in humans, whereas the SARS virus found in masked palm civets is much more homologous to that found in humans (National Institutes of Health, 2013). This suggests the possibility of the virus experiencing certain mutations within masked palm civets after being transmitted from bats and before being transmitted to humans (National Institutes of Health, 2013). Considering the uncertainties regarding the discovery of the origins of SARS, the research on the latter has been stagnant since 2013 (National Institutes of Health, 2013).

MERS-CoV Outbreak

Also known as the Middle East Respiratory Syndrome, MERS-CoV was first identified in Saudi Arabia in 2012 (World Health Organization, 2019). It was labelled a zoonotic virus, much like SARS and SARS-CoV-2 (World Health Organization, 2019). Approximately 80% of the cases were reported by Saudi Arabia and about 35% of the reported patients passed away due to the virus (World Health Organization, 2019).

Origins of MERS-CoV

It is widely believed that MERS originated in bats and was transferred to camels in the distant past (World Health Organization, 2019). In fact, MERS was identified in dromedaries across several countries in the Middle East as well as Africa and South Asia (World Health Organization, 2019). Strains of MERS identical to that in humans were found In 22.8% of the sampled camels, which proves to be a high prevalence

(Ji, 2020). To trace the primary origin of MERS, researchers tested samples from bats found living 7 miles away from the home of the first known infected person (Rettner, 2013). Identical strains of MERS found in humans were found in 100% of the bats they sampled (Rettner, 2013). An experimental study conducted on Jamaican fruit bats showed that all bats showcased evidence of infection, but none showed any clinical signs of disease (Al-Tawfiq et al., 2016). However, it was then discovered that antibodies for the virus existed in dromedary camels, cattle, sheep, goats and other camelid species (Al-Tawfiq et al., 2016). This makes it so that these bats constitute a reservoir for MERS and that it is highly likely that the virus made use of an intermediate host in order to be passed onto humans (Al-Tawfiq et al., 2016). In fact, two farmers were diagnosed with MERS in Qatar in October of 2013 (Al-Tawfiq et al., 2016). Researchers then tested the camels on the same farm and found that 11 out of 14 of them tested positive for nasal swabs for MERS (Al-Tawfiq et al., 2016). In addition, a study that obtained the full genome of MERS from a camel in Qatar demonstrated that the genome sequence of the virus within camels is nearly identical to that found in humans, strongly suggesting the existence of an intermediate host (Al-Tawfiq et al., 2016).

Comparison of COVID-19 to SARS and MERS

These three coronaviruses share many common details: the fact that they all most likely originated in bats, the fact that they all possibly had an intermediate host, and, unfortunately, the fact that the science behind the widespread of these viruses has yet to be determined.

***Viruses* -Kevin Xu**

Introduction to viruses

Viruses are submicroscopic particles that technically are not living organisms, normally seen as "organisms at the edge of life", since viruses can only partially meet the criteria for living. For example, living organisms often require their own metabolism or must be able to reproduce naturally without any external aid, two tasks that viruses are not able to perform. However, these infectious particles still possess genes in the form of nucleic acid and evolve by natural selection. It is due to this ambiguous standing that opinions on whether viruses should or should not be considered living vary greatly. Maybe unknown to you, these deadly tiny killers are everywhere. Outnumbering living organisms 10 to 1, you can find 10 million of them in a single teaspoon of seawater. Although some viruses have the power to potentially kill millions of people in a relatively short amount of time, most viruses are completely harmless to humans since they are very picky as to who they infect, most being able to infect only a particular species.

Replication

Since viruses don't have a metabolism and therefore can't replicate on their own, they must infect other cells, hijacking their metabolism and organelles to produce more viruses. To do so, viruses have developed many ways, which are normally related to their shape. The complex bacteriophages inject their genetic information into the host cell, while others trick the cell receptors and bud into the cell through endocytosis. The coronavirus uses its envelope to merge with the cell through "direct fusion". After infecting the host, two possible outcomes exist: the first is that the cell will start to build more and more of the virus until they explode or lyse and die, this is called the lytic cycle, the second is the lysogenic cycle, where the viral genetic material is added to the host cell's own genetic material, with every replication, the newly added genetic information is passed on, until finally some external factor will trigger the cell into the previous lytic cycle.

Characteristics

Viruses come in all kinds of shapes and sizes, some are helical with a tube shape, some icosahedral (20 faced), and some have complex shapes like the famous bacteria eating bacteriophage. Most viruses are tiny, typically 100 times smaller than the average bacteria, while some can grow larger than bacteria. The two main components of these pathogens are the nucleic acid, DNA or RNA, the most important part of the virus which contains the information to replicating itself, like other living organisms,and enveloping the nucleic acid is something called the capsid, which protects and shields the genetic information from outside threats. Some viruses also have envelopes surrounding them, just like the coronavirus, which helps the virus better sneak into the host cell.

Baltimore Classification

The most common way of classifying a virus is with the Baltimore classification, which separates viruses into 7 different classes depending on the type of nucleic acid that is present in the virus. Coronaviruses are a type IV virus, positive-sense (5'-3' direction) single stranded RNA viruses, which are the most common type of plant virus. However, there are many other ways to classify viruses such as by looking at the type of organism that the virus will infect, an example of this is the bacteriophage the name given to viruses that infect bacteria, or by looking at its shape. Coronavirus is a betacoronavirus, in the same family as the 2003 SARS virus, which normally infects bats, although they often infect other species.

Entrance & effects **-Tejeshwer Singh**

ACE2

When a person gets infected, they inhale droplets containing the virus. Consequently, this comes in contact with various parts of our body. Specifically, when the virus lines the inner walls of our nose, that's when things can get tricky (Wadman et al., 2020). This region in our body is rich in cell surface receptors, called, angiotensin-converting enzyme 2 (ACE2). Generally, viruses correspond to intracellular parasites; they try to replicate themselves in order to prosper. Current research showcases how the SARS-CoV-2 is able to do so via ACE2. These membrane proteins are joined to the sympathetic nervous system (Foley 2020). Their role consists of binding to the ACE2 hormone. Therefore, acting through AT1 receptors, which stimulate cardiac growth (Zisman 2005). Scientists believe that the nature of covid-19 can initially evade our immune system by latching on this receptor and gaining access into to the human body (Cristiani et al.,).

Pulmonary consequence

As blood circulation carries oxygen throughout the body, it gets interrupted by the viruses' activities. Our immune systems tries to fend off this virus, therefore releasing inflammatory molecules called "chemokines". In return, these molecules summon more immune cells to try and fend off this virus. As a result, a mess of fluid and dead cells is left behind.

Causes

Sars-CoV-2 can wreak havoc on many of our organs. Researchers have enumerated many theories to try and explain the extent of the damage caused by the novel coronavirus. Scientists believe that these devasting effects is not solely caused from respiratory failures.

A theory is that ruptured blood vessels in the endothelia tissue can result in major clots leading to devastating impacts (Bernstein and Eunjung Cha, 2020). This theory provides a possible outlook on why so many parts of the human body are affected by the virus, such as the heart, kidneys, nervous systems, blood vessels and etc. Another theory is that the consequences result from an exaggerated immune response. This is commonly called a cytokine storm that attacks the entire body, a consequence of the chemokine molecules mentioned above. As the molecules fend off the virus, the immune systems start producing an uncontrollable amount, that's when these molecules intended to protect us, attack us.

Nervous system

As scientists gain insight on the virus' impacts, they noticed that the nervous system was affected. They observed patients suffering from brain inflammation encephalitis, seizures and sympathetic storms. There have even been cases of patients losing their sense of smell. A potential theory is that the virus causes a depression in the brain stem reflex, responsible for detecting oxygen levels. Other theories involve cytokine storms that can cause brain swelling or exaggerated blood clots which can result in seizures (Wadmna et al., 2020). However, the neural cortex and brain stem possess ACE2 receptors, indicating a possible pathway to the virus. Although, it has yet to be seen if the virus impacts the brain through these pathways.

Covid-19 characteristics and consequences
- James Jing

General Structure of Coronaviridae

Covid-19 is the new corona virus that emerged in China. There are different type of viruses and some cause diseases. In fact, Covid-19 causes respiratory illness.[i] The whole sequence of the genome of the virus has been acquired using Illumina and nanopore. Illumina is a biotechnology company. The analysis indicated that the virus has prominent features of the coronavirus family and is part of the Betacoronavirus 2B lineage, one of the four genera of coronaviruses. The full-length genome sequence resembles to the SARS-like coronavirus strain with 96% identity.[ii] Covid-19 is a member of Betacoronaviruses like the Severe Acute Respiratory Syndrome Human coronavirus (SARS HCoV) and the Middle East Respiratory Syndrome Human coronavirus (MERS HCoV). HCoVs generally are positive-sense and they are usually very long (30,000 bp) single-stranded RNA. Its size ranges from 27 to 32 kb, (1kb is the same size as 1000 nucleotides), they are significantly larger than other RNA viruses.[iii]

Health Consequences of the Virus

Common symptoms of Covid-19 include fever, dry cough, tiredness, aches, pain, nasal congestion, sore throat, diarrhea. The symptoms start mild and gradually intensify. Older individuals with high blood pressure, heart, lung problems and diabetes are more prompt to develop the symptoms presented. Anyone can catch the virus and become ill. Severe cases can cause pneumonia, severe acute respiratory syndrome, kidney failure and death.[iv] In a study with 204 Covid-19 patients, half of them experienced digestive problems. These problems include, lack of appetite, diarrhea, vomiting and abdominal pain.[v]

Death rate

As of April 26, 2020, there are 2 804 796 confirmed cases and 193 722 deaths with 213 countries and territories affected. The death rate of this virus is roughly 7%.[vi] As of April 26, 2020, there are 1 079 785 closed cases, with 81% recovered or discharged and 19% death. There are currently 1 886 704 active cases, with 3% of the patients in critical state and 97% in mild condition.[vii]

Transmissibility

For transmissibility, the virus spreads from person to person. When a person coughs or sneezes, small droplets will come out from the nose or mouth. A person breathing in these droplets from an infected person will get infected themselves. The same consequence happens if they touch a surface where the droplets landed, and they touch their eyes, nose, or mouth. This will allow the virus to enter that individual's body.[viii] The infectious or incubation period lasts from 1 to 14 days.[ix] However, a study with 181 infected patients have shown that the median incubation of the sample was 5.1 days. There is a small possibility that the symptoms will develop after 14 days after the exposure. This data is collected by determining the possible time of exposure of a patient until they show symptoms.[x]

Recovery Period

Using existing data, researchers concluded that the recovery period of for mild cases of Covid-19 is around 2 weeks. For severe cases, this period could be extended from 1-4 weeks, therefore making the period 3-6 weeks.[xi] From the global data so far, roughly 98% of all cases are adults, meaning that adolescents and infants seem to be less affected by Covid-19. There is no conclusive answer to this phenomenon but there are a few possibilities. Younger children get many normal viral infections, this could possibly prepare them for Covid-19, helping them combat this virus more efficiently.[xii] Other possibilities include the fact that children participate in less activities outside compared to adults, or that they have been exposed to less smoke and pollution compared to adults, therefore, having healthier lungs.[xiii]

Looking at Canada's data as of April 23, 5% of all infected individuals in Canada are 19 years or younger, 24% are 20-39 years old, 15% are 40-49 years old. There is 17% of patients aged 50-59 years old and around 21% are 60-79 years old. Finally, around 16% of patients are 80 years and older.[xiv]

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Social and economic impacts **-Bhromor Rahman**

The economic situation has worsened as April's report shows two million losses and joblessness is up at 13%. For students, the situation is even more dire: 37% of jobs filled by 15 to 24-year old's in the February jobs report (pre-lockdown) or slightly more than 200 000 jobs have been wiped out. In Quebec, about 800 000 jobs total disappeared. When it comes to companies, the PM has made it clear that there will be no bailouts; only bridge loans. Employers were granted a 75% wage subsidy (CEWS), but with some small businesses on razor thin profit margins, entry level workers are let go to retain veterans. For those who are currently unemployed, renewable CERB benefits offer 2000$ a month for four months, but eligibility criterias left many out of the loop. This was addressed by the government with the newest CESB benefits offering 1250$ per month for students mostly as a stop-gap measure for expected lost income in the summer as good student jobs disappear. The measure was not unanimous and led to partisan bickering among parliamentarians. The Bloc supported the measure as is, but the NDP criticized it as inadequate as the 750$ difference between the CERB and CESB makes a big difference for a student who has to rent housing. The Conservatives were the biggest vocal critics as many of their farmer constituents wanted students to go work for them on their farms as seasonal workers are unavailable and labor shortages add to the already dire crop loss in the agricultural sector. However, the rollout for the measure was very poorly executed and the Tories were immediately shot down. Some even compared the measure to the Great Leap Forward (大跃进) implemented by Chairman Mao in China from 1958 to 1962 that resulted in at least 20 million deaths. Hyperbole aside, farmers need help and the government proposed a 252 million $ aid package which disappointed many farmers as the industry is set to lose almost 3 billion $. Provincial and the Federal governments look forward to reopening the economy soon, but with no vaccine in sight, uncertainty still looms. As for the economy at large, there is an open discussion about our supply lines and China. One one side, free marketers have defended free trade as it generates lower prices for consumer goods, but economic nationalists insist that the threat of China can no longer be ignored and that protectionism is the only alternative (see Panier Bleu). In fact, there is an increasing desire in Western countries to hold China responsible for the virus and punish the Chinese Communist Party. Meanwhile, Xi Jinping has been losing patience over the US government's insistence that the virus originated in a Wuhan lab. I don't think that there is any risk of a hot war, but we could very well be at the dawn of a new Cold War. Finally, a controversial move from the PMO this week banning certain guns by decree. This, as well as all the spending without a budget in effect (making it effectively a slush fund) has worried civil libertarians that the country might be slipping into tyranny.

In the US, the USD being the world reserve currency, the Fed has done absolutely everything to save the US economy and mitigate the damage. This has led it to get involved all the way down into the high-yield market and may even go all the way to stocks. The concern for some economists is the creation of zombie companies. That is, companies who only have enough revenue to service debt and are unable to invest in growth. Some states have begun reopening some businesses.

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COVID-19 LITERARY REVIEW MAY 2020: GENETICS

***Anatomical regions affected by the virus* -Linda Li**

"SARS-CoV-2 particles were found in ultrathin sections of human airway epithelium. Human ACE2 was found to be a receptor for SARS-CoV-2 as well as SARS-CoV. However, the S protein of SARS-CoV-2 binds to human ACE2 more weakly than that of SARS-CoV, which is coincident with the fact that SARS-CoV-2 causes less severe infection in patients than SARS-CoV. [….] SARS-CoV-2 mainly attacks the lungs in the beginning and probably also attacks, to a lesser degree, other organs that express ACE2, such as the gastrointestinal system and the kidneys. Nevertheless, respiratory dysfunction and failure are the major threat to the patients and the major cause of death." (Yi, Lagniton, Ye, Li, & Xu, 2020) "The researchers confirmed the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing, adding support to the theory this new pneumonia virus can also cause nervous system damage. It is therefore likely that other pathogenic bacteria, such as bacteria, may destroy the blood–brain barrier, and secondary intracranial infections may cause headaches, projectile vomiting, visual loss, and limb convulsions interact with the brain's hypothalamus resulting in physiological changes including
increase in body temperature and fever. Additionally, the response results in vasodilation and increase vascular permeability. As such, with corresponding fluid accumulation, causing increased breathing capabilities and by extension breathing difficulty." (Sheshe, Nazifi, Labbo, Khalid, Yahya, Muhammad, & Haruna, 2020)

Invasion

"SARS-CoV2 utilizes its structural proteins to gain entry into the host cell cytosol as well as suppress signaling pathways particularly with the Toll-like receptors (TLR). Usually, the interaction between the viral nucleic acid is with TLR7 and TLR3. This interaction initiates a signal cascade involving the transcriptional factors IRF3 and NFkB. These transcriptional factors are further translocated into the nuclei where they activate the machinery for expression of Pro-inflammatory cytokines and interferons particularly IFN1. IFN in turn activates the JAK-STAT pathway via phosphorylation of STAT-1 and -2. The combine activated forms of STAT-1 and -2 further form complexes with IRF9 with the immediate release of active Interferon stimulating genes (ISGs) resulting in a massive suppression of viral replication" (Sheshe, Nazifi, Labbo, Khalid, Yahya, Muhammad, & Haruna, 2020)

"In general, after a virus invades the host, it is first recognized by the host innate immune system through pattern recognition receptors (PRRs) including C-type lectin-like receptors, Toll-like receptor (TLR), NOD-like receptor (NLR), and RIG-I-like receptor (RLR). Through different pathways, the virus induces the expression of inflammatory factors, maturation of dendritic cells, and synthesis of type I interferons (IFNs) which limit the spreading of the virus and accelerate macrophage phagocytosis of viral antigens. However, the N protein of SARS-CoV can help the virus escape from the immune responses." (Odor, Neun, Banpoe, Clark, Heaton, Hoogenboom, Patel, Brown, & Kamming, 2020)

Transmission

in patients with severe COVID-19 symptoms. [….] Owing to the fact that the patients with COVID-19 often suffer from severe hypoxia, hypoxia injury may cause subsequent nervous system damage. [….] Angiotensin-converting enzyme 2 (ACE2) is a cardio-cerebral vascular protection factor existing in a variety of organs, including the nervous system and skeletal muscles, playing a major role in regulating blood pressure and anti-atherosclerosis mechanisms. Meanwhile, ACE2 is also an important target for various CoV and influenza viruses. Binding to ACE2 receptors, the above-mentioned viruses may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage. In addition, given that SARS-CoV-2 spike protein could interact with ACE2 expressed in the capillary endothelium, the virus may also damage the blood–brain barrier and enter the CNS by attacking the vascular system." (Wu, Xu, Chen, Duan, Hashimoto, L. Yang, Liu, C. Yang, 2020) "However, its pathophysiology involves viral entry in respiratory droplets into the lungs via the airways. Major target of the virus is the alveolar cells which play critical roles in gaseous exchange during respiration. Interaction between the viral Spike proteins and the ACE receptor ensures viral entry into the alveolar cells with the concomitant of structural disintegration. The Inflammatory response initiated was due to release of pro-inflammatory cytokines such as IL-6 and TNF-alpha. These two cytokines

"The main transmission risks for all coronaviruses are exposure to droplets and contact transfer of virus. Droplets are heavy and usually disperse within a maximum 2 m radius after coughing and sneezing by an infected patient. [….] Although SARS-CoV-2 RNA can be detected with polymerase chain reaction (PCR) testing over long periods in bodily fluids, this does not necessarily correlate with the period that each individual is infective for." (Odor, Neun, Banpoe, Clark, Heaton, Hoogenboom, Patel, Brown, & Kamming, 2020)

"The inherently high recombination frequency and mutation rates of coronavirus genomes allows for their easy transmission from different intermediate hosts. Structurally, they are positive-sense single stranded RNA (ssRNA) virions with characteristic spikes projecting from the surface of capsid coating. Their genome is nearly 27 to 31 Kb long, largest among the RNA viruses, with 5'cap and 3' polyA tail, for translation. Their spherical capsid and spikes give them crown-like appearance due to which they were named as 'corona', meaning 'crown' or 'halo' in Latin. Coronavirus consists four main proteins, spike (S), membrane (M), envelope (E) and nucleocapsid (N). The spike (~150 kDa) mediates its attachment to host receptor proteins. Membrane protein (~25-30 kDa) attaches with nucleocapsid and maintains curvature of virus membrane. E protein (8-12 kDa) is responsible for the pathogenesis of the virus as it eases assembly and release of virion particles and also has ion channel activity as integral membrane protein. N-protein, the fourth protein, helps in packaging of virus particles into capsids and promotes replicase-transcriptase complex (RTC)." (Kumar, Verma, Singhvi, Sood, Gupta, N. Singh, Kumari, Hira, Nagar, Talwar, Nayyar, Anand, Rawat, Verma, Negi, Y. Singh, & Lal, 2020)

Binding to cell and main receptors

"CoVs are a subfamily of large and enveloped viruses containing a single strand of sense RNA. They can be divided into four genera, *i.e*., alpha, beta, gamma, and delta, of which alpha- and beta-CoVs are known to infect humans. The envelope spike (S) glycoprotein binds to its cellular receptors angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) for SARS-CoV and MERS-CoV, respectively, and then membrane fusion occurs. The viral RNA genome is released into the cytoplasm; after replication of the viral genome, genomic RNA accompanied by envelope glycoproteins and nucleocapsid proteins forms virion-containing vesicles, which then fuse with the plasma membrane to release the virus." (Yi, Lagniton, Ye, Li, & Xu, 2020)

"SARS-CoV-2 (COVID-19) binds to ACE2 (the angiotensin-converting enzyme 2) by its Spike and allows COVID-19 to enter and infect cells. In order for the virus to complete entry into the cell following this initial process, the spike protein has to be primed by an enzyme called a protease. Similar to SARS-CoV, SARS-CoV-2 (COVID-19) uses a protease called TMPRSS2 to complete this process. In order to attach virus receptor (spike protein) to its cellular ligand (ACE2), activation by TMPRSS2 as a protease is needed." (Mousavizadeh, & Ghasemi, 2020)

Environment

"It has been reported that SARS-CoV-2 is sensitive to ultraviolet rays and heat at 56 °C for 30 minutes; ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, chloroform, and other fatty solvents, but not chlorhexidine, can effectively inactivate the virus." (Yi, Lagniton, Ye, Li, & Xu, 2020)

[…] emerged approximately at the same time as 2002-2003 SARS and contained around summer, majority of cases found near the equator within a latitudinal zone between 25 and 55 degrees north [….] While the spread of the virus shows strong correlation within the 4-12C mean daily temperature range, the additional correlation to the preferred spread range being between 25 and 55 north may suggest that the causative agent in decreasing the communicability of the virus may be increased solar radiative bombardment in the areas to the south of the 25 North line of latitude." (Poole, 2020)

Escape Detection

"Theoretically, asymptomatic carriers might arise when host antiviral defence is either strong or decoupled. When the immune response effectively limits but could not completely block SARS-CoV-2 replication, asymptomatic shedding might occur. In this scenario, the risk of transmitting to others is relatively low because of a low viral load. Alternatively, if the immune response against SARS-CoV-2 is decoupled from viral replication as in the infection of natural primate hosts with SIVs, the viral load would be higher, posing a higher risk for person-to-person transmission. A careful quantitative analysis of the replication dynamics of SARS-CoV-2 in asymptomatic carriers over time is required to clarify the validity of the two models." (Fung, Yuen, Ye, Chan, & Jin, 2020)

Other

“In this study, we found that ABO blood groups displayed different association risks for the infection with SARS-CoV-2 resulting in COVID-19. Specifically, blood group A was associated with an increased risk whereas blood group O was associated with a decreased risk, thus demonstrating that the ABO blood type is a biomarker for differential susceptibility of COVID-19. These findings are consistent with similar risk patterns of ABO blood groups for other coronavirus infection found in previous studies. For example, Cheng et al. reported that the SARS-CoV infection susceptibility in Hong Kong was differentiated by the ABO blood group systems. Patrice et al. found that anti-A antibodies specifically inhibited the adhesion of SARS-CoV S protein-expressing cells to ACE2-expressing cell lines . Given the nucleic acid sequence similarity and receptor angiotensin-converting enzyme 2 (ACE2) binding similarity between SARS-CoV and SARS-CoV-29-11, the lower susceptibility of blood group O and higher susceptibility of blood group A for COVID-19 could be linked to the presence of natural anti-blood group antibodies, particularly anti-A antibody, in the blood. This speculation will need direct studies to prove. There may also be other mechanisms underlying the ABO blood group-differentiated susceptibility for COVID-19 that require further studies to elucidate.” (Zhao, Y. Yang, Huang, Li, Gu, Lu, Z. Zhang, L. Liu, T. Liu, Y. Liu, He, Sun, Wei, G. Yang, X. Wang, L. Zhang, Zhou, Xing, & P. G. Wang, 2020)

Introduction- Shi Tao Zhang

"Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases. Six coronavirus species are known to cause human disease. Four viruses — 229E, OC43, NL63, and HKU1 — are prevalent and typically cause common cold symptoms in immunocompetent individuals. The two other strains — severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) — are zoonotic in origin and have been linked to sometimes fatal illness. SARS-CoV was the causal agent of the severe acute respiratory syndrome outbreaks in 2002 and 2003 in Guangdong Province, China. MERS-CoV was the pathogen responsible for severe respiratory disease outbreaks in 2012 in the Middle East. Given the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of their genomes, and increasing human–animal interface activities, novel coronaviruses are likely to emerge periodically in humans owing to frequent cross-species infections and occasional spillover events. (Zhu, Zhang, Wang, Li, et al., 2019) They annotated three genomes of 2019-nCoV, which were sequenced from samples collected on December 30 and January 1 by the National Institute for Viral Disease Control and Prevention, part of the Chinese CDC and are available through GISAID.. Then they compared them to bat SARS-like coronaviruses, human SARS coronaviruses, and human Middle East respiratory syndrome coronaviruses (MERS-CoV)." "The authors found that there were only five nucleotide differences—in a total genome of about 29,800 nucleotides—among the three 2019-nCoV genomes. They also identified 14 open reading frames, predicted to encode 27 proteins, including four structural and eight accessory proteins. Previous coronavirus research indicates that accessory proteins may mediate the host response to the virus, which can affect pathogenicity, and may make up part of the viral particle. Jiang and colleagues noted differences in the amino acid sequences of SARS-CoV and 2019-nCoV. For instance, one SARS-CoV accessory protein, known as 8a, is absent in the new virus. Other accessory proteins varied in length. In 2019-nCoV, 8b is 37 amino acids longer than in SARS-CoV while 3b is shorter by 132 amino acids."

"The structural proteins are very highly conserved between all coronaviruses, whereas accessory proteins are generally unique to each specific group of coronaviruses," explains Fehr. The amino acid sequences show "the connection of this virus to the SARS-like coronaviruses and a little bit more distant relationship to SARS coronavirus."

"The researchers determined that 2019-nCoV is most closely related to bat SARS-like coronaviruses, from which SARS-CoV evolved, and more distantly related to MERS coronaviruses. Still, they did not find a single bat SARS-like coronavirus in which all the proteins were most similar to those of the new coronavirus. Instead, some 2019-nCoV proteins are more similar to those of bat SARS-like coronaviruses, while accessory proteins 3a and 8b are most similar to the SARS-CoVs."

"Our "analysis of genome data of 2019-nCoV together with other coronaviruses clearly shows that, although this novel virus has high sequence similarity to SARS virus, they belong to distinct phylogenetic branches and were both derived from SARS-like virus isolated in bats." (Oleana, 2020)

"Viruses are always mutating, especially RNA viruses like this one, coronavirus SARS-CoV-2. When a person is infected with the coronavirus, it replicates in their respiratory tract. Every time it does, around half a dozen genetic mutations occur," says Ian Jones at the University of Reading, UK.

When Xiaolu Tang at Peking University in Beijing and colleagues studied the viral genome taken from 103 cases, they found common mutations at two locations on the genome. The team identified two types of the virus based on differences in the genome at these two regions: 72 were considered to be the "L-type" and 29 were classed 'S-type'."

"A separate analysis by the team suggests that the L-type was derived from the older S-type. The first strain is likely to have emerged around the time the virus jumped from animals to humans. The second emerged soon after that, says the team. Both are involved in the current global outbreak. The fact that the L-type is more prevalent suggests that it is "more aggressive" than the S-type, the team say.

"There do appear to be two different strains," says Ravinder Kanda at Oxford Brookes University in the UK. "[The L-type] might be more aggressive in transmitting itself, but we have no idea yet how these underlying genetic changes will relate to disease severity," she says.

"I think it's a fact that there are two strains," says Erik Volz at Imperial College London. "It's normal for viruses to undergo evolution when they are transmitted to a new host."

"It is vital to know how many strains of the virus exist. Around the world, multiple groups are working on a

vaccine for the virus. Any vaccine will need to target features that are found in both strains of the virus in order to be effective."

"The differences between the two identified strains are tiny. In fact, they can't really be considered to be separate "strains", says Jones. And many of the genetic differences won't affect the production of proteins, and so won't change the way the virus works, or the symptoms it causes, he says. One is not more deadly than the other." (Hamzelou, 2020)

Introduction- Anthony Bai

Coronaviruses are the biggest group of viruses belonging to the Nidovirales order (Fehr & Perlman, 2015).Coronaviruses are spherical and have their names because of their halo-like shape when viewed under the microscope, which are caused by their most distinguishing features: the club-shaped spike projections coming out from its surface. These spikes give the appearance of a solar corona, thus prompting the name, coronaviruses. This virus is part of a large family of RNA viruses. In comparison, there is also the family of DNA viruses. Coronaviruses are further subdivided into four groups, the alpha, beta, gamma, and delta coronaviruses (later updated to include toroviruses). These groups' divisions are based on phylogenetic clustering: a method that analyzes patterns in communities such as from an evolutionary or biological perspective. (Devine & Bohannan, 2006).

Genome

The typical arrangement of a coronavirus genome is a single strand of RNA. It contains a non-segmented, positive-sense RNA genome. (Fehr & Perlman, 2015). Coronaviruses are linear. This linear organization of the coronavirus genome mostly consists of

- 5'-leader-UTR-replicase
- S (Spike)
- E (Envelope)
- M (Membrane)
- N (Nucleocapsid)
- 3' UTR-poly (A) tail

Coronavirus genome also has accessory genes that are almost all nonessential for replication, although they are significant in viral pathogenesis: development of diseases. These accessories make up only about 10 kilobases (measurement unit) of the viral genome, which is, relatively, not a lot. In fact, the coronavirus is around 32 kilobases long . (Fehr & Perlman, 2015) It is the biggest known RNA virus. However under a larger picture, this virus is still small and comparable to a simple organelle. In comparison, most bacteria genomes are bigger; and compared to the genome of humans, the size of coronavirus is minimal. (DiMaio, 2012)

Two essential genes

Casually said, viruses are lazy. Coronaviruses are no exception. They use most of the host cell's machinery to make what they need to replicate (5). Viruses have genes that encode for at least two crucial proteins; replicase, and a capsid. The replicase gene of coronaviruses occupy two-thirds of the genome (about 20 kb). It utilizes a 5' cap structure along with a 3' poly (A) tail, that allows the coronavirus to mimic a mRNA that will induce the translation of replicase polyproteins. As for the capsid, generally referred to by the broader term nucleocapsid, is helically symmetrical. Nucleocapsids are not simple barriers, they are complex and must be sufficiently stable in the environment to protect the contained nucleic acid genome of the coronavirus, and at the same time play multiple roles in the interaction between the virion and host cell (J. H., Strauss, E. G. Strauss, 2008).

Coronavirus replication in laboratories.

Viruses can be recreated in laboratories. Using a young technology called synthetic biology. In general, such cloning requires a combination of biology and engineering expertises. In order to recreate a virus, its genome must be firstly known. This preliminary step can be achieved through various methods, such as bioinformatics.(Wimmer, Mueller, Tumpey & Taubenberger, 2009) The first genome sequences of SARS-CoV-2 were released between January 10 and 11th. It took until the end of January 2020 when successful isolation and culture of SARS-CoV-2 was reported from patients in Australia (Akst, 2020). When the genome is identified, researchers can proceed at synthesizing the virus. Synthesis of viruses has multiple applications. Mostly, it can help develop vaccines. Theoretically, it could also make an illness more virulent or drug-resistant, as well as revive long-eradicated diseases.

Biosecurity and synthetic biology

There are biosecurity measures put in place to control the use of synthetic biology. Without proper oversight, cloning viruses could be relatively easy to achieve, using genetic material acquired online. This possibility has made governments raise awareness, and worry that such innovations could be used to make biological weapons and be dangerous in the wrong hands. In the United States, with the collaboration of various companies, the U.S. intelligence community is involved in tracking the use of synthetic biology to ensure safety. In addition, programs have been created, such as the Functional Genomic and Computational Assessment of Threats, a project designed to warn researchers of which genetic combinations might be harmful before they're ever made in a laboratory (Spalding, 2018).

Today, reawakening dormant diseases requires significant scientific expertise and laboratory resources. Generally, only state actors are equipped to use such techniques. However, innovation is quick

and constantly pushes boundaries. In addition, genetic synthesis is becoming increasingly affordable. Two decades ago, the creation of a synthetic copy of one single nucleotide cost 10$. The new coronavirus gene contains 30,000 nucleotides. Yet, today, to build this new coronavirus, each of its nucleotides cost under 10 cents. As a result, reduction in price allows researchers to develop more copies of the virus (Wetsman, 2020).

Laboratory standards for cloning coronavirus

Under the NIH Guidelines, there are specific conditions in which the coronavirus can be cloned. NIH has categorized coronavirus as a BSL of Group 2. BSL-2 laboratories are equipped to study moderate-risk infectious agents that pose a risk if accidentally swallowed, inhaled, or exposed to the skin. BSL-2 laboratories include hand washing sinks and eye washing stations. They have doors that close and lock automatically. They have equipment to decontaminate waste, including an incinerator (NIH, 2018).In comparison, BSL 4 laboratories, the most sophisticated ones, require isolated zones within a larger building or may be housed in a separate, dedicated building. It handles chemical manipulations under laboratory cabinets or under full-body, air-supplied suits (Boyle, 2020).

First cloning of the new coronavirus

The first cloning of the new coronavirus was challenging and difficult to manipulate. Coronaviruses are known for their large size and ability to frequently recombine their chromosomes, resulting in occasional instability. Many alternative genome analysis methods were thus developed. In Swiss, one method consists of using a yeast-based synthetic genomic platform. This yeast method allowed researchers to successfully reconstruct coronaviruses. In fact, researchers were able to engineer and resurrect chemically-synthetized clones of the new coronavirus. When successfully recreated in laboratories, distribution of coronavirus templates requires various licenses.

Yeast

The reason for using a yeast cloning system, instead of choosing other methods to clone, is the ability of yeast to recombine overlapping DNA fragments in cellulo, which led to the development of a technique called “transformation-associated recombination”; TAR cloning. The main advantage of the TAR cloning system is that the genome of the virus can be fragmented to at least 14 overlapping pieces. These pieces can be re-assembled with remarkable efficacy. Indeed, usually, more than 90% of the clones are correct. This method allowed researchers to complete the cloning of coronavirus within one week. In fact, the appearance of the novel coronavirus in China at the end of 2019 prompted Swiss researchers to test the applicability of an already developed genomics yeast platform to reconstruct the virus. Based on the released genome sequence and chemically synthesized DNA fragments from Australia mentioned previously, researchers fragmented the genome into 12 subgenomic DNA fragments. Fragments were manipulated; and from an additional isolated viral RNA obtained from a Munich patient, researchers amplified certain regions of the fragments and TAR cloning was immediately initiated. This was the first successful cloning of the novel coronavirus.

Diagnostic Assays -Joyce Li

Testing of SARS-CoV-2 is mainly done using the reverse transcription polymerase chain reaction (RT-PCR) method (Tiner, 2020), which has the advantage of directly determining the presence of viral RNA (Kent, 2020). This allows for diagnosis of infected individuals before the apparition of symptoms, which is very helpful for early quarantining intervention in order to "break [the] transmission chain"(Kent, 2020, paras.6). A swab is taken from the patient's upper respiratory tract (Tiner, 2020), and the virus RNA is isolated in a laboratory setting. "DNA polymerase reverse transcriptase [...], DNA building blocks, cofactors, probes and primers that recognize and bind to SARS-CoV-2" are then added to the viral RNA sample (Tiner, 2020, paras.10). As PCR is only an effective detection tool for DNA, the viral RNA must first be converted to its complementary DNA strand with the action of the enzyme reverse transcriptase (Tiner, 2020). The viral template is then destroyed by enzyme activity, and a DNA version of the viral genetic information is generated from the complementary DNA strand (Tiner, 2020). Through the action of heat, the double helix viral DNA is separated, leaving probes and primers free to latch onto gene segments specific to SARS-CoV-2 (Tiner, 2020). According to Nature Education, these primers, which consist of small, nucleic acid segments, act as the "start" signal for the DNA polymerase enzyme to begin synthesis of the viral DNA on both strands (n.d.). Once synthesis is complete, the probes hybridized with the template DNA strands are detached and begin to emit "visual signals", such as fluorescence (Tiner, 2020, diagram 3). The two copies of the original, double-stranded viral DNA (original viral RNA correspondent bonded with its complementary) resulting from the synthesis then undergo the same, copying procedure (Tiner, 2020). Since each cycle essentially doubles the amount of DNA to be copied, the visual signal emitted by the probes after each synthesis is exponentially amplified which, Dr. Rodino explains, "[...] can be easily detected as a positive result. If the virus is not present, the probes do not stick, there is no signal release and it is a negative result" (as cited in Tiner, 2020, paras. 17).Though widespread in laboratory settings and fairly accurate, the RT-PCR test requires specific instruments to operate and appears to be more costly and difficult to use (WHO, 2020) than serological tests that diagnose viral presence by looking at concentrations of viral antigens or human antibodies (Kent, 2020). Unlike the RT-PCR test, these antigen and antibody oriented tests usually work with blood samples and can be used by inexperienced individuals, enabling patients themselves to perform diagnosis at home and, depending on the test, to obtain results within the hour (WHO, 2020). Unfortunately, both antigen- and antibody-detecting assays come with their inconveniences. Previous experience with antigen-based diagnostic tests "for other respiratory diseases such as influenza" suggest that "the sensitivity of these tests might be expected to vary from 34% to 80%"(World Health Organization [WHO], 2020, paras. 6), which measures poorly against the "80-85% specificity" of the PCR test (Kent, 2020, paras. 9). Furthermore, the possibility of cross-reaction with similar antigens of the common cold, also a type of coronavirus, raises the risk of false-positive results (WHO, 2020). As for antibody-based testing, the assay is only effective after the host's adaptive immunity mounts a response against the virus, since it is only then that the body releases antibodies specific to SARS-CoV-2 (WHO, 2020). Given that an adaptive response "can take 7 to 10 days to mobilize completely" (Helbert, 2017, p.3), the test does not allow early diagnosis, which limits the possibilities of patient treatment and isolation (WHO, 2020). Furthermore, in individuals with "weak, late or absent antibody responses", such as the elderly or the immuno-supressed, there is a risk of false-negative results that doesn't exist with RT-PCR testing (WHO, 2020, paras. 9). Ultimately, despite their interest as inexpensive and simple-to-use assays, serological tests are not currently recommended by the World Health Organization in clinical diagnostic settings given their lack of accuracy (WHO, 2020).

ACE2 mechanisms

Recently, the ACE2 receptor has been widely identified as the culprit responsible for the viral entry of SARS-CoV-2 into the human host cell (Cristiani et al., 2020). Counter-intuitive as it may seem, however, down-regulation of ACE2 receptors is actually associated with higher risks of severe infection symptoms due to ACE2's regulatory role on the angiotensin-renin system, on blood-clotting factors, and on the innate immune response.

ACE2 receptors are a type of membrane-attached enzymes that participate in the interactions between hormones of the Renin-Angiotensin-Aldosterone system (RAAS) which mainly functions to regulate blood-pressure (Cristiani et al., 2020). The hormone angiotensinogen is cleaved by renin, and becomes angiotensin I. If it comes in contact with ACE2, angiotensin I is converted into angiotensin, composed

of 9 amino acids, but with the enzymatic activity of ACE, it is cleaved into angiotensin II which is then turned into angiotensin$_{1-7}$ (7 amino acids) by the ACE2 receptor (Verdecchia et al., 2020). Though ACE2 acts on both angiotensin I and angiotensin II, its "catalytic efficiency [...] is 400 times higher on angiotensin II than on angiotensin I"(Verdecchia, 2020, section 2), which makes it crucial in angiotensin$_{1-7}$ formation. The interactions in the hormone system can be seen as two separate, counter-regulatory axes; ACE2, along with angiotensin$_{1-7}$ and the Mas receptors to which this binds, consists of a pathway that counteracts the effects of ACE, angiotensin II and the AT1 receptor (Verdecchia et al., 2020).

The conversion of angiotensin II into angiotensin$_{1-7}$ has an important regulatory role given that angiotensin II activity is responsible for numerous "adverse reactions which include[s] myocardial hypertrophy and dysfunction, interstitial fibrosis, endothelial dysfunction, enhanced inflammation, obesity-associated hypertension, oxidative stress and increased coagulation" (Verdecchia et al., 2020, section 4). Furthermore, the angiotensin II pathway exacerbates inflammation reactions by stimulating macrophages into producing lymphocyte recruiting chemokines (Bernstein et al., 2018), such as IL-8 which calls neutrophils to infection sites (Helbert, 2017), and inflammatory cytokines such as IL-6 and TNF (Verdecchia et al., 2020). Innate immunity responses are also enhanced by angiotensin II's activation of Toll-like receptor 4 (TLR-4), and the increase in ACE receptor expression in cells forming a granuloma forming cells suggests its use in stimulating the bactericide properties of macrophages, given that granulomas are clusters of macrophages intended to isolate a foreign pathogen the body is unable to destroy by lysis (Helbert, 2017). This is particularly relevant, given the close association of cytokine storms with the acute respiratory distress syndrome (ARDS) occurring in most severe and fatal cases of SARS-CoV-2 (Mehta et al., 2020). Cytokine storms are uncontained spikes in innate immune activity that occur when the immune system is struggling to contain an infection; specific cytokines (messenger molecules of the immune system), such as IL-6 and TNF, are released to massively recruit phagocytic lymphocytes, like macrophages and dendritic cells, and inflammation reactions are enhanced, leaving blood vessels dilated and permeable (Helbert, 2017). Patients often die, thereafter, from "vascular hyperpermeability, multiorgan failure" (Jose et al., 2020, paras. 2) or septic shock (Helbert, 2017). Furthermore, this state of hyperinflammation disrupts the "negative feedback loops and physiological anticoagulants" (Jose et al., 2020, paras. 3) that serve to control the production of thrombin, a clotting factor, which leads to higher risks of coagulation in the lungs in particular and thus, organ failure (Jose et al., 2020). The angiotensin II pathway comes to compound several negative effects of cytokine storm, namely ACE's strengthening of already exacerbated inflammation reactions and angiotensin II's promotion of thrombosis. As such, the ACE, angiotensin II and AT1 receptor axis is suspected to worsen the already severe conditions of SARS-CoV-2 patients.

The role of the angiotensin II pathway in SARS-CoV-2 is important to take note of because the balance between the angiotensin II pathway and its counterpart, the angiotensin$_{1-7}$ pathway is, from the virus's entry into human cells, disrupted (Verdecchia et al., 2020). Studies found that the viral spike protein that mediates entry into human cells by binding to ACE2 receptors also down-regulates said-receptors, even separated from its other viral components (Verdecchia et al., 2020). This has the cascading effect of increased angiotensin II concentrations, given that there is less ACE2 activity to convert it into angiotensin$_{1-7}$ (Verdecchia et al., 2020), which of course leads to more severe patient symptoms. Correlations between severe lesions in the lungs and respiratory tract and the reduction in ACE2 receptors have been observed (Verdecchia et al., 2020). Conversely, increased activity of the angiotensin$_{1-7}$, ACE2 and Mas receptor pathway has been seen to soothe inflammation, prevent fibrosis in lung tissue and provide anticoagulation effect (Verdecchia et al., 2020). Furthermore, the "negative correlation between ACE2 expression and SARS-CoV-2 severe outcomes" would justify the propensity of the elderly in suffering grave symptoms while children are left mostly unaffected (Cristiani et al., 2020, section 2). Indeed, ACE2 receptor levels appear to decrease with age, and children seem to possess a relatively large "concentration of ACE2 receptors in [their] lung pneumocytes" (Cristiani et al., 2020, section 2). As such, despite being the doorway for SARS-CoV-2 entry into the human body, high ACE2 receptor concentrations seem to have an overall positive effect in attenuating viral symptoms.

Binding to cell and main receptors

The spike proteins of this novel virus bind to its human cellular receptor called the angiotensin-converting enzyme 2 (ACE 2). However, before SARS-Cov-2 makes its successful entry into a cell, there is an

important step. The spike proteins need to be activated by an enzyme called the protease to attach itself to the ACE2 receptors, and then, it will undergo transcription and translation. The protease is an enzyme that plays an important role in breaking down proteins into amino acids but also in cell division. The protease in question is called TMPRSS2 (Mousavizadeh & Ghasemi, 2020, as cited by Hoffman et al., 2020).

Anatomical regions affected by the virus

Since the ACE 2 is found to be the human receptor of SARS-Cov-2, organs that express this enzyme are the ones mainly affected; namely, the lungs, the gastrointestinal system and the kidneys. The alveolar cells in the lungs are the major targets since they play a very important role in gas exchange during cellular respiration and provide a direct entry for respiratory droplets into the lungs (Sheshe et al.,2020). Furthermore, other research has confirmed that this new virus can cause nerve damage between the blood-brain barrier and enter the central nervous system (CNS) by penetrating the vascular system. When this new pneumonia virus's particles bind to the ACE 2 receptors, it also causes very elevated blood pressure that increases the risk of a cerebral hemorrhage in patients (Wu et al., 2020 as cited by Baig et al., 2020).

The importance of taxonomy and classification -Michael Zhang

Finding whether a viral outbreak is caused by a novel or already explored virus is an important step to determining approaches in studying and controlling the virus and its pathology. Rigorous naming and classification of viruses can aid in focusing efforts in the medical field as well as deciding the direction of future research and public policies. Newly emerging viruses often lack internationally approved methods, standards and procedures to name the causative agents of the virus, study its genome and determine and ascertain its pathology as well as communicating this information to the appropriate labs and experts. The novelty of a virus is one of the concerns of virus classification, and its task requires analysing its similarities to other coronaviruses in order to establish a clearer representation of the virus' main characteristics. It can however be difficult to decide whether a new virus should be considered a new species or merely a novel strain of an existing one: this is done by comparing its genome to other virus affecting the same host species or to monophyletic virus groups. There is no exact taxonomic position for SARS-CoV-2 within the subgenus Sarbecovirus (as of beginning May). While CSG (Coronaviridae Study Group) from ICTV (International Committee on Taxonomy of Viruses) established that SARS-CoV and MERS-CoV were each the first of a new species within their subgroups, Sarbecovirus and Merbecovirus respectively, and as such the two have unique names. However, Sarbecovirus has since garnered hundreds of virus (species being a group of viruses with traits generally distinguishable from other species, though the present taxonomy of viruses is often disputed), principally isolated from humans and bats, which are grouped not due to related diseases or pathology but due to their phylogenetic characteristics, which explains SARS-CoV-2's nomenclature. SARS-CoV-2 greatly differs from SARS-CoV in its wide disease spectrum and transmission efficiency; the vagueness of the name COVID-19 is partly to accommodate for that variety in symptoms of the disease (CSG, 2020)

General Information

COVID-19 is caused by the SARS-CoV-2 coronavirus, which is one of seven coronaviruses known to affect humans; four of them are more common and cause seasonal colds: 229E (Alphacoronavirus), NL63 (Alphacoronavirus), OC43 (Betacoronavirus), HKU1(Betacoronavirus) while the other three, which are all betacoronaviruses, can lead to more severe symptoms or even death: MERS-CoV, SARS-CoV and SARS-CoV-2 (Brunilda, 2020).

Coronaviruses are of the subfamily Orthocoronavirinae, family *Coronaviridae*, order *Nidovirales*, realm *Riboviria* (realms are the largest taxonomic rank in virology, as established by the International Committee on Taxonomy of Viruses). They are classified into five genera (alpha-, beta-, delta-, gamma- and toroviruses) and two subfamilies. Their genomes vary between 25kb and 31kb in length, making them the largest known RNA viruses.

Betacoronaviruses are commonly categorized into four evolutionary lineages, each with its distinctive accessory genes: A, B, C and D. Lineage B includes the novel SARS-CoV-2 as well as its relative (though not directly descended from one another) SARS-CoV. Other species were largely extracted from bats.

Covered with bubble-like surface projections, their virions (colloquially adult coronaviruses) are roughly spherical, and make contact with host cells by binding with a spike protein to host-specific cell receptors. Coronaviruses have genomes that are organized into 5'non-structural protein coding regions: 2/3 correspond to replicase genes, and there are also 3'structural and nonessential accessory protein coding regions.

The heptameric sequence, 5'-UCUAAAC-3', is common to betacoronaviruses, with the SARS-CoV TRS (Transcriptional Regulatory Sequence) having 5'-ACGAAC-3' as the core sequence. After entry into the cell (whether through endocytic pathways of fusing with cell membrane), the virion uncovers itself before beginning the replication of its RNA genome using full-length genomic and subgenomic negative strand intermediates. The copies of the virus' genetic material are encapsidated, making virions which grow into smooth walled vesicles in the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). They then mature in the Golgi, from which they enter exocytic vesicles to reach the plasma membrane, which is where they exit the cell. (Yang, & Leibowitz, 2015)

ACE2

Angiotensin-converting enzyme 2 (ACE2) has been shown to be a functional receptor for SARS-CoV-2 to enter host target cells. ACE2 belongs to the membrane-bound carboxydipeptidase family and is widely distributed in the human body, including the heart, kidney, small intestine, and, to a lesser extent, the lung. Lung ACE2 expression is concentrated mainly in type II alveolar cells and macrophages and modestly in bronchial and tracheal epithelial cells.

Human ACE2 has been confirmed to be a functional receptor on the cellular membrane to which SARS-CoV binds itself to enter host cells by using its transmembrane spike glycoprotein; once attached to the cell, SARS-CoV-S protein priming by cellular surface proteases (ex: transmembrane protease serine 2 (TMPRSS2)) occurs, allowing the fusion of viral and cellular membranes and resulting in SARS-CoV entry and replication in the target cells. Knockout of ACE2 in mice experimentally infected with SARS-CoV greatly reduced viral infection and replication, suggesting that the binding of the SARS-CoV-S protein to ACE2 is crucial for SARS-CoV infection. Recently, it has been shown that the SARS-CoV-2-S protein shares nearly 80% amino acid identity with the SARS-CoV-S protein. (Yang, & Leibowitz, 2015)

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COVID-19 LITERARY REVIEW MAY 2020: TREATMENT

Aspects of an Accessible, Effective Treatment for COVID-19

Laurence Liang

Abstract

The development of an effective treatment against COVID-19 needs to take various factors into account, such as the demographics and socioeconomic status of vulnerable populations, the propagation of COVID-19 and the viral life cycle and the respective immune response.

This article analyzes these factors, and specifies that an effective treatment against COVID-19 should meet the following criteria:

1. Affordable to patients of all socioeconomic situations
2. Deliverable in a rapid timeframe
3. Focused on treating severe cases of COVID-19
4. Targeted to known phases of the virus' life cycle, such as entry, and immune system detection.
5. Targeted to help the host immune system, such as curbing a potential cytokine storm, and triggering specific particles that have a longer effectiveness against future infections

Developing Treatments for Populations with High Vulnerability to COVID-19

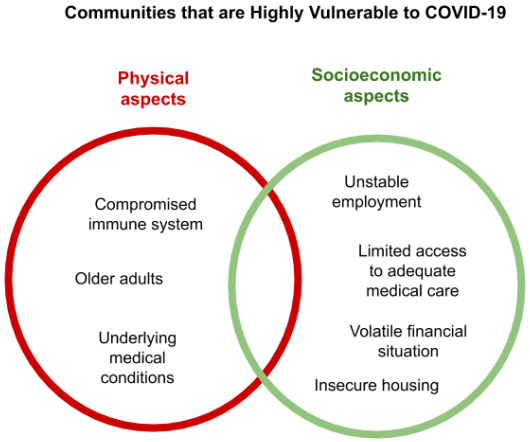


Fig 1: *Communities that are highly vulnerable to COVID-19*

The effects of a COVID-19 infection is disproportionate when taking physical and socioeconomic factors into account.

From a physical standpoint, the individuals who are more vulnerable to COVID-19 are older adults, individuals with underlying medical conditions, and individuals with a compromised immune system. (Government of Canada) The individuals who show the highest recovery age are of a young age, as a study on COVID-19 in Wuhan suggests that individuals under the age of 50 have a case mortality rate of less than 1%. (Verity et al, 2020)

From a socioeconomic standpoint, individuals impacted by insecure housing or unstable employment are vulnerable, as well as communities with lower income. Individuals from these communities might not have the means to easily access adequate medical care. In addition, some individuals might not be able to stop working amid the current pandemic due to their financial situation, and the type of housing in these communities may not allow individuals to effectively practice social distancing. (Government of Canada 2020, EuroHealthNet, 2020)

In summary, some individuals are more at risk and might be disproportionately affected by COVID-19. Thus, medical treatment against COVID-19 should be made affordable to all, and should be delivered as quickly as possible, as the housing arrangement of disadvantaged communities might not slow down the transmission of COVID-19.

Comparison of COVID-19 Infections with SARS and MERS Infections

Comparison of Coronavirus Infection Statistics

Disease	Fatalities	Case fatality rate	Infections	Reproduction Number
SARS	812	14-15 %	8 439	~ 3
MERS	866	35 %	2 519	2.0 - 6.7
COVID-19	**300 000 +**	**3-4 %**	**4 000 000 +**	**2.2 - 2.7**

Data: World Health Organization, The Lancet, John Hopkins University, as of May 17, 2020

Fig 2. *Comparison of Coronavirus Infection Statistics*

The SARS-CoV-2 virus responsible for COVID-19 belongs to the same family of viruses that caused SARS and MERS, known as coronaviruses. While they share similar characteristics, SARS-CoV-2 has caused at least 350 times more fatalities than SARS or MERS individually as of May 17, 2020. (World Health Organization, 2019, n.d, John Hopkins University, 2020) The high incidence of SARS-CoV-2 compared to the spread of SARS and MERS could be understood by analyzing the characteristics of each disease and its respective virus, and understanding these underlying causes could lead to the development of an effective treatment. These characteristics, however, do not clearly explain the high incidence of COVID-19.

COVID-19 has an estimated case fatality rate of 3-4%. (World Health Organization) This is lower than the case fatality rates of SARS (14-15%) and MERS (35%). (Ruan, 2020)

COVID-19's reproduction number, the average number of people who will catch the disease from an infected person, is between 2.2-2.7, which is lower than the value for SARS (average of 3 in the absence of health measures), and lower than the most extreme estimated values for the MERS reproduction number (2.0 - 6.7). (WHO, 2003) (Majumder et al, 2014)

By solely analyzing case fatality rates and reproduction numbers, it is difficult to explain the high incidence of COVID-19 when compared to SARS and MERS. One possible but contested explanation is the significance of asymptomatic transmission of COVID-19, spreading COVID-19 to others without the infected person showing signs of infection. This hypothesis would require more data to be properly considered or recognized as credible.

Since the fatality rate and reproduction number of COVID-19 do not differ significantly from those of SARS and MERS, it is difficult to establish an exact explanation on the high number of deaths caused by COVID-19 based on these numbers. If asymptomatic transmission is to be a significant factor in raising the incidence of COVID-19, it would be difficult to treat the disease by solely identifying and isolating asymptomatic carriers, as tests would need to be administered to entire populations, unless such tests can be executed in an inexpensive and rapid way, and isolating carriers of the disease might not be possible in some communities. However, as COVID-19's fatality rate is lower than SARS and MERS, additional research should be conducted to perfect treatment for patients in critical, life-threatening conditions, as most patients recover from an initial infection.

Development of a COVID-19 Treatment based on its Pathogenesis and the Host's Immune Response

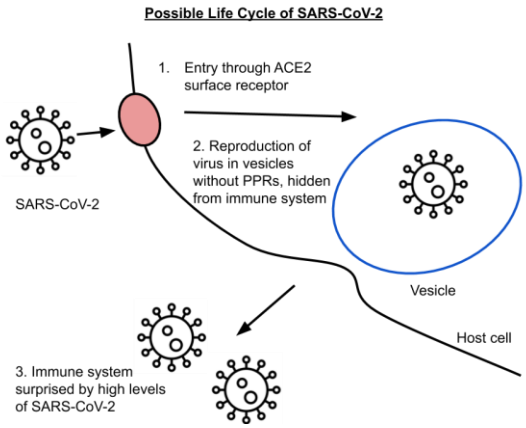


Fig 3. *Possible Life Cycle of SARS-CoV-2 (virus outline from Vector Stock)*

A treatment for COVID-19 can be developed by targeting its viral life cycle or the host immune system's reaction in fighting SARS-CoV-2, the virus that causes COVID-19.

Specific elements of SARS-CoV-2 are known to researchers. For instance, SARS-CoV-2 enters host cells through a surface receptor (a protein) called ACE2. ACE2 is prominent in cells that form the lungs, heart, renal tract, and gastrointestinal tract. Thus, creating a treatment that targets ACE2 could hold promise, and research in this subfield is ongoing. (Lin et al, 2020)

Another likely property about SARS-CoV-2 is an evasion from the immune system during its preliminary stages of infection. The coronaviruses of SARS and MERS, SARS-CoV and MERS-CoV, evade the immune system by reproducing in compartments in cells called vesicles. These viruses trigger the creation of specific vesicles that do not contain a type of protein called a PPR (pattern recognition receptor) that signals the immune system when a foreign

particle is present. Because the immune system is not aware that a virus is present, the virus (SARS-CoV or MERS-CoV) replicates. When the immune system realizes that viral particles are present, SARS-CoV or MERS-CoV will have already attained high levels. Facing this situation, the immune system reacts: sometimes, the immune system overreacts, triggering a "cytokine storm" that causes inflammation, leading to organ failure or possibly death in severe cases (cytokines are a family of proteins used by the immune system). Because SARS-CoV-2 is very similar genetically to SARS-CoV and MERS-CoV, it is likely that it shares similar characteristics that the other two viruses have, and possibly undergoes the same process. Thus, developing a treatment for COVID-19 could focus on the early-detection of SARS-CoV-2 to trigger an early immune response (the guiding principle that vaccines use) or to directly curb the damage caused by the cytokine storm. (Kindler & Thiel, 2014) (Xiaowei et al, 2020)

Therefore, possible areas of interest in the development of a treatment for COVID-19 can target the entry of SARS-CoV-2 into a host cell, the early detection of SARS-CoV-2 by the host immune system, and methods to curb the cytokine storm that can occur.

Specifications on the Type of Antibodies and their Memory in SARS Patients

The immune system uses antibodies, a type of protein, to neutralize foreign particles in a host's body.

Antibodies have responded in different ways to a SARS infection. IgM, a type of antibody that regulates immune activity, tends to disappear 12 weeks following an infection in patients, while IgG, another antibody that plays a similar role, is present for a long duration following infection. As antibodies can effectively recognize proteins belonging to SARS-CoV, they play an essential role in the host's immune response. As SARS-CoV-2 is very similar to SARS-CoV, a similar antibody behaviour could be observed. (Xiaowei et al, 2020)

Thus, the role of different types of antibodies in preventing a SARS-CoV-2 infection can play an important role in its treatment.

Discussion

The analysis of concerns from different viewpoints illustrate that the development of a treatment for COVID-19 is not solely a scientific problem, but also a socioeconomic problem, as communities have disproportionate access to potential treatments for COVID-19.

This article highlighted considerations in the development of a potential treatment, and specified relevant fields of interest, as mentioned in the opening abstract of this article.

Thus, as COVID-19 is a rapidly evolving situation with an unknown end result, it is best to develop a treatment by focusing on known aspects of SARS-CoV-2, and any effort to deepen research into the outlined fields is a step closer to a universal treatment for COVID-19.

Risk Factors

Emma Rodriguez

The elderly population is considerably more at risk of fatality due to COVID-19. In Italy, the median age of death was 79 for men and 82 for women (Roland and Markus, 2020). Also, fatalities caused by the virus are experienced mainly by those with at least one comorbidity, most importantly heart disease, specifically hypertension, and diabetes (Wang, He, Yu, et al., 2020; Li, Liu, Wang, et al., 2020) In New York City, one of the global epicentres, up to 94% of deaths have had at least one comorbidity (Rabin, 2020).

The main reason behind the disproportionate risks in these two cases is the cytokine storm caused by the body, experienced mainly by the elderly and those with pre-existing conditions. Cytokines are a group of proteins secreted by cells for intracellular signalling and communication, with one of their functions being the regulation of immune and inflammatory responses (Tisoncik, Korth, Simmons, et al., 2020). Inflammation caused by the excessive release of cytokines spreads throughout the body through the systemic circulation after beginning at a local point (Tisoncik, Korth, Simmons, et al., 2020). The body's response to an excess of cytokine often includes the generation of pain and an increase of blood flow and temperatures, often at the response of the local tissue (Tisoncik, Korth, Simmons, et al., 2020). Healthy adults have capable immune systems (both humoral and cell-mediated) that can limit infection progression so that the virus doesn't reach the alveoli, preventing the body's cytokine storm (Abdulamir and Rand, 2020). While the elderly and the immuno-comprised lack a strong immune response at the beginning of the virus (Abdulamir and Rand, 2020). Therefore, the virus is able to spread to the alveoli where the immune system gets more aggressive, leading to cytokine storms. The number of white blood cells and neutrophils in elderly cases is significantly higher than the rest of the middle and young aged patients (Abdulamir and Rand, 2020). The subsequent alveolar and interstitial inflammation caused by the body's response lead to damage of lung tissue and the filling of alveoli with inflammatory exudate (Abdulamir and Rand, 2020). This inflammation results in hypoxia, as well as respiratory failure and may cause collateral damage in other organs like liver and kidney (Abdulamir and Rand, 2020). The damage to the lung tissue experienced in critical cases is caused by severe inflammation, not by direct damage by the virus itself (Abdulamir and Rand, 2020). This can also explain why children have not been as strongly affected by the virus, as they are less capable of creating a vigorous cytokine storm attacking the lung tissue (Abdulamir and Rand, 2020).

Furthermore, the elderly might be more at risk because of the changes to their lung anatomies that alter the functions of the respiratory systems, such as a "reduced airway clearance, reduced lung reserve, and reduced defence barrier function" (Liu, Chen, Lin, et al. 2020). They are also more susceptible to multi-system organ damage, and even failure (Liu, Chen, Lin, et al. 2020).

Moreover, COVID-19's causation of lung infections explains the high proportion of deaths of patients suffering from heart disease. These infections increase the burden on the heart while raising the blood sugar, making the infection more difficult to control (Liu, Chen, Lin, et al. 2020). Additionally, both hypertension and diabetes are commonly treated with angiotensin-converting enzymes (ACE) inhibitors, which increase the expression of angiotensin-converting enzyme 2 (ACE2) (Madsbad, 2020). COVID-19 binds to target cells through ACE 2 in epithelial cells, perhaps explaining the easier infection of COVID-19 in these patients and the increased risk of fatality (Madsbad, 2020).

Another risk factor may be gender. In New York City, currently, around 60% of deaths are male (Rabin, 2020). Though no answer has been conclusively found, both biological and behavioural patterns may explain the difference in mortalities. Women have stronger Th1 immune responses (Fishcher, Robinson, Jung, and Lehmann, 2015). These early attacks on the virus could prevent the deadly impacts of the cytokine storm, discussed earlier. Furthermore, men commonly smoke more often than women and smoking have been associated with adverse outcomes of the virus because of its impacts on the lungs (Fishcher, Robinson, Jung, and Lehmann, 2015). Moreover, various studies have shown that men are less likely to wash their hands and seek care earlier in an illness (Courage, 2020).

Treatment methods and Vaccines

Negin Amini

Pharmacological Drugs:

There are currently no sure-fire solutions against SARS-CoV-2 pathogens and, therefore, the identification of antiviral agents and pharmacological treatments to combat this pathogenic disease is urgently needed. Since the beginning of the identification of this virus, there have been multiple probable pharmacological treatments and amongst all of them, Remdesivir has been recognized as the most promising therapy.

COVID-19 belongs to the family of *Betacoronavirus,* which also contains the middle Eastern respiratory syndrome (MERS-CoV) and SARS-CoV. There are several drugs such as Lopinavir-Ritonavir, corticosteroids, remedisvir and ribavirin ,which have been used to combat the previous infections, yet their rate of effectiveness has remained controversial. There are currently multiple FDA-approved drugs against SARS-CoV-19 such as Ribavirin, Chloroquine, Remdesivir and Favipiravir. Remdesivir is an antiviral drug that was first developed by Gilead Sciences to combat the Ebola Hemorrhagic Virus (EBV) in Africa. (Sanders.J, Monogue M et all, 2020). In 2015, the effectiveness of this treatment against the Ebola virus was considered to be insignificant. Remedisvir's importance became apparent when it showed its potential to inhibit coronavirus polymerase.

Chloroquine

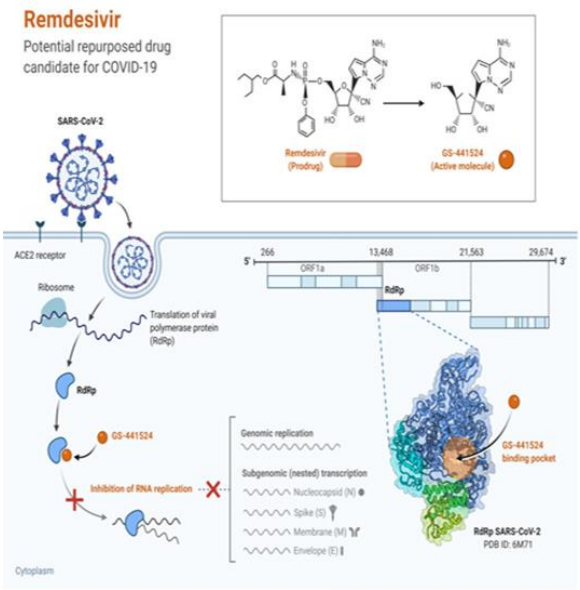
These drugs were primarily used to treat Malaria, systemic lupus and rheumatoid arthritis. They are considered safe drugs and have been proven to eliminate the COVID-19 virus with high efficiency on laboratory dishes. These experimental results were yielded on March 24th, 2020. Chloroquine was deemed to be highly effective in the treatment of SARS-CoV as it disrupts viral reproduction in humans. It is currently being highly used as a treatment for SARS-CoV-2, but negative side effects or symptoms are a trend in patients treated with hydroxychloroquine. The scheduled regimens (Daily doses for 5 days of 400-600mg) have proved to be responsible for nausea, pruturis, headache, and fatal arrhythmias (Sanders.J, Monogue M et all, 2020). Despite these results, the treatment has been approved by many drug safety organizations around the world as an emergency method due to its scarcity. This drug first binds to the receptors of the virus to inhibit its entrance into the cell. This drug later manages to penetrate the cell and stops its reproduction capabilities (Sanders.J, Monogue M et all, 2020). After the outbreak of COVID-19 in China, the government claimed that 100 patients were recovered after treatment, but due to a lack of proof for this claim, this drug has been classified as an experimental drug. In addition, there was no gold standard for research studies and the experiment was also not randomized.

Remdesivir

Remedisvir is an adenosine analog that specifically targets the single-stranded RNA viruses and delays the chain termination of RNA viruses (Wang, M., Cao, R., Zhang,2020). The composition of the SARS-CoV-2 is non-structural proteins such as nsp8 and nsp12. According to the kinetics of the enzymes, RNA-dependent RNA polymerase (RdRp) incorporates the active triphosphate form Remdesvir into RNA (Gordon, C., Egor, Woolner, E., 2020). The corporation of Remdesivir at the position of "i" causes the termination of RNA synthesis at the position of $i + 3$(Gordon, C., Egor, Woolner, E., 2020). These results were also obtained from studying RdRp's of other strains of Betacoronavirus families such as SARS-CoV and MERS-CoV. The reason which makes Remdesivir an outstanding approach against SARS-COV-2 is its high selectivity for internalization of its natural nucleotide counterpart ATP. According to the clinical studies, the triphosphate from Remdesivir forms 2-c-methylated compounds which include drugs such as Sofosbuvir , which have been recognized for the treatment of hepatitis C, and other antiviral drugs such as Favipiravir and Ribavirin (Gordon, C., Egor, Woolner, E., 2020). In addition, the data of the University of Alberta showcases that Remedisvir is a direct-acting- antiviral drug that inhibits the RNA polymerase. If this drug is placed at a distance from the RdRp of a viral infection such as LASSA, it won't terminate the RNA polymerase function (Gordon, C., Egor, Woolner, E., 2020). This drug is mostly used for the urgent patients of COVID-19 to prevent the progress of lung infection and pneumonia caused by the SARS-CoV-2 pathogen (Gordon, C., Egor, Woolner, E., 2020). The toxicity of Remdesivir was evaluated under multiple clinical trials."The pharmacokinetics of Remdesivir was evaluated in single and multiple-dose phase-1 clinical trials show that the 63 intravenous infusions between 3 mg to 225 mg were well tolerated and without the occurrence of kidney or liver toxicity"(Sanders.J, Monogue M et all, 2020). In other trials, Remdesivir is being tested for a 200mg dose which is followed by

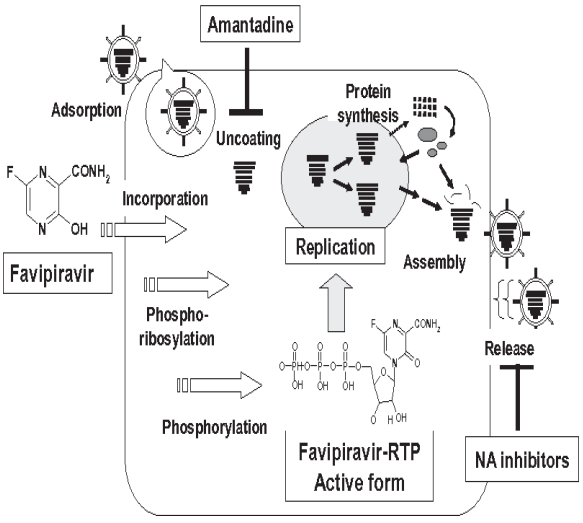
a 100 mg dose to treat patients, and there is no evidence of kidney or liver toxicity.(Sanders.J, Monogue M et all, 2020). Even though that there are no liver or kidney toxicity case reported, this

Mechanism of reaction of Remdesivir



prescription is not recommended for the patients whom their estimated glomerular filtration rate is less than 30ml/min.

Mechanism of reaction of Favipiravir:



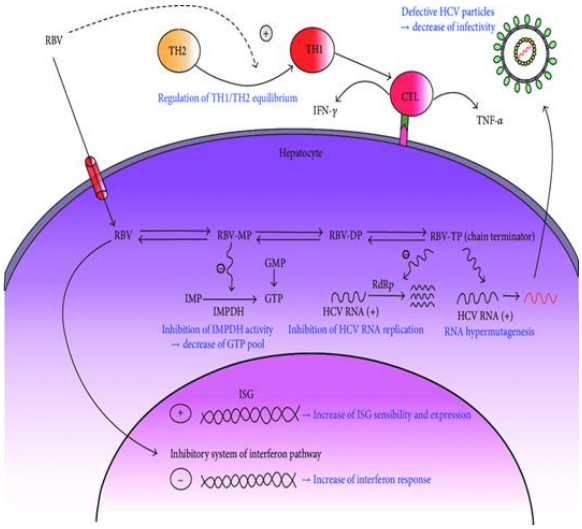
Favipiravir:

The other drug which targets the RdRp is Favipiravir. Favipiravir was discovered by Toyama Chemical in Japan and it is a modified pyrazine analog that also combats Influenza. Moreover, Favipiravir illustrates its promise in the treatment of dangerous pathogens such as Ebola virus, Lassa virus and now it is under investigation for COVID-19. Similar to Remdesivir, Favipiravir selectively inhibits the RNA polymerase of the pathogen and prevents the replication of the viral genome. The mechanism of action of Favipiravir remained a controversial portion of studies. Some sources claim that the active Favipiravir will be incorporated into the RNA polymerase of the nascent RNA strand and inhibits RNA elongation and viral proliferation. Other studies also have shown that the presence of purine analogs in Favipiravir can contribute to the reduction of its antiviral activity. In addition, various dosing of Favipiravir is related to the type and amount of infection. Favipiravir has been widely used in countries like Japan to cure the patients who are persistent against other treatments and drugs which treat Influenza. The dosing variations contain lower Favipiravir EC50 values , which are being used to treat Influenza type A and B. Yet for treating life-threatening viral diseases such as Ebola and Betacoronavirus families, the loading is 69 doses higher than what is prescribed for Influenza (Sanders.J, Monogue M et all, 2020). It is important to mention that Favipiravir has been recently used in the United States of America due to COVID-19 breakout. Before 2020, Favipirvair was not approved by the FDA and was only used in Japan as a prescribed drug to treat Influenza. The dosing recommended for the patients with COVID-19 is about 2400 mg to 3000 mg every 12 hours*2doses which is “also followed by a maintenance dose (1200 mg to 1800 mg every 2 hours)”(Sanders.J, Monogue M et all, 2020). This agent has a mild effect on patients. Based on the information obtained from the clinical trials which test Favipiravir, the lethal dose for oral and intravenous in mice is approximately more than 2000mg/kg and in rats, the lethal dose for oral Favipiravir is more than 2000mg/kg (Sanders.J, Monogue M et all, 2020). This lethal dose in monkeys is more than 1000mg/kg. The symptoms of overdose include, but not restricted to nausea, decreased locomotor activity and loss of body weight. The overdose symptoms in monkeys, rats and dogs include adverse effects on hematopoietic tissues and decreased production of erythrocytes and an increase in liver function parameters such as AST (alkaline

phosphatase) and ALT (alanine aminotransferase). In addition, Favipiravir is a teratogenic drug , and therefore, it's prescription to pregnant women is strictly avoided. There is no current data regarding the toxicity in the human body.

Ribavirin

The other controversial drug which is also approved by the FDA of America is Ribavirin. Ribavirin is a guanine analogue that inhibits RdRp activity. Ribavirin is a drug that inhibits the RNA polymerase of COVID-19 but has limited cooperation in SARS-CoV and requires high concentrations. The patients who were diagnosed with SARS-CoV were required to take 1.2g to 1.4g orally every 8 hours followed by combination therapy.(Sanders.J, Monogue M et all, 2020). In high doses, Ribavirin causes serve-dose-dependent hematologic toxicity. According to the data obtained from SARS-COV trials, this drug results in hemolytic anemia in most of the patients (Sanders.J, Monogue M et all, 2020). Therefore, in order for this drug to function safely, there is a necessity to prescribe this drug with other drugs. This method is known as combination therapy. In addition, the prescription of this drug to pregnant women is strictly inhibited , since it is known as a teratogen. Similar to other drugs, Ribavirin also targets viral replication mechanisms.(Te, H., Randall, G, 2020). This drug was first discovered to treat hepatitis C. In hepatitis C, The FN-alfa present in Ribavirin has the potential antiviral activity which induces the IFN-stimulated genes to encode proteins that inhibit t viral replication (Te, H., Randall, G, 2020). In addition, IFN-alfa "promoted T-helper cell differentiation of the T-lymphocytes over Th2 cells to increase the production of interleukin and IFN-gamma"(Te, H., Randall, G, 2020). Moreover, this drug targets the RNA polymerase of the viral particle. It uses adenosine kinase to convert itself to RMP (ribavirin monophosphate). It then converts itself to dephosphorylated and triphosphorylated forms by nucleoside monophosphate and diphosphate kinase (Te, H., Randall, G, 2020). Ribavirin triphosphate is said to be more effective than Ribavirin monophosphate for targeting the RNA polymerase initiation site. Ribavirin triphosphate mainly bonds to the nucleotides of the RNA polymerase and as a result, inhibits the binding of correct nucleotides which make the RNA of the viral particle. Thus, it contributes to the reduction and inhibition of viral replication in the host cell.



Mechanism of action of Ribavirin

Adjunctive Therapies

Adjunctive therapies are the set of treatments that are combined with primary therapies in order to increase the effectiveness of the therapy.

Corticosteroids

The main aim of corticoids is to decrease the inflammation related to the lungs. There were 76 observational studies in patients who were infected with the Betacoronavirus family (Sanders.J, Monogue M et all, 2020). Even though the patient's lung inflammation was improved with prescription of Corticosteroids, it had severe side effects. The side effects were reported to be associated with delayed viral clearance from the respiratory tract and blood. In addition, they were also complexities related to hyperglycemia and avascular necrosis (Sanders.J, Monogue M et all, 2020) . Moreover, they increase the rate of mortality in patients , and therefore are known to be a high-risk method to approach patients with COVID-19. They create secondary infections and therefore, they remain in the category of the controversial drugs.

Anti-cytokines and Antibiotics

The monoclonal antibiotics are directed towards the cytokines which are responsible for the creation of the inflammation caused by COVID-19. There is significant organ damage in the lungs and the GI tract due to amplified immune response against the pathogens of COVID-19. It has been discovered that IL-6 is the key to the inflammation related to cytokines (Sanders.J, Monogue M et all, 2020). The monoclonal antibiotics are used to specifically

decrease the inflammation caused by these cytokine clouds. A monoclonal antibiotic called Tocilizumab , which is also approved by FDA, treats the cytokines released by COVID-19 (Sanders.J, Monogue M et all, 2020). Studies showed that 400 mg of Tocilizumab was effective in 91% of the patients to improve the respiratory function (Sanders.J, Monogue M et all, 2020). The lack of a comparator group limits the interpretation and possible risks related to the prescription of this drug to the patients.

Convalescent Plasma

This method was first introduced by the Chinese government. Convalescent plasma is the plasma of the recovered patients. This method has previously been used to treat patients infected with SARS, Chickenpox and measles (COVID-19 and Convalescent Plasma: Frequently Asked Questions, 2020). There are two uncertainties in this method. First is that this treatment was not randomized in China , and the second problem with this treatment protocol is the timing of the injection of plasma into the patients' body. The patients who are eligible to be donors are classified into 4 groups:(Biologics Evaluation and Research. (n.d.). Investigational COVID-19 Convalescent Plasma - Emergency INDs, 2020)

- Compatible blood types between the donor and acceptor
- The patient must have been infected with COVID-19
- Prior to donation, the patient must have no symptoms of COVID-19
- After the donation of plasma, the sample must be tested for HIV.

It is important to mention that the donation should not affect the donator's immune system and weakens it. In addition, the donation should not make the donor more susceptible to COVID-19.

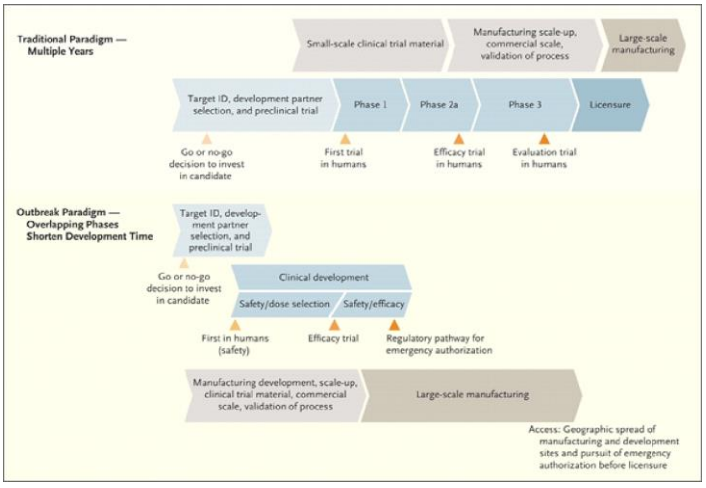
Vaccination Protocols

There are currently multiple vaccine trials initiated around the world, yet none have come with accurate results. It is important to mention that the production of vaccines during a pandemic is more challenging than the production of vaccines after a pandemic. The traditional method of vaccine development usually takes multiple years to be developed , while during the pandemic this amount of time is shortened. In addition, their difference is not just limited to the time of the vaccination, but also includes the process in which the vaccine is developed.

Most of the vaccination strategies related to COVID-19 are focused on DNA based vaccines. The first time that the DNA vaccine entered a clinical trial for patients was during the Zika virus breakout. Most of the m-RNA vaccines improve the stability of protein translations efficiency against the pathogens.

Sinovac BioTec

Sinovac Biotech is a Chinese based company and an experienced vaccine maker company. This company contributed to the production of vaccines for Hepatitis A and B, H5N1 influenza and the bird flu. This company has tested its COVID-19 vaccine on 8 Rhesus macaques (CohenApr, J., Heidt May, A., et all, 2020). The first group was infected with SARS-CoV-2 with tubing down their tracheas. Three weeks after they received the vaccines, the lungs of the infected Rhesus macaques were cleared and they didn't develop a full-blown infection (CohenApr, J., Heidt May, A., et all, 2020).



The monkeys who received the highest dose of vaccine were immunized more effectively. In the next

step of the experiment, the monkeys were infected with the COVID-19 pathogen (CohenApr, J., Heidt May, A., et all, 2020). The researchers claimed that they were not able to identify the trachea in the lungs. After they received the viral drops of the vaccine, the inflammation was controlled (CohenApr, J., Heidt May, A., et all, 2020). They then injected a high dose vaccine to the monkeys which cleared the traces of the lungs (CohenApr, J., Heidt May, A., et all, 2020). The researchers of this company mixed antibodies taken from monkeys, rats and mice and produced the experimental vaccine. They used this vaccine to treat patients in China, Italy, Switzerland, Spain and the UK. In case of approval, the vaccine will move to the third traditional phase (CohenApr, J., Heidt May, A., et all, 2020)

ASTRAZENECA

AstraZeneca is a British drugmaker company. They claimed that they will support the vaccine development which is led by Oxford University. There are currently 1100 candidates for this trial (AstraZeneca Joins U. of Oxford and Spinout to Develop COVID-19 Vaccine., 2020). In case of success, they inspect to produce over 100 million vaccines and export them out of the UK. The core of this vaccine is ChAdOx1 which is an adenovirus (AstraZeneca Joins U. of Oxford and Spinout to Develop COVID-19 Vaccine, 2020). Adenoviruses are from virus families which have mild effects on humans and are present in chimpanzees. The researchers injected the experimental vaccine on monkeys. ChAdOx1 is then combined with the SARS-CoV-2 pathogen to be tested on monkeys (AstraZeneca and Oxford University announce landmark agreement for COVID-19 vaccine,2020). ChAdOx1 has been used in the past to treat Ebola, Chikungunya, Rift Valley fever and MERS. British scientists had encouraging results on Rhesus macaques (AstraZeneca Joins U. of Oxford and Spinout to Develop COVID-19 Vaccine, 2020). The scientists claim that by the end of July they will be able to evaluate the effect. The main idea of these trials is to administer the vaccines to members of the first circle of contacts of people who fall ill with the virus and then to observe whether the virus contaminates the second circle (AstraZeneca Joins University of Oxford and Spinout to Develop COVID-19 Vaccine, 2020). They claimed that later they will be able to observe the vaccination mechanism and evaluate it at the same time.

Table 2. Selected antigens and vaccine platforms that have been tested for SARS-CoV and MERS-CoV (Modified from [50-52])

Vaccine platform	Immunogen	Phase	Advantage	Disadvantage
DNA	Full-length Spike, or S1 • IM follow by electroporation	Phase I, II (NCT03721718)	• Rapid production • Easy design and manipulation • Induce both B and T cells responses	• Efficient delivery system required • Induce lower immune responses when compare with live vaccine
Viral vector	Full-length Spike or S1 • Vector used: ChAd or MVA	Phase I (NCT03399578, NCT03615911)	• Excellence in immune induction	• Varies inoculation routes may produce different immune responses • Possible TH2 bias
Subunit	Full-length Spike, S1, RDB, nucleocapsid • Formulated with various adjuvants and/or fused with Fc	Preclinical	• High safety profile • Consistent production • Can induce cellular and humoral immune responses	• Need appropriate adjuvant, • Cost-effectiveness may vary
Virus-like particles	RDB, S or Co-expressing of S1, M, and E • Produced in baculovirus	Preclinical	• Multimeric antigen display • Preserve virus particle structure	• Require optimum assembly condition
Inactivated	Whole virus • Inactivated by Formaldehyde or gamma irradiation	Preclinical	• Preserve virus particle structure • Rapid development • Excellence in neutralizing Ab induction • Can be formulated with various adjuvant	• Possible cause hypersensitivity • Possible Th2-bias
Live-attenuated virus	Mutant MERS-CoV and SARS-CoV or recombination with other live attenuated virus	Preclinical	• Excellence in induction of T and B cells responses • Site-directed mutagenesis can be tailor made	• Risk of reversion to a virulent strain • Cold chain required • Not suitable or sensitive population such as infants, immunocompromised or elderly individuals

ChAd: Chimpanzee adenovirus vector, MVA: Modified Vaccinia Ankara

Herd Immunity and Diagnosis methods
Roger Pang

Without any proper vaccine or artificial methods of stopping the spread of SARS-Cov-2 in the community, herd immunity might be the solution. This concept relies on the basis that a majority of the population in a specific community have acquired immunity to the virus. Herd immunity has previously shown to be a highly effective solution to large scale pandemics such as polio or smallpox. However, they have all been achieved through vaccination. As of April 2020, no vaccines have been proven effective to help individuals in the development of antibodies that can prevent the development of SARS-Cov-2. (D'Souza & Dowdy 2020).

The development of immunity to SARS-CoV-2 is possible through a patient's immune system. There is a possibility of the natural development of viral antibodies that can counteract the reproduction and impact of SARS-CoV-2, it is known that it usually takes 5 to 10 days for one to develop antibodies. However, not everyone has proven to be immune after contracting it as there have been cases in which a patient has contracted SARS-CoV-2 twice.

There is a possibility that SARS-CoV-2 might be present yearly due to its high mutation rates. If that is the case, new methods of treatments and vaccines will need to be redeveloped regularly (Dutchen 2020).

Nucleic Acid Testing

This technique detects a particular nucleic acid polymerase in a patient's sample. It is used to detect the presence of SARS-CoV in blood or saliva. The sample is added in a test tube in which a qualitatively discernible reaction takes place. The process works by aligning and analyzing viral genomes. This method has proven to provide accurate results, but the process is slow and optimal surrounding conditions are required to maximize accuracy (Udigama & al., 2020).

Protein Testing (Antibody Testing)

Protein testing can be highly effective as the viral concentration of SARS-CoV-2 is not uniform throughout the body. Testing for the presence of the virus in saliva may be inconsistent as the viral load can vary throughout the progression of the virus. By looking for antibodies for SARS-CoV-2 in one's circular system, it is possible to determine if that individual is infected or has been infected by SARS-CoV-2. However, one challenge may come from the observation that many antibodies developed against other coronaviruses may influence the test as they possess similar traits, thus leading to cross-reactivity in tests (Udigama & al., 2020).

COVID-19's Impact on People & Society
Etsub Yifru

"The COVID-19 outbreak affects all segments of the population and is particularly detrimental to members of those social groups in the most vulnerable situations, and continues to affect populations, including people living in poverty situations, older persons, persons with disabilities, youth, and indigenous peoples. Early evidence indicates that the health and economic impacts of the virus are being borne disproportionately by poor people. For example, homeless people, because they may be unable to safely shelter in place, are highly exposed to the danger of the virus. People without access to running water, refugees, migrants, or displaced persons also stand to suffer disproportionately both from the pandemic and its aftermath – whether due to limited movement, fewer employment opportunities, increased xenophobia etc.

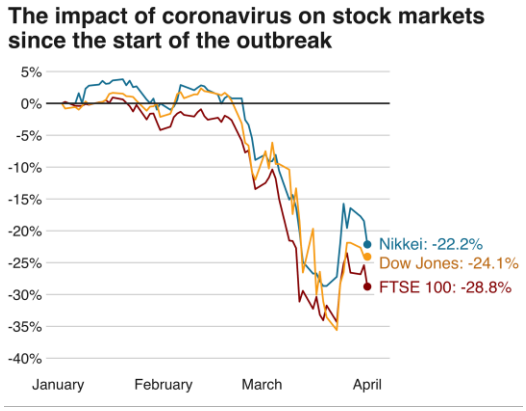
If not properly addressed through policy the social crisis created by the COVID-19 pandemic may also increase inequality, exclusion, discrimination and global unemployment in the medium and long term " (United Nations Department of Economic & Social Affairs, 2020). In order to minimize the negative consequences, protection systems may be required since "comprehensive, universal social protection systems, when in place, play a much durable role in protecting workers and in reducing the prevalence of poverty, since they act as automatic stabilizers. That is, they provide basic income security at all times, thereby enhancing people's capacity to manage and overcome shocks" (United Nations, 2020).

Impact on Social Activities & Cultural Practices

Social distancing has become the new normal, and the situation has profoundly affected how people go about their daily lives, especially now that they are spending more time at home. For those who are in an already precarious situation, this pandemic has led to greater levels of stress and anxiety (Zaharieva, 2020). Social isolation is having a negative impact on people's mental health and specialists argue that this has severe health consequences for a number of socio-economic groups, especially those who are more vulnerable. Thus, some ways to help this issue are online medical consultations, virtual thematic discussions and group activities offered by social workers. Furthermore, the current pandemic has led to the cancellation of numerous sporting and cultural events around the world such as the International Ice Hockey Federation (IIHF)'s world women's hockey championship (Thompson, 2020). Since the virus is highly contagious and has forced every human being to avoid making physical contact with people who are not members of their immediate family with whom they live, the way people greet each other has drastically changed. As people are avoiding to greet with handshakes or hugs, other alternatives have been found: bowing like in Japanese culture, foot shakes, and elbow bumps. According to Winnipeg etiquette expert Jessica LoRusso (2020), although the traditional handshakes and high fives might be on their way out, even in a world without handshakes, it is possible to greet each other normally by acknowledging the other person and making them feel validated in order to greet them the best we can.

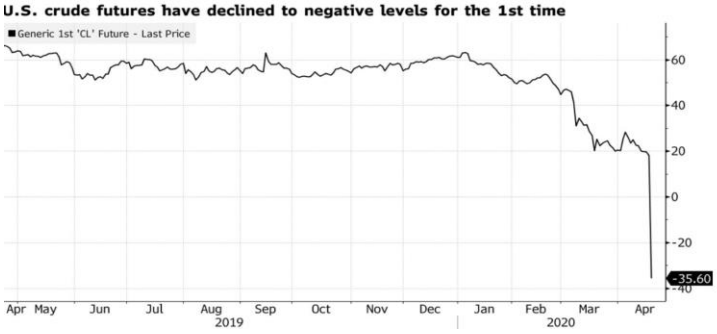
COVID-19's Impact on the Economy

The pandemic has caused significant shifts in stock markets worldwide. These big shifts have affected investments worldwide: the DOW Jones Industrial Average, Nikkei, and FTSE 100 index have all decreased substantially since the outbreak began on December 31st (especially the DOW and FTSE index). With a decrease in investment, this may destroy economic growth (Brown et al., 2020).



(Bloomberg, 2020)

Although global markets have somewhat recovered, especially since the passing of a coronavirus aid bill that was done by the US Senate, some economic analysts fear that they could still be volatile. Experts believe that one way to minimize the negative consequences is that central banks slash interest rates such as what a central bank has already done in the UK (Brown et al., 2020). Since stocks have decreased in value, slashing interest rates will encourage people to borrow more and this will help boost the economy. With regards to unemployment, it is a big issue in the US because unemployment rates have reached a record high and this will forever negatively affect the decade-long economic expansion for one of the world's largest economies, The US benchmark of oil dropped below 0 for the first time, which means that "oil firms have resorted to renting tankers to store the surplus supply and that has forced the price of US oil into negative territory" (Walker, 2020). Furthermore, the travel & tourism industry has also been badly impacted by the pandemic because of the global flight restrictions which have closed a lot of country borders (Brown et



al., 2020).

(Bloomberg, 2020)

The Role of Technology in Mitigating the Negative Consequences of COVID-19

Hyeonjeong Kwon

Governments are implementing effective technologies to fight the outbreak ("Digital technologies", 2020). Governments are funding and developing their own digital technologies to measure and migrate the impact of COVID-19. Providing digital communication channels for reliable information on COVID-19 developments are essential tasks as many people rely on the internet the most with lockdowns and other social distancing measures (2020).

Smartphones are significant in contact tracing and other epidemiological investigations. Ottawa Public Health is also considering developing a mobile application for efficient tracking of the movement of people with COVID-19 and to notify those who may have contact with them (Jones, 2020). For instance, in Korea, the Ministry of the Interior and Safety developed an application for self-diagnosis to report one's health conditions. Those who leave designated quarantine areas without permission are immediately reported to the government official ("Notice of Self-Quarantine", 2020).

Software developers all across the globe are also contributing to mitigate the impact of COVID 19 by crafting technical tools to combat the virus. They are developing and applying new technologies for enhancing the efficient measures of the outbreak, testing, diagnoses, and treatments.

Apple and Google are developing application program interfaces (APIs) and operating-system level technology to assist in enabling the contact tracing. They are collaborating in launching Bluetooth-based contact tracing functionality into apps from public health authorities to enhance the security of the users while efficiently delivering the information needed to combat the virus (Hendela, 2020).

A French Pharmaceutical company, Sanofi, and a Silicon Valley startup company, Luminostics, are developing a technology for self-testing package that consumers can use via smartphone's optics, controlled by an iOS or Android app paired with an adapter, in combination with "glow-in-the-dark" nano-chemistry and signal processing artificial intelligence ("Sanofi and Luminostics", 2020).

Deep learning and Artificial Intelligences (AIs) are also used to combat COVID-19. Traditional Artificial Intelligence technology allowed predefined parameters based on the knowledge of experts (Hosny et al., 2018). Explicit parameters were no longer needed as advanced AI methods were discovered. According to research conducted by the Department of Radiology, Wuhan Huangpi People's Hospital, and other institutions, Artificial Intelligence was able to distinguish more than 90% of sample lungs with COVID-19 from pneumonia and other non-pneumonic lung diseases using chest CT. Utilizing AI is time-efficient as it is 60 times shorter than human detection (Li et al., 2020). Chest CT observed to have higher sensitivity of diagnosis of COVID-19 compared to initial reverse-transcription polymerase chain reaction (Ai et al., 2020). Although it is still in the phase of research, DeepMind is attempting to develop a system called "AlphaFold" that predicts several under-studied proteins associated with SARS-CoV-2, the virus that causes COVID-19 ("Computational Predictions", 2020).

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