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## Tracking Our Progress Through the COVID-19 Pandemic

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The year of 2020 was one that will live in our minds forever. Many political events, civil rights movements, and other historical movements took place. Though these moments themselves should be remembered, the most life-altering experience for most people was the pandemic. The world was halted, jobs were lost, relationships ruined, some struggling for survival. All of this caused by a microscopic enemy, the SARS-CoV-2 coronavirus.

Patients started to come to hospitals in Wuhan, China with a pneumonia with an unknown cause. Late in December of 2019, a cluster of these cases appeared. Health care workers quickly noted that these patients all had a common experience, going to a Hunan market. This suggested that the cause of this pneumonia-mimicking disease was a transmissible agent. With this recognition, shotgun sequencing was used to identify the etiologic agent by early January, with the development of a diagnostic PCR test just two days after that. The advancement of scientific technology shines here and is quite astonishing. This same process took four years with HIV. This sequencing allowed scientists to recognize the virus as a beta coronavirus, the biology of this virus will be discussed later on. They believe this virus came from bats originally, but is also very closely related to a coronavirus that has been identified from pangolins. They hypothesize the transmission went from bat to pangolin, back to bats, and then to humans, although the epidemiology was not certain at this time.

This is not the first pathogenic human coronavirus to hit the scene fortunately. In 2003 we had SARS that caused 8,000 cases with an 11% fatality rate, and MERS in 2011 causing 2,500 cases with a 34% fatality rate. Both of these did not have a very high transmissibility though. Then in this last year SARS-CoV-2 ravaged the planet, causing 171 million cases to this day, with only 3.6 million deaths, for a fatality rate of 0.5-1%. Some researchers claim that a virus with SARS-CoV-2 transmissibility and MERS fatality rate is one to invoke great fear.

While these past epidemics were tragic in and of themselves, they proved beneficial when the COVID-19 pandemic hit the world. Researchers had a head start on some of the biology, transmission tactics, and epidemiology of coronaviruses because of these past outbreaks.

As mentioned, humans have long been infected by coronaviruses, especially because it is one of the viruses responsible for the common cold. It was previously established that the diseases caused by these viruses are highly contagious viral infections that can be spread through inhalation or ingestion of viral droplets. So what makes up this virus?

The SARS-CoV-2 genome is approximately 30,000 nucleotides long, encoding for four structural proteins and several non-structural ones. The four structural proteins are the nucleocapsid protein (N), membrane protein (M), spike protein (S), and the envelope (E) protein. The capsid is the protein shell, where inside there is an N-protein bound to the virus's single positive strand of RNA. The M protein is most abundant on the viral surface and is believed to be the central organizer for the virus assembly. The E protein is a small membrane protein composed of approximately 76 amino acids and plays an important role in virus assembly, membrane permeability of the host cell, and virus-host cell interaction. Immediately, the S protein and the Hemagglutinin-esterase dimer (HE) were identified as a main focus for researchers. The S protein is integrated over the surface of the virus and mediates the attachment of the virus to the host cell surface receptors and fusion between the viral and host cell membranes. The HE is thought to be important for the infection of the host cell (Boopathi, Subramanian et al.).

The SARS-CoV-2 genome contains only 13 genes, but more than 27 proteins are made through some viral trickery employed by the virus. Even though the virus can utilize the cellular machinery available to it, it needs to abide by the rules these machinery function by. In

eukaryotic cells like ours, we get one gene made into a protein per messenger RNA (mRNA). The 5' cap on this mRNA strand recruits the ribosome, which starts reading when it hits a start codon, and keeps reading until it runs into a stop codon and then falls off. Everything downstream from that stop signal is not seen by the ribosome. This is a problem for the virus because it does not just have one gene on its mRNA, it has 13. Lucky for the virus, it has a way to get around it. It encodes multiple different proteins in a single gene, the 'giant gene', ORF. It does this by inserting these genes into just the one open reading frame by removing those start and stop signals. This allows for up to 16 proteins to be made just from the ORF. The virus also encodes its own protease enzyme, which allows the new polyprotein to be sliced into its individual protein subunits (Hartenian et al.).

What about the genes downstream of the ORF? The virus uses a second strategy which involves generating new RNA copies which are sub-genomic length (sub-genomic RNAs). They all have the same 3' end but vary in lengths based off of how many genes they are encoding. This happens because as the viral copying machine is making these RNAs, at the boundary between each of these genes on the right-hand side is a transcriptional regulatory sequence. This signal basically gives the RNA copying machine the option of stopping or continuing on, and it is not clear exactly how this works yet. By making these sub-genomic RNAs, each of the downstream genes has the chance to be represented as the first gene that the ribosome sees.

Additionally, all RNA viruses need to encode their own RNA copying enzymes, called an RNA-dependent RNA Polymerase (RDRP). This is because our own cells do not have this type of enzyme for the virus to steal. The coronavirus replisome is highly sophisticated and may even challenge some DNA replisomes. Generally, RNA copying enzymes make a lot of mistakes such as inserting the wrong nucleotide every thousand bases. These error-prone polymerases are what

drives the high rates of mutations seen in many RNA viruses, but we do not see this same thing with this coronavirus. The reason for this is because this virus encodes its own proofreading mechanism. This little “machine” follows along with the polymerase, and if the polymerase makes a matching error, the editor kicks that nucleotide out and allows for the correct match to replace it. This is also a possible explanation for why this coronavirus genome is much larger than other RNA viruses.

So where does all of this take place, and how has our cell not detected it? Well, the virus creates new “rooms” into which it can go and replicate. These “rooms” are actually interconnected double membrane vesicles that are taken from the endoplasmic reticulum, and are referred to as replication and transcription complexes (RTCs). There are two possible reasons the virus does this. First, it allows the virus to copy its genome in a secret place. The cytoplasm of the host cell is full of sensor proteins that are looking for anything foreign. If they detect something unusual, they will alert the cell which in turn alerts all neighboring cells and induces a broader immune response. A prime suspect these proteins are looking for is double stranded RNAs because these do not usually form in our cells. Because it is inevitable that the replication of the viral genome will produce double stranded RNAs, the virus hides its replication in a compartment where it cannot be detected by the host. Second, it allows the virus to concentrate everything it needs to copy and transcribe its genome in one place, making it a more efficient process (Knoops et al.).

Once the methods of this coronavirus were understood in more detail, countries needed to decide what they were going to enforce to stop the spread of this disease. Europe was the center of the virus in March and April, but was able to bring that surge right back down. They enforced an actual nationwide lockdown, where normally life was completely stopped. In France, the third

lockdown meant that most shops will remain closed, and there was a nightly curfew at 7pm. Spain mandated masks for locals and tourists even outdoors. In Greece, people were only allowed to leave their homes between the hours of 5am and 9pm only if they have a good reason for doing so – such as a doctor’s appointment or going to work. Earlier in the year the Czech Republic had the highest weekly incidence of COVID-19 infection in the world. They mandated that only two people were allowed to meet at a time, unless they were in the same household, a nightly curfew, and all non-essential shops were closed. In the United States, we had a mask mandate and a shut down. The United States had a lot more politicized approach it seemed, which could explain why we never reached an acceptable baseline in case numbers.

Another critical aspect of this pandemic is the effect it had on individual’s mental health. It goes to say that these were stressful times for most people, being locked in your house, not seeing those you care about, and feeling pressured to work if seen as an essential worker. A survey of 562 people from May 2020, revealed an increase in alcohol and cannabis use among people in the United States, suggesting people turned to these substances to relieve their stress and anxiety. This same survey showed that 43% of these people were feeling nervous, anxious, or on edge (Lee, 2020). In the United Kingdom, other studies show that 37.5% of people met clinical criteria for generalized anxiety, depression, or health anxiety at that time (Rettie, 2020).

Before going into vaccination efforts, it is important to discuss a central idea known to immunology. There are three main properties of the immune system- specificity, diversity, and memory. There was a theoretical construct built quite some time ago, called the clonal selection theory, constructed around ideas about the immune system. It said that the immune system is composed of individual clones of cells, many different cells that are different from each other by their specific receptors. These clones have a predetermined receptor. When the virus comes into

the system, the cell that has that receptor that recognizes it will expand through clonal expansion. What this means is that when you get the pathogen coming back a second time, you have more cell that can recognize it (Arneth, 2018).

While there were many efforts going into vaccines, three companies were able to get through the process and receive acceptance for emergency use – Moderna, Pfizer, and Johnson & Johnson. Within 66 days of the SARS-CoV-2 genomic sequence being published, a phase 1 clinical trial for Moderna’s mRNA vaccine happened, which is a world record. They were able to accomplish this because of the pre-clinical development spent after the MERS outbreak in anticipation of a coronavirus outbreak. Essentially this vaccine protects against lung and nose SARS-CoV-2 replication (Corbett, 2020). Both Pfizer and Moderna vaccines are mRNA based, which are a new type of vaccine. These vaccines essentially teach our cells how to make a protein that triggers an immune response in our body. This happens because this new protein is displayed on the cell surface and our immune systems recognize that the protein does not belong there and begins producing antibodies and building up our immune response. They do not use an inactive form of the virus, and the mRNA never interacts with our DNA in any way. The Johnson & Johnson vaccine uses the traditional approach (CDC, 2021).

Vaccinations have been critical for this pandemic, many health officials explained they do not think the virus would leave our lives if we did not achieve herd immunity. Since there are cases where people can get infected twice, vaccines seemed like the best option. To this day, there are 136 million people fully vaccinated, and 169 million people with at least one dose. This means 41% of the U.S. population is almost entirely immune, which is not enough to achieve herd immunity, but the numbers are growing every day. Pfizer has taken the lead in vaccine numbers, counting in at 70 million fully vaccinated people. Serious side effects are extremely

rare, with the most common side effect reported being fatigue and pain at the injection site (CDC).

In the end, this pandemic has shown a lot about the human population that we might not have seen without it. We were fortunate for the past coronavirus outbreaks, otherwise we would not have had vaccines as quickly as we did. It is important to pay attention to every disease that hits our population, no matter how small, because it may come back bigger just like the coronavirus population did to us.

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