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The COVID-19 Pandemic and its Influence on the Human Immune System

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Abstract

COVID-19 rapidly infected the world, and scientists continue to research how the disease spread and killed as many as it did by analyzing how it affects the human immune system and referring to past pandemics. Since the pandemic is ongoing, scientists do not fully understand how the virus works and if lockdowns were effective. Nevertheless, a discussion on what is known about COVID-19's influence on the human immune system is needed. With an understanding of the COVID-19 pandemic, scientists can make more effective treatments for COVID-19 and learn how to manage future pandemics.

Immune System

The immune system is a beautifully complex network that orchestrates an army of defenses to protect the body against pathogens, such as harmful bacteria and viruses. Without the immune system, humans would be vulnerable to sickness and would not have a long lifespan. Though immunology is a vast subject, to give an understanding of how COVID-19 works, the basics of the human immune system are covered. In humans, there are two types of immunity: innate and adaptive.

Innate Immunity

Innate immunity is composed of defenses the body naturally has to combat pathogens and disease. This form of immunity consists of protections humans are born with, such as skin, hair, and mucus. Without innate immunity humans would have a brief life, for it helps prevent and combat unwanted bacteria and viruses that attempt to enter the body. When pathogens do enter, they can cause severe illness or death. Furthermore, not only does innate immunity consist of the integumentary system, but also enzymes, macrophages, other white blood cells, and natural killer cells.

The integumentary system and mucosal defenses are the most effective and basic barrier against pathogens and are considered the first line of defense. Skin, or the integumentary system, is composed of many cell layers that renew over time and can secrete oils that make it hard for microbes to grow or enter the body. Thus, it is important for the skin to be maintained so it can retain healthy bacteria to fight invasive pathogens the skin encounters from the air and everyday surfaces. This is why washing hands after encountering contaminated surfaces is important in the prevention of infections such as the common cold or methicillin-resistant *Staphylococcus aureus* (MRSA) infections. It is also imperative to

avoid touching the mouth, nostrils, and eyes as they are openings to the inside of the body, which are vulnerable to infection if touched with unclean hands. If the integumentary system is bypassed, the respiratory system is lined with mucosal cells that secrete mucous and enzymes. Mucus can trap pathogens and prevent them from spreading in the body. Hence if one catches a cold, they will usually cough up or sneeze out mucus containing pathogens to expel them from the body.

However, it is the second line of defense that can be fatal to pathogens. The second line of defense in innate immunity consists of cellular and chemical defense mechanisms, which can overlap with the adaptive immune system. Once a pathogen enters the body, there is a plethora of innate mechanisms to combat infection, one of them being inflammation.

When one thinks of inflammation, they often think of redness and swelling of an injury, associated with pain. However, it is also a complex use of cells and chemicals to fight pathogens. When a pathogen enters a wound in the skin the pathogen, such as bacteria, it is first recognized by what are called toll-like receptors (TLRs) located on immune cells such as macrophages, epithelial cells, or dendritic cells (Kawasaki & Kawai, 2014). Because TLRs are located on different types of immune cells, there are different kinds that respond differently depending on the location of infection. For example, "macrophages express TLR4, which has a specificity for … compounds present on the outside of Gram-negative bacteria" (Parham, 2009, p. 45). In total "Humans have ten TLR genes" (Parham, 2009, p. 46) each specific to a particular cell and each recognizing different pathogens. Once a pathogen is noticed, effector cells such as "basophils," a type of white blood cell, "and mast cells" which "are both proinflammatory chemical-secreting cells" bind to the pathogen and initiate the inflammatory response (McKinley et al., 2016, p. 856). One of these chemicals

secreted by effector cells is “histamine, which increases both vasodilation and capillary permeability” (McKinley et al., 2016, p. 856). This helps provide more blood flow to the injury. Increased blood flow allows for more blood serum proteins, white blood cells, and macrophages to come to the scene to eat or attack invading pathogens.

There are five main groups of white blood cells, also known as leukocytes: neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils being the most abundant and basophils being the least. Each white blood cell has a specific job to target types of pathogens. Neutrophils and monocytes like to phagocytize pathogens, which means they engulf or eat the pathogen. Eosinophils prefer to target parasitic worms, but also seem to play a role in asthma and allergic reactions (McKinley et al., 2016, p. 857). Basophils, as previously noted, secrete proinflammatory chemicals such as histamine. There are two types of lymphocytes which include natural killer (NK) cells (large granular lymphocytes), which are a part of innate immunity, and small lymphocytes, which are part of the adaptive immune system. NK cells specifically target cells infected with viruses (Parham, 2009, p. 51).

In addition to TLRs, there are blood serum proteins named complement that assist in signaling effector cells, also known as immune cells, of the presence of pathogens. Complement proteins have roles in both innate and adaptive immunity. In innate immunity, there are three ways complement can assist: opsonization, cytolysis, and inflammation. In opsonization, a complement called “opsonin” tags pathogens for “phagocytosis” (McKinley et al., 2016, p. 858). This makes the pathogens more attractive to cells like macrophages and neutrophils. Cytolysis takes longer time but involves complements C5 through C9 “forming a protein channel in the plasma membrane” of an infected cell “called a membrane attack complex (MAC),” which causes the cell to swell and rupture (McKinley et al., 2016, p. 858).

Complement also activates effector cells and signals for neutrophils and macrophages to come to the site of infection, which promote inflammation.

Once effector cells are activated, they can release proteins called cytokines. Cytokines increase vasodilation, which means blood vessels widen in the infected site causing the visual aspects of inflammation such as redness and heat. Cell permeability is also increased to allow for blood plasma to flow into the site of injury. The increase in fluid in the area causes swelling, also known as edema, which presses on nerves to prompt pain. Cytokines stimulate the walls of capillaries in the area to make cell-adhesion molecules (CAMs), which cause white blood cells to adhere to the capillaries and flow to the site of infection. Common cytokines produced are interleukin (IL) 1, IL-6, CXCL8 (formerly IL-8), IL-12, and tumor necrosis factor-α (TNF-α). CXCL8 is a chemokine, which is a cytokine that "direct[s] the flow of leukocyte traffic" to sites of "tissue damage or infection" (Parham, 2009). Natural killer (NK) effector cells also make cytokines. NK cells are known for their ability to kill "unwanted cells" by releasing chemicals, such as "*perforin"* (McKinley et al., 2016, p. 856). When NK cells are simulated by IL-12, they release IFN-γ, which specializes in killing virus infected cells (Parham, 2009, p. 65).

In summation, innate immunity consists of various immune defenses, which humans are born with, to combat pathogens. These defenses include, but not excluded to, skin, mucous, inflammation, and cellular defenses. Nonetheless, the innate immune system is not impenetrable. Some pathogens are clever and can bypass innate immunity to cause infection. Thus, adaptive immunity exists.

Adaptive Immunity

Adaptive immunity takes place at the same time as innate immunity, but its responds slower if it has not encountered the pathogen previously. Just as innate immunity contains the first and second line of defense, the adaptive immune system is designated as the third line of defense. There are two main responses in adaptive immunity: cell-mediated immunity and humoral immunity.

Cell-mediated immunity brings us back to the second type of lymphocytes mentioned in innate immunity— small lymphocytes. Small lymphocytes can be broken down into two main types: helper T-lymphocytes and cytotoxic T-lymphocytes. In cell-mediated immunity, antigen-presenting cells (APC) are used to display an antigen to a helper T-lymphocyte. Almost all immune cells can be an antigen presenting cells, such as white blood cells. Antigens consist of pathogen components rather than the entire pathogen. For example, the protein capsid of a virus, which is the capsule of a virus containing genetic material, or a piece of the cell wall of bacteria would be considered an antigen. APCs are effector cells that display an antigen to either type of T-lymphocyte (McKinley et al., 2016, p. 866). The antigen on the presenting cell will be attached to a "transmembrane protein" which is called a major histocompatibility complex (MHC). MHC class 1 molecules are on any cell, but APCs can have MHC class I & II molecules. (McKinley et al., 2016, pp. 864-869)

In addition to different MHC molecules on cells presenting antigens, T-lymphocytes must also have the appropriate CD proteins that react with these molecules. A helper T-lymphocyte has CD4 proteins, while the cytotoxic T-lymphocytes have CD8 proteins on their surface. Both lymphocytes have T-cell receptors (TCR) which analyze the antigen to see if it is foreign or self. CD4 proteins function with MHC class II and CD8 function with MHC

class I. If the antigen is foreign, the response depends on which T-lymphocyte is seeing the antigen. If the helper T-lymphocyte determines the antigen is foreign, it will release IL-2 which activates the T-helper cell to clone itself and make what it called memory helper T-lymphocytes. These clones will remember the antigen that triggered their creation and assist in the elimination of that specific antigen. On the other hand, when a cytotoxic T-lymphocyte recognizes an antigen as foreign, it cannot do anything until it receives IL-2 from activated helper T-lymphocytes. Once activated by the IL-2, the cytotoxic T-lymphocytes will multiply just as the helper T cells did, creating memory cytotoxic T-lymphocytes. Activated cytotoxic T-lymphocytes will go on to target infected cells with the pathogen it recognizes by releasing perforin and granzymes which induce apoptosis, or programmed cell death, of infected cells. (McKinley et al., 2016, pp. 874-875)

The second part of adaptive immunity is humoral immunity, also known as antibody-mediated immunity, which involves B-lymphocytes. Unlike T-lymphocytes, B-lymphocytes do not need antigens presented to them by another cell because their B-cell receptors (BCRs), which are also made of antibodies, allow them to attach to antigens directly (McKinley et al., 2016, pp. 875-876). Since the antigens are not presented via cells, B-lymphocytes react to antigens that are free-floating in the body. Once an antigen binds to the BCR of a B-lymphocyte the antigen will cross-link with another BCR. The antigen will then be presented to an activated helper T-lymphocyte with MHC class II molecules. Instead of releasing IL-2, the helper T-lymphocyte will release IL-4 which activates the B-lymphocyte. An activated B-lymphocyte proliferates and differentiates into plasma cells and memory B-lymphocytes (McKinley et al., 2016, pp. 875-876). Plasma cells produce antibodies. Different from memory T-lymphocytes "(5 to 7 days)," B-lymphocytes have a much longer lifespan

"(months to years)," which results in long term immunity (McKinley et al., 2016, p. 876). Antibodies can function in various ways to combat pathogens and will help prevent future infection if one is exposed to the same pathogen a second time in the antibody's lifespan. It does this by working like a lock and key. The Institute for Quality and Efficiency in Health Care (2020) explains it well by saying, "an antibody only attaches to an antigen if it matches exactly, like a key in the lock of the antibody."

Antibodies are Y-shaped proteins, composed of light chain on each upper arm and 2 heavy chains that reach up through the middle into the upper arms (Figure 1).

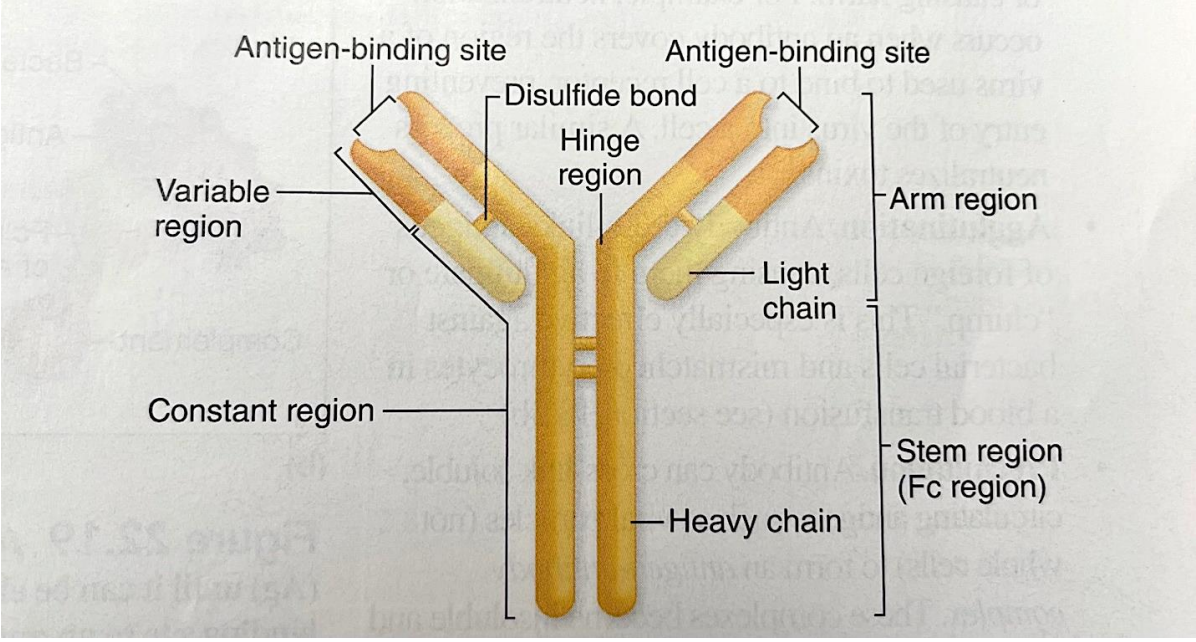

Figure 1. Structure of an Antibody. Image taken from McKinley et al. (2016, p. 877).

According to Parham (2009, p. 97), the variable regions, which are the top half of the antibody chains in the arms are what bind to antigens, which is why they are referred as fragment antigen binding (Fab). On the other hand, the vertical portion of the antibody is called the fragment crystallization (Fc) region. Antibodies have three main ways that they combat pathogens: agglutination, precipitation, and neutralization. Agglutination is when an

antibody “cross-links antigens of foreign cells,” like bacteria, “causing them to” bunch together (McKinley et al., 2016, p. 878). A good example of this is when two different blood types are mixed, the blood clumps together and becomes thick. This is why it is important to know a patient’s blood type. Precipitation is when antibodies “cross-link soluble” antigens to make a “antigen-antibody complex” (McKinley et al., 2016, p. 878). The complex forms a precipitate that phagocytic cells like macrophages can engulf. The most important process for fighting viral infections is neutralization. Neutralization is when antibodies overwhelm a pathogen by surrounding it, making it unable to infect cells (McKinley et al., 2016, p. 878).

In addition, McKinley et al. (2016, p. 879) notes there are five different types of antibodies, also known as immunoglobulins (Ig). These types vary in their Fc region which enables them to have different abilities. The five immunoglobulins are IgG, IgM, IgA, IgD, and IgE. IgG is the most abundant. Found in the blood and lymph, IgG can perform in all the ways antibodies combat pathogens, especially in neutralization. IgM is usually composed of five antibodies held together with a J chain. It mainly participates in agglutination and is short lived. IgA is found as a monomer or dimer of two antibodies and is commonly found in mucous membranes of the respiratory and intestinal tract to prevent pathogens from causing infection. IgD is a common antibody that acts as a receptor on B-cells. IgE is commonly found on mast cells, basophils, and in the blood. When IgE is bound to an antigen it releases histamines, and like eosinophils, it can kill parasitic worms.

Immunoglobulins can also influence complement proteins and NK cells. The Fc regions of immunoglobulins like IgG and IgM can activate specific complement proteins to trigger complement fixation or opsonization. In opsonization the antibody attached to complement on pathogens like bacteria can attach to phagocytic cells via their Fc region,

making the pathogen have a higher chance of being recognized and phagocytized. As for NK cells, IgG can bind to “specific receptors” on them also with their Fc region, to cause the NK cells to release perforin/granzymes to kill the cell infected with the pathogen, usually a virus. (Willey et al., 2020)

What is a Virus?

A virus is a non-living, microscopic, infectious pathogen that injects its DNA or RNA into a host cell, so it can make multiple copies of itself. The influx of copies destroys the host cell to allow the virus to spread and infect other cells. This is the beginning of an infection. Viruses can have a range of shapes and sizes, for example, a bacteriophage looks like a spider-like machine with legs, and coronaviruses are round, but covered with spike proteins. According to Fenner et al. (1987), in simple viruses, they are composed of a nucleocapsid where there is a single DNA or RNA surrounded by a proteinaceous membrane called a capsid. As viruses increase in complexity sometimes this nucleocapsid is surrounded by another membrane called the matrix, which can also be surrounded by a phospholipid bilayer covered with glycoproteins. In viruses the capsid can also be either helical or icosahedral (Fenner et al., 1987). However, like snowflakes, every virus is unique. They are also not alive, as they lack metabolism and require a host to reproduce by mooching off the metabolism of living cells. Thus, they are just a packet of DNA or RNA with machinery to allow them to enter cells. Once a virus enters a cell, it hijacks cell machinery such as ribosomes and DNA replication enzymes to replicate more of itself. Bacteria on the other hand, are living organisms because they have their own metabolism and reproductive mechanisms.

COVID-19 and the Immune System

In March 2020, the world was hit with the coronavirus disease of 2019 (COVID-19) pandemic. It first started out as an epidemic in China, and quickly spread globally killing millions. COVID-19, also known as, SARS-CoV-2 is a coronavirus characterized by its spherical shape, spike surface proteins, and a nucleocapsid containing "positive sense single stranded RNA" (Bajaj et al., 2021). It is unclear and highly debated where SARS-CoV-2 originated from, but some research states the genome is similar to bat coronaviruses. Though, it is a mystery of how SARS-CoV-2 transferred to humans and how it mutated to the extent of infecting hundreds of millions of people. SARS-CoV-2 stands for severe acute respiratory syndrome – coronavirus number 2. As its name suggests, it is a viral infection that primarily targets the respiratory system, and it is the second of its kind. Symptoms of SARS-CoV-2 include fever, chills, cough, shortness of breath, fatigue, body aches, headache, loss of taste or smell, sore throat, runny nose, nausea, and diarrhea (Centers for Disease Control and Prevention, 2022). In the past, there have been two other coronavirus pandemics in the 21st century: MERS-CoV and SARS-CoV-1. Neither of them were as highly contagious nor devastating as SARS-CoV-2. However, not all coronaviruses are classified as dangerous. The common cold, which could be caused by a variety of viruses is sometimes caused by a coronavirus. These common human coronaviruses are named 229E, NL63, OC43, and HKU1 (*Common Human Coronaviruses* | CDC, 2020). What makes SARS-CoV-2 special is its transmissibility and mutated attraction for human ACE2 receptors and its ability to affect multiple organ systems. Given its recent discovery there is much to be researched about SARS-CoV-2, but there are clues as to how it affects the immune system.

COVID-19 and Innate Immunity

If SARS-CoV-2 meets the skin and is not washed off; touching the mouth, nose, or eyes is an entry point for COVID to cause infection. Mucus and hair in the nose add protection, but it they do not work 100% of the time. Thus, it will be discussed how the virus evades and encounters the innate defenses of the human body.

According to Bajaj et al. (2021), COVID-19 is covered with "surface spike glycoproteins" that enter cells through angiotensin converting enzyme 2 (ACE2) receptors. The reason for this is because the spike proteins have mutated in a way where they are more attracted to ACE2 receptors. Once attached to cells containing these receptors, they can enter cells by endocytosis, which will be explained later, and replicate its DNA rapidly. Thus, cells with a higher concentration of ACE2 receptors are instantly targeted by the virus. Cells that have an abundance of these receptors are "airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lungs," which is why COVID-19 can cause respiratory distress. The lungs are not the only organ COVID-19 can target. Any cell containing ACE2 receptors is susceptible to infection, and there are many of them. Cells present in the heart known as cardiomyocytes and pericytes, as well as cells in the intestine, kidneys, testis, brain, and many others have ACE2 receptors. Thus, COVID-19 can affect multiple organs, which explains the variety of symptoms the virus creates.

Once SARS-CoV-2 enters the cell, multiple innate systems components respond to the virus. Upon entry, SARS-CoV-2 starts to replicate its RNA and cause the cells to release pro-inflammatory chemicals, which cause the cell to enter pyroptosis, which is programmed cell death like apoptosis, but instead caused by inflammation or swelling of the cell (Birra et al., 2020). Pyroptosis causes the cell to expel its contents, including copies of the virus and

damage-associated molecular patterns (DAMPs), which are virally infected "ATP, nucleic acid, … and cytokines," which signal nearby cells to release "pro-inflammatory cytokines and chemokines such as IL-6, IL-10, macrophage inflammatory protein (MIP) 1-alpha and 1-beta" which signal immune cells to produce interferon-gamma (IFN-γ) at the site to make more pro-inflammatory chemicals to stop the virus, but the virus can sometime evade this process and end up making it worse by causing a "pro-inflammatory feedback loop" (Bajaj et al., 2021, p. 6). IFN-γ is an interferon often released by NK cells. When activated by IL-12, activate macrophages release IL-12, which can create a loop of the activation of more and more NK cells and macrophages (Parham, 2009, 65). In a heathy immune system, this will eventually stop when the virus is fought off, and is controlled, and inflammatory cytokines will defeat the virus. In weakened immune systems, this process can become dysregulated causing an out-of-control positive feedback loop resulting in the overproduction of inflammatory chemicals, which is referred to as a "cytokine storm." This can cause lung and multi-organ tissue damage, which can lead to lethal cases of acute respiratory distress syndrome (ARDS) (Bajaj et al., 2021). Cytokine storm predominately occurs in the elderly population. Damage occurs because the cells become inflamed, which can cause damage to cellular components, leading to dysfunction or apoptosis of cells.

Furthermore, NK cells are highly involved with toll-like receptors (TLR). Since COVID-19 is a virus, there are three types of TLRs that can potentially take action to combat the virus: TLR3, TLR7, and TLR8. In studies with mice infected with similar viruses like SARS-CoV and H1N1, TLR3 is highly involved, and it was assumed it would be the case for SARS-CoV-2; however, some studies have revealed that TLR7 and TLR8 may be more involved than TLR3 (Birra et al., 2020). TLR7 and TLR8 both act in endosomes. Endosomes

are vesicles formed in cells when pathogens are wrapped by the cells' membrane as they enter the cell, which is also called endocytosis. Once SARS-CoV-2's single stranded RNA is in an endosome of an immune cell, it will bind to either TLR7 or 8. If it binds to TLR7/8, different pathways can be triggered such as the MyD88 pathway which leads to the production of pro-inflammatory chemicals and type I interferons to bring more immune cells to the site of infection (Birra et al., 2020). Type I interferons created by the MyD88 pathway are IFN- α and β, which can stimulate the Janus activated kinase-signal transducers and activators of transcription (JAK-STAT) pathway. The JAK-STAT pathway put simply is a series of signals that transfer information to the nucleus to activate gene expression. To do this, JAKs are activated by cytokine receptors, leading to the phosphorylation and activation of signal transducers and activators of transcription (STAT) that move to the nucleus to regulate gene expression. In this case, the JAK-STAT pathway would end up making interferons to kill SARS-CoV-2. Nonetheless, SARS-CoV-2, in some cases, has found a way to evade this mechanism.

Besides having spike proteins attracted to ACE2 receptors and the capability to cause tissue damage via cytokine storm in humans with susceptible immune systems, there are more ways in which SARS-CoV-2 can evade innate mechanisms such as blocking the production of transcription factors such as IRF3 and NF-κB which assist in the production of interferons. If interferons are made, SARS-CoV-2 can also block their signaling pathways by blocking or destroying the interferon receptors on infected cells to prevent the activation of the JAK-STAT pathway (Lei et al., 2020). It cannot be said for sure how SARS-CoV-2 does this, but there are proteins associated with SARS-CoV-2 that might have influence. According to Lei et al. (2020), out of over a dozen proteins that come from SARS-CoV-2 one

protein shows promise in the virus's ability to evade innate defenses—ORF6. Open reading frames-6 (ORF6) is a protein that inhibits the movement of IRF3 and STAT1 into the nucleus of infected cells (Lei et al., 2020). If there is less IRF3 and STAT1 in the nucleus the JAK-STAT pathway will not be able to function efficiently at making interferons, thus resulting in SARS-CoV-2 replicating with less determent.

From current research, SARS-CoV-2 is very complex and cunning when it comes to innate immunity. From its specialized spike surface proteins that are attracted to ACE2 receptors to bypass innate immunity to enter cells, and its ability to make proteins that further confuse immune defenses shows how the disease infected the world so quickly. With an influx of pro-inflammatory chemicals that are meant to kill the virus, SARS-CoV-2 uses it to a deadly extent, in some cases, to cause tissue damage and multiple organ failure via a cytokine storm. As discussed in the Innate Immunity of this thesis, there are many mechanisms involved in the innate immune system, and much of it is still being studied. Given that SARS-CoV-2 is a recent disease, much of the research done on how it affects the innate immune system is minute and needs further research, which will require decades of study.

COVID-19 and Adaptive Immunity

Eventually T-Helper lymphocytes (CD4+ T cells), cytotoxic T-lymphocytes (CD8+ T cells), and B-lymphocytes will recognize an antigen of SARS-CoV-2 and neutralize the virus.

Cytokines such as IFN-ɣ activate macrophages and cellular immunity. In some cases, T cells and antibodies are enough to eliminate the virus, but in others it can cause severe illness and death due to various reasons. These evasive mechanisms can include an attack on T cells and

B-cells, and further overproduction of pro-inflammatory chemicals. All of which, could be enhanced depending on one's genetics and age.

As explained previously, T-cells are integral to adaptive immunity in the secretion of interferons, cytokines, and death of virus infected cells. In severe cases of COVID-19, the virus can also infect the cells that are meant to destroy it— T cells. According to Shen et al. (2022), SARS-CoV-2 can infect T cells and cause them to spread the virus or self-destruct inducing, lymphopenia in some cases, with CD4+ cells being the most affected. Some patients ended up having the entirety of their lymphocytes destroyed in the blood by the virus. However, it is still being studied how SARS-CoV-2 infects T cells, as they lack ACE2 receptors. Nor do studies know why COVID-19 favors CD4+ T cells rather than CD8+ T cells. Furthermore, T-cells when combating the virus also release pro-inflammatory particles, which if uncontrolled like the innate immune system, can cause a cytokine storm, which can in turn kill lymphocytes. Nonetheless, with the death of T-cells the immune response is weakened, which is associated with acute cases of COVID-19.

In addition to T cell death, B cells are also impacted in acute COVID-19 infections. Opposite of T cells, memory B cells were increased in severe cases (Chen et al., 2022). The increase may be due to the reduction in T cells or influx of pro-inflammatory chemicals. For the most part, B cells do not seem to have a negative impact in severe cases and are focused on making antibodies. According to Sette and Crotty (2021), "Neutralizing antibodies develop rapidly in most SARS-CoV-2- infected people" within 5-15 days of symptoms (p. 865). In an effective response to the virus, B cells make IgG the most along with IgA, and IgM to neutralize SARS-CoV-2 via binding to the spike proteins (Sette & Crotty, 2021). As

stated before, IgM antibodies usually participate in agglutination and are short lived, while IgA mainly protect mucosal membranes in the lungs, and IgG focuses on neutralization.

In summation, though SARS-CoV-2 can evade the immune system to cause infection and sometimes death in those who are immunocompromised, adaptive immunity is highly effective at combating viruses. Often people will have symptoms of COVID-19, but their immune system will eventually stop the infection and create immunity. Acute SARS-CoV-2 cases seem to have a common factor in having an influx of pro-inflammatory chemicals which cause a cytokine storm that can cause tissue damage. Preliminary research also suggests that T-lymphocytes can be infected with COVID-19 and destroyed, which correlates with statistics that severe COVID-19-infected patients often have lymphocytopenia. However, more research on the mechanisms of COVID-19 infection is needed.

Adaptive Immunity Duration and Long COVID

After infection, memory T and B cells and antibodies have a certain amount of time they remain in the body for protection until they decay. Some immunity lasts decades, while others only last a few months. Scientist do not know the reason why immunity to some infections last longer than others. For example, researchers tested for antibodies in 91–101-year-old's who had been exposed to the 1918 Influenza virus, and they found antibodies still present, meaning the immunity for the virus lasts 90+ years (Yu et al., 2008). Though not enough time has passed to do a longitudinal study of this duration in COVID-19 patients, the preliminary findings show that immunity might not last long. With this knowledge, there may be a better understanding of how long immunity lasts for making vaccines and when people can expect to be at risk for re-infection.

Most longitudinal studies done on the topic of SARS-CoV-2 immunity span from 6 to 8 months. According to Dan et al. (2021), who did a study on SARS-CoV-2 immunity duration analyzing both types of T cells, B cells, and IgG antibodies, found that IgG antibodies for SARS-CoV-2 spike protein stay active 6+ months, memory B cells increase in number even after 6+ months, but both types of T cells decreased "with a half-life of 3-5 months." However, Cohen et al. (2021) found that T cells have a longer "half-life of 200 days," which is about 7-8 months. This is good news as antibodies and B cells are not decaying but remaining over 6 months. It is highly likely immunity can last over a year but might not last as long as immunity to the 1918 influenza. Though, longer longitudinal studies are needed, especially since the two studies mentioned had differing results.

In addition to previous studies on the longevity of immunity to SARS-CoV-2, though unlikely, there have been cases of being re-infected with COVID-19 within 90 days, which is

a shorter timeframe than memory T/B lymphocytes half-lives. This is likely due to being infected with a different variant of SARS-CoV-2. Currently, there are two variants being monitored: Delta and Omicron. Each variant can have sub-variants. Currently being monitored by CDC (2020), 19 subvariants are being monitored with XBB.1.5 taking up most cases between 11 December 2022 to 17 March 2023. Since T cells and B cells are only specific for an individual antigen, a different variant or subvariant would require different memory T and B cells. Thus, if one was infected with XBB 1.5, recovered, and then encountered BQ. 1.1, they could be re-infected with SARS-CoV-2. Given the body has already developed some sort of immunity, if a re-infection does occur within a year of the first infection, it usually is not as severe. Different variants also explain people being re-infected multiple times with COVID within the 3 years it has been around. Though, there is the possibility of exceptions such as those who are immunocompromised and those who never fully recovered from COVID-19.

During the COVID-19 pandemic, there arose a special syndrome or side effect of SARS-CoV-2 infection that lasts for an abnormal amount of time in some patients. Patients recover from infection but are left reeling from the side effects, which can last from 3 months to years. The term for this syndrome was coined, Long-COVID. In a news article published by Scientific American written by Sutherland (2023), the data estimated in February of 2022 stated Long COVID would affect “16 million adults in the U.S. and had” already “forced between two million and 4 million Americans out of the workforce.” Though anyone can get Long COVID if they were infected with SARS-CoV-2, those who had more severe cases may be more likely to have Long COVID, though this is not always the case. Symptoms of Long-COVID can include the following: chronic fatigue, difficulty breathing, heart issues

like postural orthostatic tachycardia syndrome (POTS), brain fog, attention issues, insomnia, body aches, headaches, and post-traumatic stress disorder (PTSD) symptoms (Crook et al., 2021). There could be various causes to these symptoms. Difficulty breathing and heart issues may be due to lung and heart damage since they both have cells with ACE2 receptors which SARS-CoV-2 can bind causing high concentrations of pro-inflammatory chemicals in those areas. According to Crook et al. (2021), the pro-inflammatory attack on the heart can alter the heart physically and cause the involuntary nervous system to malfunction causing abnormal heart rate conditions such as POTS. POTS is characterized as a syndrome where transitioning from a lying or sitting position to standing induces tachycardia which can cause dizziness and fainting (Cleveland Clinic, 2017). In fact, researchers are seeing more and more associations as autonomic nervous system dysfunction, cognition issues, lack of sleep, anxiety/depression, and pain can all stem from Long COVID suggesting that it may be the result of neurological disease induced by SARS-Cov-2. POTS also can cause the same symptoms of Long COVID, such as shortness of breath, headaches, fatigue, brain fog from lack of oxygen, muscle weakness, sleep disturbances, pain, and gastrointestinal issues. All of which can induce anxiety, depression, and PTSD like symptoms. Researchers have some ideas as to why SARS-CoV-2 can cause dysautonomia.

According to Sutherland (2023), Long COVID might be caused by viral particles entering the central nervous system (CNS), immune cells entering the brain, or an inducing of an autoimmune disorder. It is unknown how viral particles from SARS-CoV-2 bypass the blood brain barrier, but one way hypothesized by researchers is that since SARS-CoV-2 can potentially cause loss of taste and smell by binding to ACE2 receptors in neurons of the olfactory bulbs, the virus could also potentially travel through the neurons to the brain. Once

in the brain, they can infect areas that control breathing and the heart, as well as brain cells such as astrocytes which are glial cells involved in the structure and protection of neurons, hence cognition issues. Furthermore, immune cells such as macrophages can enter the brain, and may have contributed to COVID-19 patient deaths. The reason for this is because macrophages are not as specific as T and B cells at targeting viruses. It will go after viruses and things it deems foreign but will also cause "damage [to] nearby tissue" by releasing "free radicals, cytokines" and making blood vessels more permeable to increase inflammation in the brain (Sutherland, 2023). Sutherland (2023) also mentioned a study that found high amounts of TNF-a, IL-6, and IFN-ß which are signs of pro-inflammatory chemical release. Lastly, another potential cause of autonomic dysfunction is that antibodies could be targeting normal cells as well as infected cells. Antibodies that target normal cells are called autoantibodies, and they could be targeting healthy nerve cells even after SARS-CoV-2 infection, which would contribute to the known symptoms. (Sutherland, 2023)

Nevertheless, the immune system is excellent at combating SARS-CoV-2 and produces lasting immunity. However, immune system mechanisms meant to fight SARS-CoV-2 backfire, in some cases, and create an influx of pro-inflammatory chemicals that can cause organ damage. SARS-CoV-2 can also mutate quickly, enabling it to have many different variants, all of which need specific T and B cells to fight them, making reinfection within 90 days possible, but unlikely the same variant. Lastly, SARS-CoV-2 can also enter the brain to cause dysfunction in the autonomic nervous system to cause a post-viral syndrome called Long COVID, which can last months to years, depending on the severity. Thus, adequate treatments for Long COVID to improve the quality of life after SARS-CoV-2 need research.

How Does COVID-19 Affected People of Different Ages?

Just as every fingerprint is unique, everyone has their own unique immune system. SARS-CoV-2 seems to affect everyone differently. Age is a contributor as children typically had the lowest risk of mortality from COVID-19, while elderly seem to be of the highest risk. Genetics are also thought to be a factor due to how it hits families differently. For example, some families were entirely wiped out by the virus and were more likely to be placed on ventilators, while other families had symptoms but naturally recovered or were entirely asymptomatic. There are commonalities in how the immune system functions, but how much it works can be different depending on age, history with viruses, genetics, and if one is immunocompromised.

Children vs Adults

Those who stayed up to date during the COVID-19 pandemic may remember media outlets and doctors mentioning that children were more protected against the virus than adolescents and elderly. Using data from National Center for Health Statistics (2023), approximately 0.15% of COVID deaths in the United States are people within the 0–18 years old range. This compares to adults aged 19-44 that make up 4% of deaths, and adults aged 45-64 who make up 20.4% of U.S. deaths. Nonetheless, not everyone may know the reason for this difference. A child's immune system is at the beginning of building up immunity to a wide range of viruses and needs a higher amount of protection mechanisms than an adult. Children for this same reason have a stronger innate immunity than adaptive immunity. To compensate for this is, children have an enlarged thymus, increased amount of red bone marrow, and potentially decreased infiltration of pro-inflammatory cells in the lungs.

COVID-19 is also combated more readily, as children often have recurrent and co-infections. Though this does not work with all viruses, as children are highly at risk for the flu.

Innate immunity is the primary system in children to combat infection, as adaptive immunity cannot act until it has encountered a pathogen. This results in children having a higher concentration of NK cells and other innate defenses; however, researchers do not think this is the only reason due to children being susceptible to other respiratory infections such as RSV. Thus, most researchers look to the difference in adaptive immunity.

In adults, many memories T and B cells are already circulating in the blood and organs involved in the immune system, as many were made due to pathogens introduced in childhood. Nevertheless, the human body is wonderfully made to compensate for this challenge in childhood by having an enlarged thymus. The thymus is an organ that is responsible for the maturation of CD4+ T lymphocytes and CD8+ T lymphocytes after they are produced in the bone marrow. When a child encounters a pathogen, it is met with an army of T cells. The naïve adaptive immunity will then begin making its first antibodies. Around puberty when a thymus "reaches a maximum weight of 30-50 grams," the thymus starts to shrink slowly and is replaced with adipose tissue in adulthood; however, this is because the amount of T cells needed are already produced (McKinley et al., 2016, p. 840). Though, as one gets older there can be circumstances in which the T cells in the body decrease, making adults, especially the elderly, more susceptible. Furthermore, a strong adaptive immunity often increases the production of pro-inflammatory chemicals, which can lead to complications. Thus, the weakened adaptive immunity in children, meaning they do not have many memory T and B cells, actually helps them. Furthermore, there are more components to the immune system in children that grants them protection.

In childhood, there is primarily red bone marrow in the bones, which slowly decreases in adulthood to mainly yellow bone barrow. Red bone marrow is composed of stem cells that can become red blood cells (RBC), white blood cells (WBC), plasma cells, and B-lymphocytes. This increased amount of plasma cells and B-cells contribute to greater protection against pathogens in childhood. Thus, in adulthood, since there is a lower amount of red bone marrow there is also a lower production of B cells. Once again, this is not the only contributor.

In addition to increased innate and adaptive immune defenses, some researchers hypothesize there is a lower infiltration of pro-inflammatory cells in the lungs of children, which can cause complications such as a cytokine storm. This is potentially due to a decrease in ACE2 receptors present on cells in the lungs compared to adults. According to Lingappan et al. (2020), a preprint study "found that *ACE2* … expression in airway epithelial and alveolar … cells increases with age, with very low expression in infants and young children" (pp. L40-L41). With the decrease in ACE2 expression, viral infection with SARS-CoV-2 would be slowed reducing the risk of a cytokine storm, and a more adequate amount of pro-inflammatory chemicals fighting the virus. Newborns also specifically have shown to have lowered TLR-induced responses, which further decreases the production of pro-inflammatory chemicals. Hence, a lower mortality risk in children.

In addition to a possible lack of ACE2 presence in the lungs, Zimmermann and Curtis (2020) suggests that co-infections also give children an upper hand when it comes to infection. Since, children often battle common viruses including common human coronaviruses (the common cold), they can often be in the process of building immunity to multiple infections at once. So, there is a potential that if a child is battling another infection

already, it could “interfere with the replication of SARS-CoV-2” due to already activated innate defenses from recurrent viral infections (Zimmermann and Curtis, 2020, p. 434).

On a side note, Zimmermann and Curtis (2020) also suggest that the microbiome may be involved with certain bacteria potentially having an impact on SARS-CoV-2. However, more research is needed.

In summation, it is hypothesized that children are more protected against COVID-19 because of enhanced innate immunity from recurrent infections, increased naïve T and B cell production and decreased amount of memory cells, decrease of ACE2 in the lungs which reduced risk of cytokine storm, and potential increase of certain microbiota. Though, like most COVID-19 research none of this has been confirmed and more research is needed to determine why children are more at risk for diseases such as RSV and the flu than SARS-CoV-2.

Elderly and Immunosenescence

Unlike children, elderly have the highest mortality rates when infected with COVID-19. With data from National Center for Health Statistics (2023), elderly aged 65 and comprise 75.5% of the deaths in the United States as of March 4, 2023. This is due to many factors including immunosenescence and comorbidities.

Though children have a weakened immune system that reduces pro-inflammatory cytokine production, elderly also have a weakened immune system. Unlike children who have strong innate immunity and a functioning adaptive immune system, an elderly immune system is dysfunctional, often having a higher risk of cytokine storm. The weakened immune system is due to what is called immunosenescence. Senescence is the dysfunction or deterioration of the immune system due to increased age. For example, when one gets older,

the brain starts to shrivel and get smaller. Wrinkles and thinner skin are also associated with age. In immunosenescence, there are multiple mechanisms of immunity that malfunction or deteriorate. In innate immunity, recognition of antigens malfunctions due to decreased function of toll-like receptors on macrophages, which increases cytokines, and there is a decrease in NK cell function, so less infected cells are killed (Mueller et al., 2020). Immunosenescence also affects adaptive immunity. Linking back to children who have a large thymus producing naïve T lymphocytes, which starts to decrease in size after puberty, in elderly the thymus is virtually nonexistent and mainly composed of adipose tissue. The lack of new T lymphocytes causes elderly to rely on memory T cells and the remaining naïve T cell population, resulting in a slower recognition of foreign antigens and a longer time for memory T cells to be made against COVID-19. Literature says that the memory cells and antibodies made under immunosenescent conditions have lower affinity to the antigens they are targeting (Bajaj et al., 2021). Thus, they have low effectiveness in combating the disease. According to Bajaj et al. (2021), senescent T cells are characterized by a lack of the surface protein, CD28, which is involved with the production of telomerase to lengthen the DNA of the cells. Senescent cells are associated with mutations that cause some of them to produce chemicals, such as cytokines, which can cause inflammation. This may be why those who are considered elderly develop other diseases such as arthritis, and inflammation related issues. Decreased function of the immune system also prevents senescent cells from being destroyed, which allows the production of pro-inflammatory chemicals to be left unchecked and causes other cells to become senescent. The term for chronic inflammation in the body due to immunosenescence is called inflammaging (Mueller et al., 2020). With the production of senescent cells secreting pro-inflammatory chemicals, and the downregulation of innate

and adaptive immunity, the older people are left highly susceptible to SARS-CoV-2, especially if they have comorbidities.

Comorbidities such as type II diabetes mellitus, high blood pressure, and obesity as well as other comorbidities that affect ACE2 receptor concentrated areas such as heart and lung disease are at a higher risk for COVID-19 mortality. Cancer patients undergoing immunosuppressive therapy are also at risk. Obesity places pressure due to increased fat/adipose tissue around and in organs. Bajaj et al. (2021) found research that says visceral fat tissue can act as a "reservoir for the virus" and can cause a build-up of pro-inflammatory chemicals because it contains higher levels of ACE2, which SARS-CoV-2 can bind, allowing immune cells to enter the tissue (p. 8). Furthermore, obesity can make it harder for the lungs to function, resulting in higher risk of mortality due to the virus, since it targets the lungs posing risk of pneumonia and lung damage due to inflammaging. These same risks are associated with type II diabetics since a high portion of these individuals are obese. However, ACE2 plays another role in type II diabetics and hypertensive elderly patients.

Besides SARS-CoV-2 infection which triggers the release of pro-inflammatory chemicals, the enzyme ACE2 has anti-inflammatory effects because it can change the conformation of angiotensin 2 so that it makes anti-inflammatory chemicals rather than pro-inflammatory chemicals. In type II diabetics and patients with high blood pressure, studies have revealed that ACE2 expression potentially decreased (Bajaj et al., 2021). Although, it is important to note that this is still debated in the scientific community, as there is conflicting literature on this, with some claiming that it is increased. If it is increased it would explain the increased risk of infection of SARS-CoV-2, but downregulation would occur due to SARS-CoV-2 blocking ACE2 from binding to receptors. While, if research is correct in

downregulation of ACE2 expression, those with diabetes would be predisposed to higher production of pro-inflammatory chemicals through the pro-inflammatory angiotensin 2 pathway. In combination with SARS-CoV-2, ACE2 would further be dysregulated, and inflammation increased, causing the high mortality rate in patients with this co-morbidity. Another commonality in immunosenescent patients with comorbidities is the production of T helper 10 lymphocytes which are regulated by IL-6 to create proinflammatory chemicals such as IL-17 and IL-22 (Bajaj et al., 2021). Unfortunately, COVID-19 increases IL-6 as previously mentioned, which increases this populations' risk for cytokine storm. Nonetheless, these are not the only variables that may contribute to increased death in elderly infected with COVID-19.

Just as the thymus is smaller in elderly, there is less red bone marrow present in the bones. This means that older people also have less naïve B-lymphocyte production. With this decrease, there are less B-lymphocytes to make memory plasma cells and B-cells to make antibodies against SARS-CoV-2, which is another variable toward more severe forms of SARS-CoV-2 in the elderly population. However, it is unknown if this is a true cause of death associated with COVID-19.

Furthermore, there are some studies that conflict with the previous theories as to why the elderly are at a higher risk for mortality with SARS-CoV-2. According to Damayanthi et al. (2021), older males, dementia patients, and elderly who suffer from dyspnea are the most at risk for mortality. The study found these groups had higher risk of death when pulling data from different studies done on elderly COVID-19 patients, yet, the amount of research done is limited given the earliness of the pandemic. It is theorized males are at a higher risk because they might have more ACE2 production than women, which makes them more

susceptible to the disease. Dementia patients with COVID-19 also had high mortality ($p<0.05$). It is unknown what causes dementia patients to have a higher mortality, but it may be due to them being immunocompromised. Given many dementia patients are disoriented and in isolated environments, they also may recognize the virus too late. Patients with dyspnea may pose a higher risk because SARS-CoV-2 targets the lungs. Though, one can assume patients with dyspnea have comorbidities like mesothelioma and asthma or are smokers which struggle with breathing.

There are some who have comorbidities who do not have severe COVID-19 symptoms and/or able to survive. More research is needed because of this, but there are some guesses as to why this happens. The most obvious reason would be that some form of treatment assisted their immune system to combat the virus whether it be through monoclonal antibodies or medications such as remdesivir or paxlovid. There is also a possibility of a genetic contribution. In Mueller et al. (2020) mentioned as study by Hashimoto et al. (2019), that found that supercentenarians, people who live over 110 years old, have developed helper T lymphocytes that have cytotoxic abilities like cytotoxic T lymphocytes. This is fascinating research, that shows that some people have developed special immune system abilities that give them an upper hand over pathogens, where their immune system would usually be susceptible.

In conclusion, elderly patients are more at risk for mortality due to immunosenescence and inflammaging. Risk is especially increased when these patients have comorbidities such as diabetes, high blood pressure, cancer or immunocompromise, and lung-associated illnesses. Age, sex, and race may also be contributors. However, research is still needed to discover why older people are more at risk of death from COVID-19

compared to other ages. Immunosenescence also impacts the body in more ways than discussed. Nonetheless, the reason seems to be multi-variable, and having comorbidities does not necessarily end in death in all cases.

Are Genetics Involved in COVID Severity?

COVID-19 seemed to touch every family, but in different ways. Some would have severe symptoms and be placed on ventilators, others had symptoms but recovered, and some became asymptomatic or did not catch COVID-19 at all. There is a vast difference, between normal families no matter how healthy. One family would be wiped out entirely or severely effected in hospital, while another family would have asymptomatic members and others who had symptoms regular to a common cold and recovered quickly. This variability between families, suggests there may be a genetic or epigenetic component to COVID-19 severity.

One probable cause briefly mentioned before is ACE2 expression. The gene that encodes for ACE2 is found on the X chromosome and researchers believe those of the male sex have an ACE2 gene more expressed in their cells (Benetti et al., 2020). Different tissues can have different expressions of ACE2 as well. Thus, the expression of the ACE2 gene, and what mutations of the gene someone may have could be determinate of COVID-19 severity. These mutations and expression levels could be passed down to families, which could explain why families may vary in COVID-19 severity. Nevertheless, the ACE2 gene may not be the only gene affected by epigenetics.

Epigenetics is the study of how genes are expressed based on chemical changes on the DNA, not the code itself. For example, if there are many methyl groups on a gene, they can prevent transcription enzymes from binding to the code, preventing it from being read to

make mRNA and eventually proteins. According to Mueller et al. (2020), age and pathogens can change the epigenetics of DNA, altering "immune cell composition and function," and the production of memory cells making it easier or harder for SAR-CoV-2 to infect cells. Mueller et al. (2020) goes on to mention that coronaviruses are known to affect epigenetics. For example, SARS-CoV-1 was found to change the methylation of histones and non-coding RNAs, which increased the production of interferons, and MERS-CoV (Middle East Respiratory Syndrome Coronavirus), changed the methylation of MHC genes which alters cells' ability to present antigens. Thus, researchers will need to research how SARS-CoV-2 specifically affects the epigenome to hinder the immune system, as it may explain disease severity.

The COVID-19 Pandemic Compared to Previous Pandemics

As many know, the COVID-19 pandemic has not been the only pandemic to hit the world even in recent years. Pandemics are extremely devastating and cause many deaths. However, it is the goal of many to learn from them to prepare for the next outbreak. With COVID-19 being a virus that affects the respiratory system there are three pandemics that COVID-19 can be compared to: SARS-CoV pandemic of 2002-2003, MERS-CoV pandemic of 2012, and the Spanish Influenza H1N1 Pandemic of 1918-1919.

SARS-CoV:

Severe Acute Respiratory Syndrome caused by coronavirus (SARS-CoV-1), also known as atypical pneumonia, was the first pandemic of the 21st century, but because it was short-lived it is often called an epidemic. Compared to the COVID-19 pandemic it was on a lower-scale given it traveled to 29 countries, infected 8096 people, and killed 774 people worldwide (WHO, 2015). On the other hand, COVID-19 hit worldwide, infected > 757.2 million people, and killed > 6.85 million people as of March 2023 (World Health Organization, 2023a). SARS-CoV first started in Guangdong Province, China with first cases dating back to November 2002, yet an outbreak was not reported to the World Health Organization (WHO) until February 2003; the pandemic ended in June 2003 (World Health Organization, 2003). Thus, the SARS-CoV pandemic was short-lived. However, how does it compare to the effects SARS-CoV-2 had on the immune system?

Just as SARS-CoV-2 is theorized to have originated from bats, SARS-CoV also originated from bats. Though, their intermediate host is different. According to Cherry and Krogstad's article "SARS: The First Pandemic of the 21st Century," when the genome of SARS-CoV was discovered they compared it to Himalayan palm civets and the genome

matched 99.8% (Cherry & Krogstad, 2004). The intermediate host for COVID-19 is suspected to be pangolins, which have a "97% amino acid sequence similarity" (Abdelrahman et al., 2020, p.6). Though, a percentage over 98% would be preferable, given DNA tends to have high similarity with many other things. Like COVID-19, symptoms of SARS-CoV include fever, cough, fatigue, vomiting, and diarrhea. The similarity is due to both viruses being coronaviruses with spike proteins that bind to ACE2 as their host receptors which attack cells found in the lungs, gut, and heart. SARS-CoV, like SARS-CoV-2 is an "positive-stranded RNA virus" (Abdelrahman et al., 2020, p. 2). Like SARS-CoV-2, the main pathway SARS-CoV-1 infects is by ACE2 receptor-mediated endocytosis. Contrastingly, the toll-like receptor (TLR) that recognizes SARS is TLR3 rather than TLR7 or 8. TLR3 achieves the same result of TLR7/8 in producing type I interferons and pro-inflammatory chemicals, but it uses the TIR-domain-containing adapter-inducing interferon-β (TRIF) pathway (Birra et al., 2020). Scientists thought COVID-19 used the same pathway, but found this was not the case.

According to Abdelrahman et al.'s (2020) article, "Comparative Review of SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza A Respiratory Viruses," another difference is that SARS-CoV had a higher case fatality rate (CFR) of 15% compared to COVID-19's 1-3% CFR. SARS-CoV also displayed lymphopenia, thrombocytopenia, and leukopenia commonly found in COVID patients, yet COVID-19 overachieves in evading the innate immunity defenses and causes monocytosis, and low C-reactive protein. This is because, as it will be stated with MERS-CoV, the reason why SARS-CoV was short-lived was because of its low transmissibility. SARS-COV and MERS-CoV also had a reproduction number of 0.58 and 0.69, while SARS-CoV-2 had a great reproduction number of 3.1. The lower the number,

the lower the transmissibility. SARS-CoV-2 has polybasic cleavage sites that increase this transmissibility (Abdelrahman et al., 2020). According to Winstone et al. (2021), the polybasic cleavage sites are locations on the spike proteins on SARS-CoV-2 that can be cut by the protein, furin, which is as known as a protease, to allow the virus to more easily bind to ACE2 receptors and fuse into the cell rather than through just endocytosis. Though this idea is still being researched, scientist think that if this is the case it would make SARS-CoV-2 more transmissible. Polybasic cleavage seems unique to the SARS-CoV-2 virus and is not present on SARS-CoV. Nevertheless, because of how transmissible the virus is and how mutated it is compared to SARS-CoV, it is highly debated whether this virus mutated naturally or if it was mutated through gain of function research, which has spurred controversy.

An example of this is when the Department of Energy (DE) recently changed its stance on whether the virus resulted from a lab leak in Wuhan, China. Media sources claim that the DE thinks it is highly probable, but big government agencies and media outlets believe this theory was made with low confidence (Barnes, 2023). Both sides are not definitive, but neither should be ruled out in order to have unbiased research of the origins of SARS-CoV-2 so researchers can understand the virus and how it mutated.

MERS-CoV

Middle East respiratory syndrome coronavirus (MERS-CoV), as its name suggests, started in the Middle East in April 2012. It is theorized to have originated from bats, which then spread to camels, and then to humans (Abdelrahman et al., 2020). According to the World Health Organization, as of January 2023, the virus has reached 27 countries, where 2603 people have been infected, and 935 reported deaths with many of these cases taking

place in Saudi Arabia (World Health Organization, 2023b). The CFR of MERS-CoV is 36% (World Health Organization, 2023b), which shows that the virus has a high mortality rate. However, as explained previously, MERS has low transmissibility, which is why it did not have the devastating impact of COVID-19. Today, it is rare to get infected with MERS-CoV, but it is not impossible.

Different from SARS-CoV-2 the host receptor of MERS-CoV is not ACE2. Dipeptidyl peptidase-4 (DDP4) is the host receptor, and the dominant cell entry pathway is through cell membrane fusion (Abdelrahman et al., 2020). According to Yuan et al. (2019), there are two different spike proteins on the surface of MERS-CoV called S1, which binds to DDP4 (CD26), and S2 which causes the virus to fuse into the cell's cytoplasm. Once copies of itself spread to other cells, like SARS-CoV, TLR3 makes interferons and cytokines to kill the virus. It is also important to note that SARS-CoV-2 can potentially bind to DDP4 as well. This would be another explanation why elderly people with comorbidities like type II diabetes and obesity have an increased risk for SARS-CoV-2, as they have more DDP4 production due to immunosenescence which upregulates the production of cytokines (Bajaj et al.,2021). Though, SARS-CoV-2 affinity for DDP4 needs more research.

Furthermore, though MERS-CoV has the same symptoms as SARS-CoV-1, neither display the symptom involving loss of taste and smell as some SARS-CoV-2 cases report. A study made by Harvard Medical School found the cause of this symptom. According to Brann et al. (2020), non-neuronal cells, such as support cells, express ACE2 and can be infected with SARS-CoV-2. With these results, the study hypothesized that infection or damage of non-neuronal cells in the olfactory bulb may produce pro-inflammatory cytokines which impede odor perception, or damage of blood vessel cells could decrease blood flow to

the olfactory bulb to cause loss of smell. However, it is not definitive which or if both are the cause.

H1N1 Spanish Influenza Pandemic of 1918-1919

The most devastating respiratory related virus to ever hit the world prior to COVID-19 was the Spanish Influenza (H1N1) Pandemic of 1918-1919. The virus is estimated to have claimed "50 million" lives and to have infected "one-third of the world's population" (Centers for Disease Control and Prevention, 2019a). In this case, it is important to note that the world population one-hundred-years ago, was 20% of what it is today. If this scenario happened in today's numbers approximately 2.6 billion people would have been infected with 780 million deaths. The Spanish flu was devastating, which is why it was coined the "Mother of All Pandemics" (Taubenberger & Morens, 2006). Nonetheless, since it affects the respiratory system, some wonder if it has any comparison to SARS-CoV-2.

Unlike SARS-CoV-2, H1N1 is an influenza A virus with "negative-sense, single-stranded RNA" (Abdelrahman et al., 2020) and is a part of the *Orthomyxoviridae* family rather than the *Coronaviridae* family. They are both spherical in shape with proteins on the surface, but unlike COVID-19 which has spike proteins, H1N1 has two different types of major proteins that spike from its surface. These proteins are called hemagglutinin (HA) and neuraminidase (NA) (Sriwilaijaroen & Suzuki, 2012). HA proteins are what attach to host cells, and NA is what cuts into them for the viral RNA to enter and make more of the virus. The reason other flu viruses have names such as H3N2 or H1N7 is because there are different HA and NA proteins that can be paired together. In this case, it was H1N1. In 2009, there was another H1N1 pandemic; however, this does not mean it is the same as the H1N1 virus that occurred in 1918. This is because an influenza A virus is not upgraded in number unless

more than 50% of its genetic sequence is changed (Colman, 1994). This is due to something called the antigenic drift. Antigenic drift is when a virus has mutations in its genes created little by little over time to the extent the immune system cannot defend against it with antibodies or memory B-cells made from its older genetic makeup (Centers for Disease Control and Prevention, 2019b). The flu is a common illness just like the common cold with epidemics occurring every year for this reason, hence the suggestion for people to get the flu vaccine each year. Every year, the most popular variant of the flu monitored that year is the vaccine people are given. In fact, antigenic drift is also seen in SARS-CoV-2, in the creation of variants such as the prominent Delta and Omicron variants. Nonetheless, this is not the only way SARS-CoV-2 compares to H1N1.

Unlike SARS-CoV-2, H1N1 does not use ACE2 receptors to enter cells. HA proteins bind to sialic acid receptors, which triggers endocytosis (Abdelrahman et al., 2020). Once the virus spreads from the host cell, NA proteins step into action. In contrast to HA proteins, NA proteins cleave sialic acids from receptors on the infected cell and on HA proteins to detach the H1N1 virus from the cells so it can go on to infect other cells (Kosik & Yewdell, 2019). This, coupled with H1N1's short incubation period of 2 days, helped H1N1 evade innate immunity to infect rapidly. On the other hand, SARS-CoV-2 and MERS-CoV can have an incubation period ranging from "2-14 days" (Abdelrahman et al., 2020).

H1N1 influenza affected different age groups compared to SARS-CoV-2 which predominantly affected the elderly. H1N1 is notoriously known for its "W-shaped curve […] finding of peaks in mortality among infants, young adults, and elderly individuals," but when looking at excess mortality, the elderly was not predominately impacted by H1N1 (Luk et al., 2001, p. 1375). Thus, when looking at excess mortality, many researchers believe a portion

of the elderly were exposed to an H1N1 virus before 1918. However, children and young adults were still highly impacted by the Spanish influenza, which is different from SARS-CoV-2. It is unknown why this is the case, besides how H1N1 evades innate immunity defenses.

Notwithstanding, just as SARS-CoV-2 is a novel coronavirus in need of more research, scientists unfortunately do not fully understand the H1N1 virus that caused the pandemic of 1918. This is because 100-years-ago, scientists did not have the knowledge about influenza viruses as they do today. Much of what is known today is from recent influenza outbreaks, and from sequencing done on preserved tissue taken from cadavers who died of the virus in 1918. Nonetheless, from the little we know of the 1918 H1N1, comparisons to SARS-CoV-2 can still be gathered.

Lockdowns

In March of 2020, the United States of America started to shut down its borders and issued lockdowns for citizens to slow the spread of COVID-19 (*15 Days to Slow the Spread – the White House*, 2020). The American people and the world ensued into chaos with the stock market plummeting (Smith, 2020), toilet paper becoming scarce in grocery stores due to panic (CNN, 2020), colleges transitioning strictly to online learning (Burke, 2020), and people losing their jobs (Center on Budget and Policy Priorities, 2021). COVID-19 changed the world, and it will never be like it was pre-March 2020. Lockdowns and social distancing measures were issued to save lives; however, before and after these measures were put into place there may be confusion and debate over whether these saved more lives than hurt, and how they might have impacted the immune system.

Lockdowns: Effectiveness and Immunology

On 16 March 2020, the White House implemented lockdowns that were originally meant to only last 15 days, as the effort itself was coined "15 days to Slow the Spread." The initiative put forward by the President Donald Trump at the time included guidelines considered to be common sense such as staying home if you feel sick and washing your hands, but there were others that went further and became the lockdowns most remember. These guidelines included the following: "work or engage in schooling from home," "avoid social gatherings… of more than 10 people," avoid dining-in restaurants and instead "use drive-thru, pickup, or delivery options," "avoid discretionary travel, shopping trips, and social trips," "Do not visit nursing homes or retirement or long-term care facilities unless" you are a healthcare worker (*The President's Coronavirus Guidelines for America: 15 Days to Slow the Spread*, 2020). People followed suit, and were hopeful this would help save lives,

and it possibly did. However, the lockdowns did not end after 15 days, they were extended in most states until May, but bans on gatherings still were in place well into 2021. Furthermore, many people remained in lockdown out of their own initiative due to fear of infection or infecting others, thus lockdowns truly did not truly "end" until around August. Not to mention many other countries around the world issued lockdowns, as well as reinstated them in light of new variants. The extension of lockdowns and bans on gatherings caused concern and debate in if lockdowns really outweighed the risks (Long et al., 2021).

The truth is science cannot definitively say whether lockdowns saved more lives than it killed. However, researchers can share what they observed and use mathematical probability to have an idea of the impact, but once again it is not absolute, and never will be. Thus, what were the potential effects on the immune system caused by lockdowns?

Literature is divided on whether lockdowns were beneficial, but there are some that suggest that lockdowns do indeed save lives. In a retrospective cost-benefit analysis written by Yakusheva et al. (2022), which compared potential lives saved by lockdowns compared to potential lives lost by economic recession caused by COVID-19, lockdowns saved approximately "866,350 - 1,711,150 lives" compared to "57,922 - 254,005 lives" potentially lost due to "economic downturn." This gives support that lockdowns may have saved more lives than it hurt due to a crashing economy. In another study, total deaths from the beginning of the pandemic to 4 May 2020 were compared to an estimate of deaths if lockdowns were not implemented in European countries and found "that across 11 countries 3.1 (2.8-3.5) million deaths" were avoided due to lockdowns and concluded they "had a large effect on reducing transmission" (Flaxman et al., 2020). Though, the authors do specify that their models are limited in not looking at all variables that could contribute to these numbers such

as having incomplete data on deaths and "assumes changes in" transmissibility "are an immediate response to interventions rather than gradual changes in behavior." Thus, not definitive, but an estimate. Furthermore, from the same journal, *Nature*, another study provides support for lockdowns. According to Lai et al. (2020), using "epidemiological data on COVID-19" and simulation technology to analyze outbreak scenarios, estimated there would be "114,325 cases of COVID-19 […] in mainland China as of 29 February 2020," which was very early in the pandemic, and predicted that without lockdowns the number would have increased "67-fold higher." This is an astronomical number, and if true, a persuasive argument in favor of lockdowns. Nonetheless, there were a significant number of limitations mentioned in the study including potential bias in lockdown effectiveness and population coverage, as well as error in the simulations. Nonetheless, there is possibility lockdowns are effective in reducing spread of disease and lowering deaths, but there is not sufficient evidence to prove this, nor do these studies look at other variables such as mental health, loss of income, and long-term effects such as death due to delayed healthcare. However, another thing positive about lockdowns is well summarized by the WHO who say lockdowns "buy time" for governments "to build their capacities to detect, isolate, test and care for all cases; trace and quarantine all contacts; engage, empower and enable populations to drive the societal response" (WHO, 2020).

In addition to articles that suggest that lockdowns are beneficial, there are many articles that give evidence for the opposite. According to a review written by Yanovskiy and Socol (2022), they found that lockdowns in general, as they compared to the Spanish Influenza and COVID-19, "claim 20 times more life than they save" by doing a cost-benefit analysis. Thus, they do not recommend lockdowns, unless a cost-benefit analysis is done first

to gauge if they will have a significant effect. In a review and meta-analysis of 24 studies on lockdowns and COVID-19 mortality by Herby, Jonung, and Hanke (2022) from the Johns Hopkins Institute for Applied Economics, Global Health, and the Study of Business Enterprise, the authors concluded that lockdowns did not have a "large, significant effect on mortality" and that the stringency of lockdowns in the U.S. and Europe resulted in a 0.2% mortality decrease, and stay at home orders "reduced COVID-19 mortality by 2.9%." These low percentages conflict with previous studies that had significantly higher percentages. With the results from this meta-analysis, the deaths after lockdowns could make up for lives saved. As stated by the author, Olga Yakusheva, of the Yakusheva et al. (2022) study, which said lockdowns saved lives, admitted that her study

> "shouldn't be used to justify lockdowns now or to retroactively endorse that approach … [because] 'We know how many people died with public health measures in place, but we can't know how many people would have died without those measures in place. … all of the human toll of the lockdown won't be seen immediately. For example, the health toll could manifest later as disease progression because someone who was unemployed couldn't buy medications'" (Bailey, 2022, paras. 3-16).

Therefore, there is a limitation in studies for support and opposition of lockdowns in that they have not looked at the long-term effects of lockdowns, leaving potential that lockdowns may or may not harm more than they help. Most of these factors, such as death due to mental health issues, or not having proper screenings or access to medications during lockdowns, may have been avoided if the lockdowns only lasted 15 days, at most, to "buy time" (WHO, 2020). However, one main variable most people are concerned about is whether lockdowns affected the immune system negatively.

Research is limited on whether lockdowns negatively impacted the immune system, and studies present conflict with each other. In the summer of 2022, there was news of an *immunity gap* potentially caused by lockdowns as there was a surge in flu and RSV cases. According to Messacar et al. (2022) both the flu and RSV commonly surge in the winter season, but this did not occur in 2020 due to non-pharmaceutical interventions like masking, social distancing, and lockdowns. The result of having little exposure to these viruses and other illnesses caused an "immunity gap—a group of susceptible individuals who avoided infection and therefore lack pathogen-specific immunity to protect against future infection" (Messacar et al., 2022, p. 1663). Thus, due to lockdowns and masking, people were not exposed to certain illnesses that have short immunity, which left them vulnerable to infection once restrictions were removed. RSV is an excellent example, as another study found that due to lockdowns, there was a decrease in "RSV antibody levels … [in] women of childbearing age and infants between May to June 2020 and February to June 2021, in British Columbia (BC), Canada" (Reicherz et al., 2022, p. 1). These lead to the surge of RSV cases starting in May of 2021 to December of 2022, which affected all age groups. With data from CDC's *Respiratory Syncytial Virus Hospitalization Surveillance Network* (2022), children aged 0 to 4 had the highest peak at 64.9 per 100,000 compared to pre-pandemic numbers with a peak of 5.7 per 100,000 in mid-November, this is 1038.6% increase. Children 5 to 17 achieved a peak of 2.5 per 100,000 in mid-2022, which is higher than the peak in 2018 at the same time of 0.1 per 100,000. Other age groups, such as the elderly, also showed a slight increase. These data support the idea that an immunity gap was created by lockdowns. However, the functionality of the immune system is not changed and is incredible at fending off disease and will come into action with strength to build immunity. Some studies say that

during the lockdowns there may be another reason why infants did not catch RSV and other illnesses.

There was concern that infants born during COVID would have changes in the microbiome due to lack of exposure to illnesses, which would cause an increase in allergies. Contrariwise, in a recent study, lockdowns seemed to help the microbiome. As said by Hurley et al. (2022), in Ireland "infants born between March and May 2020 … at 12 months, less than half…had experienced any infective illness and just 17% had received a systemic antibiotic" compared to the UK where "90% of infants… in 2008 had experienced an illness by 1 year, and 80% had received a systemic antibiotic" (pp. 1-2). The most probable reason for the decrease was due to mothers staying home and breastfeeding more often than they would if they were working. Breastfeeding would allow the baby to receive immunity and bacteria from their mothers. Nonetheless, there are positives in having exposure besides the mother. Thus, the results of this study found that lockdowns reduced illness, hospitalization, and the need for antibiotics in infant possibly due to increased breastfeeding, but increased egg sensitization (response to skin prick of allergen) and atopic dermatitis (Hurley et al., 2022). A limitation to this study is the authors only studied Irish children. Thus, more research will be needed in relation to hypersensitivity to allergens and other immune/microbiome related issues potentially found in infants born globally during lockdowns.

So, should lockdowns be implemented? People during the Spanish Influenza 1918 pandemic were not told immediately of the severity of influenza, so when they saw people in vast numbers die around them, they panicked and self-quarantined themselves to a severe extent of not going out to get food (Centers for Disease Control and Prevention, 2006).

Furthermore, it was mentioned by the CDC that "In Phoenix, a rumor started that dogs carried influenza, and people were shooting their pets" (p. 7). Due to the war at the time, the media was filled with propaganda and lied in saying influenza was not something to be worried about. Thus, there was no order or directions for people to follow and they quarantined at an extreme level and did things that were unnecessary like killing their dogs. Which is why it is important that the full truth is told, and not managed. The CDC stated that

> "In San Francisco authorities took out advertisements that said: 'Wear a mask and save your life.' Masks probably didn't help, but people trusted government more and they organized to feed people. San Francisco just seemed to keep operating better" (p. 8).

It is better to tell people the truth and tell people how to adequately handle the situation, so they do not starve due to fear of going to the grocery store or kill their dogs due to false rumors. During the COVID-19 pandemic, people were well notified of the severity of COVID-19. Lockdowns were put in place, but they lasted much longer than they needed too, and there was mixed messaging on masking due to scientists discouraging against them in the beginning but encouraging them later. In the end, it is better for scientists to say what they know, what they do not know, and how they are going to find out what they do not know. There is no definitive evidence that long term lockdowns benefit in pandemics, but shorter-term lockdowns such as the 15 days originally planned could benefit governments in preparation for influx of infections and plan ways to direct people, but also consider freedoms and mental health. It would also remove the risk lockdowns may have on the immune system, such as immunity gaps.

In summation, it is heavily debated whether lockdowns did more harm than good, and this is shown in conflicting literature. However, lockdowns did effectively prevent illnesses such as the flu and RSV from peaking during the first COVID pandemic year, but this caused

an immunity gap that would result in these illnesses, including COVID, surging in 2021-2022. On the other hand, lockdowns did increase the practice of breastfeeding in Ireland, which helped give babies some immunity and needed bacteria, as well as what they receive through vaginal delivery. Lockdowns did increase egg sensitivity and atopic dermatitis in infants, which requires more research. All in all, researchers will need to ponder the benefits and risks for lockdowns and learn as much as they can in the coming years, so that they can decide whether they should be implemented in the next pandemic, or if there are better solutions.

Final Remarks

The COVID-19 pandemic was devastating due to SARS-CoV-2's ability to evade the innate immune system by infecting cells through ACE2 receptors, leading to its ability to affect multiple organ systems. The overproduction of pro-inflammatory chemicals is the primary cause of severe COVID-19, which is more common in older populations due to immunosenescence and comorbidities. Younger people are not as likely to die from COVID-19 due to the immune system's regulated defenses, such as white blood cells, natural killer cells, cytokines, toll-like receptors, T-lymphocytes, B-lymphocytes, and immunoglobulins. Scientists are beginning to understand how SARS-CoV-2 influences the immune system, but more research will reveal how it evades the immune system. Studying previous pandemics and analyzing data from patients infected with COVID-19 are a good starting point. Longer longitudinal studies are also needed to understand how long immunity lasts. More knowledge on COVID-19 will assist in understanding symptoms associated with the disease, finding effective treatments to decrease mortality, and hopefully eradicating the disease one day.

Lockdowns were another result of the COVID-19 pandemic. There is conflicting literature on whether lockdowns saved more lives than it killed due to a failing economy, decrease in health check-ups, and decrease in mental health. Research supports that lockdowns are effective at preventing disease. However, there may be negative side effects. Lack of exposure to pathogens for long periods can decrease immunity due to some memory cells and antibodies having short lifespans, leading to an immunity gap. Thus, there was an increase in RSV and Flu cases after lockdowns lifted. Lockdowns did benefit governmental planning to accommodate how the pandemic would affect hospitals and the economy. Due to the risk of an immunity gap and economic downturn, a shorter time frame may be more

beneficial than a longer time frame. Thus, lockdowns and the influence of SARS-CoV-2 on the immune system will be a topic of research for decades to come.

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