Immunology Primer to Help Understand COVID-19

Overview of Where We are in September of 2021

The following is oversimplified, but I hope it will be useful to many to help contextualize the current situation. So far, from my vantage, this pandemic fight is unfolding in textbook fashion. Based on the data I have seen, all the news is in the "best case scenario" category purely from the point of view of vaccine efficacy. Unfortunately, not enough people were vaccinated in May/June, so predictably after lifting restrictions, COVID-19 is coming back with a vengeance at the moment.

Short Version Prediction of the Future:

I believe there is sufficient evidence, including what we are learning in UT labs including mine, to indicate the vaccine and recovered patient immunity will last well past a year, maybe even for extended periods beyond that. The problem, however, is that not enough people were vaccinated in May/June and now we are experiencing a significantly more contagious Delta variant. As a result, COVID-19 is roaring back among the unvaccinated, and that poses a risk to all of us due to possible virus mutation. That is because the viral mutation rate is proportional to the number of people infected at any one time and too many people around us are infected at the moment.

> *Worst case scenario:* A mutation appears in the coming months that does beat the vaccine, then we will all need a reformulated booster, something that Pfizer and Moderna are already equipped to produce immediately upon identification of the breakthrough variant.
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> *Best case scenario:* The current outbreak fueled by the more contagious Delta variant motivates enough people to get vaccinated so that infection rates decline and become more manageable by September or so, and no breakthrough mutation emerges. To be clear, the current vaccines are still extremely effective against the COVID-19 Delta variant. Very recent studies indicate the Pfizer and Moderna vaccines are around 83% effective against Delta vs. around 95% effective against the original COVID-19 when it comes to preventing infection, and close to 100% effective at preventing serious disease for either form of COVID.

I have been frustrated that few media outlets provide any sort of context for their often alarmist stories. For that reason, if you are curious, the following are some things to keep in mind. I have left out the majority of exquisite details (such as T cells, macrophages, immune cell markers and subtypes, and the role of cytokines) to provide only a low-resolution, "big picture"…although it is still a lot. Sorry for that, but this is a complicated situation.

Immunology Basic Principles

A critical first point is that actual infections and effective vaccinations trigger the same types of responses inside of us. During an infection or vaccination, there are a number of immunological processes to keep in mind, and they operate simultaneously.

Antibody Affinity Maturation*:* We initially respond to a new virus or vaccine using antibody gene combinations inherited from our parents (aka "germline") and these are most often only mediocre antibodies. They help stem an infection, but are not strong enough to win the war. There is a mechanism referred to as *affinity maturation* by which these initially responding mediocre antibodies are improved one mutation at a time until they are extremely potent. This takes up to a couple of weeks.

***Amplification**:* The cells that make antibodies are called B cells. We inherit something like 10^7 different antibody gene combinations from our parents. A given B cell produces many copies of only one of the 10^7 different original antibodies. We have enough different B cells in us at any one time so that all 10^7 are present at some level in our bodies.

During an infection or vaccination, any of these 10^7 types of B cells that makes an antibody *that just happens* to bind the new pathogen or vaccine molecules will start dividing, increasing the amount of the antibodies those stimulated B cells make in the blood stream. The more potent the antibody that a given B cell makes, the more often that B cell is stimulated to divide. This rapid B cell division is often called proliferation.

This amplification from rapid B cell division *combined with affinity maturation* saves our lives during an infection by allowing for an overwhelming number of potent antibodies to fill our blood stream after a week or two, hopefully before the invading virus has done too much damage.

***Differentiation**:* As antibody producing B cells divide during amplification, a small but proportionate number turn into a different kind of B cell called a memory B cell. This process is often referred to as differentiation. Memory B cells accumulate during the response, so generally the stronger the response in a given person, the more memory B cells are produced. Memory B cells are predominantly derived from the B cells making the more potent antibodies because of how all of this works.

Memory B cells have a "hair trigger" and will very rapidly divide leading to rapid amplification if it encounters a new round of virus molecules, even months or years later. A major goal of vaccines is to create this long-term memory B cell response. It can last years, but does wane slowly over time. Different responses have different periods before effectiveness is finally lost. All indications are that COVID-19 memory B cells are lasting past a year, and counting.

How to Think About Viral Infections

OK, so think of an infection as a race. If an infected patient has never seen COVID-19 and is not vaccinated, the virus particles invade certain cells and inside the invaded cells the virus particles are replicated rapidly. The infected cells then die, releasing many newly created virus particles that go on to infect more cells. More virus is made, more cells infected, more infected cells die and release more new virus particles and so on. Initially, the virus has pretty much no significant barriers to being replicated, released, and infecting more cells in *an exponential fashion*.

The immune response is activated by the presence of these foreign virus molecules, but affinity maturation/amplification takes a week or two to start ramping up an effective defense. If the COVID-19 virus had too much of a head-start, a lot of damage is done and the disease is serious. Also, note how greater exposure to more virus particles initially gives the virus a substantially better head-start in the initial exponential infection phase. Sometimes the immune response cannot catch up before there is too much virus damage to cells and the patient dies. Immune systems are degraded in older or otherwise compromised individuals explaining why COVID-19 is worse for these folks. Greater exposure to more virus particles initially can also lead to more severe symptoms.

Sheila (my wife) and I were heavily exposed at our gym on March 12 of 2020, explaining why we became pretty sick. COVID-19 particularly attacks smell receptor cells in the nose, cells in the gastrointestinal

tract, and cells in the lungs to name a few. I have never fully recovered my sense of smell, my wife has. Some people are not recovering other more important functionality after recovering from COVID-19.

Vaccines Activate Our Immune Systems Without Infecting Our Cells

A vaccination with the Pfizer or Moderna vaccine exposes our immune systems to virus molecules, but not whole virus, so none of our cells are infected or killed. These vaccines are incredibly safe and effective. The good news is that because of the way these vaccines are designed, our immune system responds largely the same way to vaccination as it does during a real infection. The difference, as I can attest, is that vaccination *does not harm our cells* like a natural COVID-19 infection does.

The technology that went into these vaccines, especially the messenger RNA (mRNA) approach, took years to develop and has a lot of great research behind it. That is why it has worked so well. Expect a couple of Nobel prizes to be awarded based on this. UT Austin's Jason McLellan also made a key contribution that improved the vaccine effectiveness. COVID-19 is actually a close genetic relative of SARS (recall there was a deadly SARS outbreak in early 2000's), so scientists have been working hard on this family of viruses for more than 15 years. The bottom line is that although it might have seemed like the COVID-19 vaccines came out of nowhere quickly, *the fact is that they represent well over a decade of careful work and breakthrough science that is extremely well-founded in everything we know about immunology*.

Understanding Antibody Levels and Immunity

After successfully fighting the infection, or after a period of time after vaccination, COVID-19 molecules are no longer present, so based on feedback mechanisms the B cells making the antibodies naturally decrease in numbers, leaving mostly only memory B cells from the response. At this point, several months have gone by, and the amount of antibody in the blood stream always wanes. Think about it: If this did not happen, we would keep increasing serum antibodies over our lifetimes as we were exposed to different pathogens and we would have no more liquid water in our blood, only antibodies! Many in the media misinterpreted the natural waning as an indication of lack of immunity when antibody levels in the blood stream subsided. Wrong! We are still protected despite waning antibody levels because of memory B cells.

What Happens When Recovered/Vaccinated People are Exposed to COVID-19?

Once the virus tries to invade a COVID-19 recovered and/or vaccinated individual even with waning antibody levels, the memory B cells are triggered. This causes the equivalent of hitting the virus with a "sledge hammer" of a rapidly amplified and potent antibody immune response before there is much virus present. We often do not feel any symptoms before the infection is eliminated when this occurs. People will, however, sometimes test positive with the highly sensitive PCR test in this short timeframe and could possibly infect others. However, with a healthy immune system, all available evidence indicates that recovered or vaccinated persons are at a very low risk of serious illness if exposed to COVID-19, including the Delta variant.

It is reasonable to assume that significantly fewer virus particles are present in COVID-19-explosed vaccinated or recovered individuals and the virus is present for a much shorter amount of time. As a result, it has recently been confirmed that vaccinated or recovered persons *present a proportionally lower risk of spreading infection* compared to a similarly COVID-19-exposed non-vaccinated person.

Update about Vaccine Effectiveness with the Delta Variant

At this point, almost all COVID infections in our area are due to the substantially more contagious Delta variant. Very recent (but not yet peer reviewed) studies from Utah, Houston, and even Central Texas, all show that the Pfizer and Moderna vaccines are a little less effective against the Delta variant (~83% effective) than they are against the original COVID-19 (~95% effective). Although still the exception, there are definitely more vaccine breakthrough infections with the Delta variant compared to the original COVID. Importantly, however, vaccinated individuals who do end up infected with the Delta variant do not exhibit severe disease, so the current surge in hospitalizations is almost entirely due to unvaccinated individuals who become infected. Unfortunately, these same studies indicate that vaccinated patients experiencing breakthrough infections with the Delta variant do have a relatively heavy load of virus particles, so at this point we must consider such patients to be contagious as long as they have symptoms.

How Dangerous is COVID for Kids?

Much of the current concern is for unvaccinated kids as schools open. An early study found that COVID-infected children were about 20 times less likely to be hospitalized compared to infected adults. In the largest study I can find, the children who were hospitalized almost always had another underlying health problem. In other words, so far, the published information is reassuring that normal, healthy children do not experience COVID symptoms as serious as adults, and by a rather wide margin. However, children do shed virus even when asymptomatic, so they are likely to be capable of spreading COVID, especially the more contagious Delta variant.

How Long Does Immunity Last?

It is still too early to know how quickly the vaccine memory B cell protection diminishes in most people. As an aside, a large blood sample was taken from Sheila and myself on our one-year anniversary of COVID-19 infection to evaluate our memory B cell responses, then we had samples taken again after being immunized. We will compare our immune profiles to the detailed UT study of our original COVID-19 immune responses that is published here (https://science.sciencemag.org/content/372/6546/1108, I am patient P3 and Figure 1 of this paper describes my full immune response to COVID-19). These studies are VERY technically difficult to run and are still in progress, but I do already know that Sheila and my antibody levels were about 2-5X higher, respectively, than what healthy younger people showed after vaccination. This is entirely expected because the vaccination triggered our memory B cell responses. Bottom line: 1 year later our memory B cell responses were solid, easily strong enough to prevent infection or serious illness.

How Effective are Masks?

Masks are incredibly effective at preventing the spread of COVID-19. This is because COVID-19 is spread primarily via respiratory particles. This can happen with pre-symptomatic and asymptomatic patients who are unknowingly shedding virus particles, therefore the absence of symptoms is not a valid reason to avoid wearing a mask. Importantly, if everyone in a room is wearing a mask, **each individual in that room is deriving two benefits: 1)** If a mask-wearing person is healthy, they are significantly limiting the number of virus particles in the ambient air reaching them, and **2)** if an individual is infected with COVID-19 and wearing a mask, they are significantly limiting the number of virus particles they are injecting into the air for all to breath. Because the Delta variant can be passed to others for a short time even among vaccinated people, until the current spike in infections is over, all vaccinated persons should also be wearing masks when they are in groups of people indoors**. It is a simple equation: The more masks that are worn by all of us indoors, the quicker the spike ends and the sooner we all get to enjoy more of our lives resembling the pre-pandemic normal.**

Summary

Here is my own take on the current situation. 1) Because the vaccine is still very effective against the Delta variant, what we are seeing right now is a surging pandemic mostly of the unvaccinated. 2) The media and most people want the vaccination story to be binary, as in each individual will be entirely protected or not at all from the vaccine. It doesn't work that way. It depends on exactly which antibodies a person responds with, how many memory B cells are made, and how many virus particles a vaccinated person is exposed to. It is therefore stochastic, most vaccinated people will respond strongly enough to not feel much of anything when exposed. This would shut down the pandemic if more people just take the vaccine!!

As for how long effective immunity lasts, we shall see. So far, this vaccine has been a strong performer, and I would bet we will get at least two or more years before it loses effectiveness based on the results from Sheila and I after one year. I will know much more about this soon.

What frustrates me is that we had a window to shut this thing down in May/June through vaccination-derived herd immunity. The more unvaccinated people that are infected from here on out, the greater the chance of new variants emerging that might beat the vaccine, then we are back to square one so that everyone needs a booster. Ugh, I hope we never get there. We had our chance to stop this once and for all!! The science worked!!

As for feeling like we are back at square one right now, we are definitely not. If you are: 1) Vaccinated, 2) Have a healthy immune system, 3) Wear a mask indoors, and 4) The virus does not mutate to beat the vaccine then you are protected from serious illness even against the Delta variant. But this current outbreak among the unvaccinated is going largely unchecked so it will get much worse quickly if nothing is done, then it might be spread even faster when unvaccinated young kids (<12 years of age) go back to school. Fasten your seat belts: If vaccination levels and other behaviors do not change, it will get very bad for the unvaccinated until September or October.

Bottom Line.

If you are a vaccinated, healthy person and you, as well as everyone around you, is wearing a good mask, the masks will limit your virus particle exposure to the point that it is exceedingly unlikely you will get seriously ill with COVID-19, even the Delta variant. However, current studies indicate that Delta is indeed more capable of infecting vaccinated people, and vaccinated patients who do experience a breakthrough infection with the Delta variant will be able to spread infection to those around them for a period of time. The latter is an important consideration for anyone with children under the age of 12 or any immunocompromised dependents at home. Note: Kids (<18 years old) are around 20 times less likely to be hospitalized compared to adult COVID patients, and the children who were hospitalized almost always had a previous underlying health problem.

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