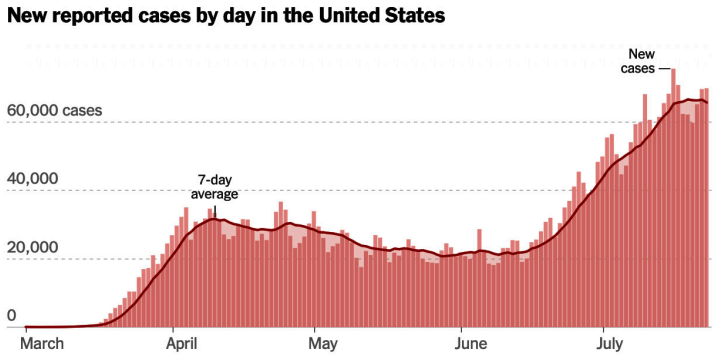
For my daughters: July 24, 2020

The Coronavirus Pandemic

What To Look For In a Vaccine

The hot days of summer have arrived in Saint Louis, with the COVID-19 surge still raging in Missouri and many other states:



What in the world is going on? As you can imagine in our polarized political climate, some people are very scared by this surge, while others shrug it off. Our leaders in Washington have tended until recently to be in the later group, arguing that the higher numbers simply reflect more testing. Besides, they add, all these new "cases" aren't really very sick and death rates aren't rising. It's all been exaggerated, they claim.

I count myself as among the "scared". Everything I read says that the new cases are often quite sick, and death rates – which often lag behind new cases by several weeks – are beginning to rise. We know the surge doesn't simply reflect more testing, because today a far greater fraction of those being tested are scoring positive. So what causes the surge? Our nation has in large measure relaxed its social distancing. – Dr. Fauci gently characterizes our national response as "too spotty." As I have said repeatedly to you in my letters, the key to defeating COVID-19 is to promote social distancing. Many of your fellow citizens stopped doing that in May and we are all of us now paying the price.

This isn't rocket science. We could quickly get back to where we were in June by behaving like we did in June. It comes down to four simple things: wear face masks around others; avoid crowded places like ballparks, zoos and amusement parks; stay out of enclosed crowded rooms like bars, restaurants and churches; open public schools only when COVID-19 case numbers subside in your community.

Unfortunately, our federal government still continues to urge exactly the opposite, pushing for full and complete reopening of all public schools and arguing that face coverings (what used to be called "face masks"), while to be encouraged, should be strictly voluntary.

The Challenge We Face

What in the world are our leaders thinking, abandoning social distancing and ignoring the resulting surge in COVID-19 cases? To calm the nation's anxiety about COVID-19, the White House has proposed *Operation Warp Speed* (A vaccine by the end of the year), and has avoided worry by themselves listening to a vaccine's hopeful promise. "*Hang on*," our leaders are telling the nation, "*there will be a vaccine soon that will eliminate COVID-19*."

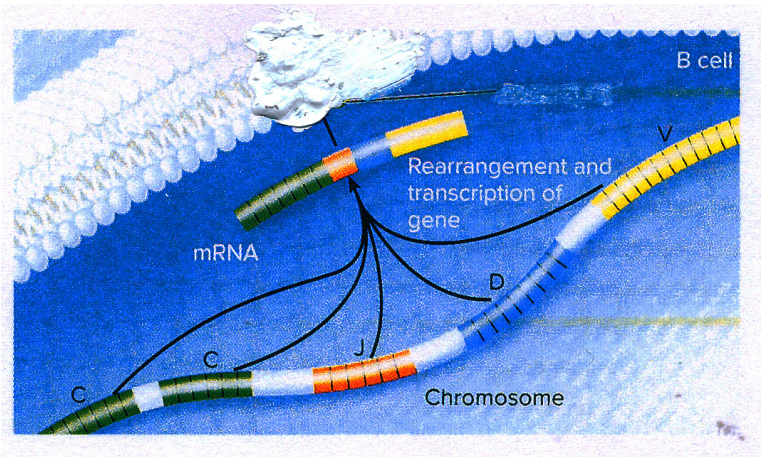
I certainly hope so. All my planning for our family's future depends on a COVID-19-free country in which I can hug my granddaughter and all three of you. But as our nation hurtles toward developing, testing and distributing a vaccine, I want my family to keep a clear eye on where we are going. I do not doubt we will have a vaccine by Spring, or perhaps with luck a few months sooner, but I worry that the development and testing of this vaccine, if rushed too quickly, will fail in its ultimate goal of removing the threat of COVID-19 from our lives.

I am writing you today to give you some background about vaccines and how they are designed to protect you, so that when "Vaccine" day comes next Spring you can make an informed judgement of which vaccine to take, and when. Of course, I will have an opinion on the subject – when have I not? – that I will share with you, but I have raised you three to do your own thinking, so in this letter I am going to review with you some of the stuff you learned in college biology class about the human immune system -- its working parts lie at the heart of the challenge ahead.

Picking Out the Bad Guys

COVID-19 is not the only microbial enemy we face. Every one of us lives our lives immersed in a sea of microbes, many of which are potentially harmful. Bacteria and viruses inhabit every breath you breath, every sip of liquid you drink, every bite you eat. They don't "hate" you, or wish you harm. Each and every one of them, in their trillions, seeks only to reproduce. But they will, if they can, enter into and reproduce within the cells of your body, killing the cells in the process, and sometimes you. Your body has an elaborate defense against the microbes attempting to invade it called the immune system, which is why we don't often get "infected" and sick. When a virus like COVID-19 gains entrance to your body, it is this immune system that protects you.

Your body contains about 200 different kinds of cells -- blood cells, muscle cells, nerve cells and many others. Among the many kinds of blood cells are those of your immune system. One type plays a key role in invader identification. Called a B cell, each one of these cells starts life the same, containing a long protein-encoding gene. This gene is built like a pearl necklace, a chain of many segments. Each segment has dozens of members, all similar to each other but each slightly different. Now here's the thing: When you are born, each B cell selects at random one or a few member of each segment (C, J, D & Y in the diagram below), and joins these selected bits together into a composite gene. The protein encoded by this composite gene is Y-shaped and called an antibody.



This random assembly of a gene sequence from a library of bits can generate a lot of different sequences! It's like shuffling a deck of cards and dealing a hand of 5 cards: there are only 52 cards in the deck, but there are more than two million possible 5-card hands (actually, 2,598,960). Here, because no two B cells make the same choices, the deck is shuffled for each cell so that the few hundred segment types within each B cell can potentially produce one of some 19 million different possible amino acid sequences.

Each B cell, having made its choice, produces just that one sequence – but there are lots and lots of B cells, each having made different independent selection of bits for its composite gene. The antibody protein encoded by a particular composite gene will bend and twist into a certain shape, but here's the thing: with so many different kinds of B cells, each with its particular composite gene, there are an awful lot of different kinds of antibody proteins being made -- any foreign molecule imaginable would fit closely to ("bind") the antibody made by at least one of them.

To understand how a vaccine uses these composite proteins to recognize a potential COVID-19 infection, we need to start with a key question: How does your immune system know what cells are you, and what are bacteria or viruses like COVID-19? The answer is simple, but takes a little explaining. Imagine you have a bag of mixed jelly beans. You are going to place them out at a party for guests to eat, but hope they don't eat all the cherry ones, as they are your favorites. How can you be sure they don't? By removing all the cherry ones before the party! The guests won't eat them, because they will not be there. It's that simple: remove what you would protect.

That is, in essence, how your immune system identifies invaders – by removing those B cells that would attack non-invaders. When you are an infant, your body runs its collection of B cells past the 200 different kinds of cells in your body, and removes any B cell making an antibody that can bind to any of your body's cells. What is left after this screening process is a collection of B cells able to recognize (bind to) any cell or molecule that is "not you." All the ones that could recognize your cells have been removed -- like removing all the red jelly beans! Neat! There are of course a lot of details I have not mentioned in this brief account-- cells called T cells that play a key role I have not told you about yet, cell interactions I have blithely ignored -- but this is the core idea, the answer to the key question of how your immune system picks out the bad guys – so simple its beautiful.

Neutralizing an Infection

The antibodies made by B cells are not weapons that kill COVID-19 particles. They are tools your body uses to identify the virus particles and render them harmless. How do they manage this? By binding to molecules on COVID-19 which the antibody recognizes as foreign. We call such "not us" molecules *antigens*. This binding renders the infecting COVID-19 particle no longer harmful – it *neutralizes* the infection. How? Well, binding to the virus particle, the antibody may simply prevent it from interacting with a human cell – just as wrapping your arms around a person prevents that person from meeting and shaking hands with someone else. Alternatively, the antibody may bind to a cell surface receptor on the human cell the COVID-19 virus is trying to enter -- like blocking a door by standing in it.

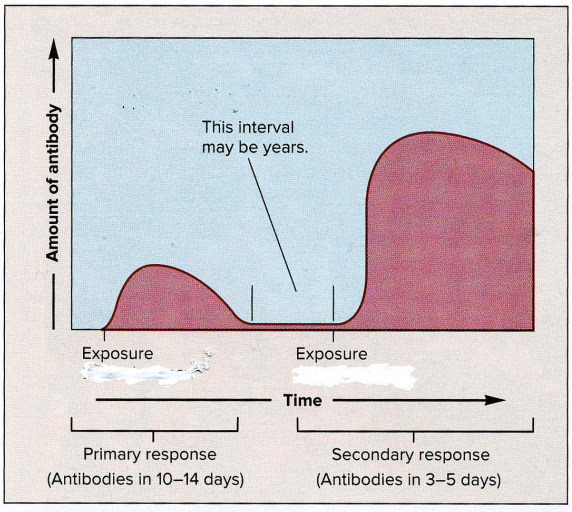
Often, however, the antibody arrives too late to prevent COVID-19's entry into a human cell. The virus has already gained entry and is busily making new COVID-19 particles within. Well, here we catch a break: protein bits of the virus are exported onto the surface of the infected cell (don't ask – it's complicated). These bits can be and are recognized by another part of your

immune defense that I have not told you about yet, called T cells. Like B cells, T cells are able to recognize foreign proteins. An army of different T cells patrol your body, scanning the surfaces of cells looking for any that display any bits of virus like COVID-19. When a T cell finds such a virus-infected cell, it kills it by rupturing the cell membrane, and so stops the infection from spreading to other cells.

Now it's a race between COVID-19 infecting and multiplying within your body's cells on the one hand, and your body's immune defenses on the other. Time to amplify your immune system's attack on COVID-19! What your body's defenses need when infected with COVID-19 are lots more B cells to grab onto the COVID-19 virus particles to block their entry into cells, and lots more T cells to kill those cells already infected with COVID-19. To achieve this, both B and T cells start madly reproducing, until there are billions of offspring of that particular version of B cell or T cell that recognized COVID-19 – each one of those billions of cells furiously manufacturing its particular antibody protein or killer T cell. The killer T cells hunt down and kill all COVID-19 infected cells, while antibody proteins made by B cells bind to any and all COVID-19 particles in your bloodstream, flagging them for destruction by macrophages (cells your body normally uses to recycle dead cells) and killer T cells. Macrophages and T cells do their killing in different ways, but again we will not go into the details here. The important point is that a lot of killing gets done. This first event in immune protection is called the primary response.

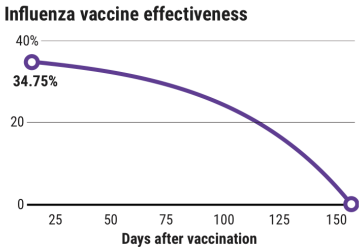
Protecting Against Future Infection

If that were all there was to it, there would be no long-term protection, just an immediate elimination of a present threat. There is no promise here of an infection-free future. BUT something minor but incredible now happens: a few of the killer T cells and antibody-manufacturing B cells sort of go into hibernation. Called memory cells, thousands remain long after the infection has been conquered -- not doing anything, just waiting. If in the future your body encounters the same invader, all of these memory cells are ready to spring into action, dividing madly and quickly filling your blood vessels with neutralizing antibody specifically directed against that invader, and T cells already specialized to kill any cells a virus like COVID-19 manages to enter. Called the secondary response, this provides your body with long-term protection – once infected and recovered, you are immune to subsequent infection!



But For How Long?

Vaccines developed for measles and other diseases often confer immunity for many years, some for a lifetime, so it's easy to fall into the assumption that a vaccine you take for COVID-19 will protect you for many years. That need not be the case, however. Flu virus mutates so frequently that new vaccines are required each year:



How about coronaviruses? There's the rub. There are seven coronaviruses that commonly infect humans: SARS, MERS, COVID-19, and four common-cold coronaviruses (229E, HKU1, NL63 and OC43). From 60 years of research we know that the common-cold coronaviruses come back year after year and infect the same people over and over again. In a New York City study conducted between 2016 and 2018, antibodies to these coronavirus increase sharply after infection and peak after about two weeks. But their presence then declined, disappearing entirely in 4-8 months.

What happened to immunity from these coronaviruses? Flu evades immunity by mutating frequently, so every year we face a different virus. Coronaviruses, which unlike flu do not mutate frequently, present our immune defenses with a different challenge: Antibodies directed against common cold coronaviruses seem to fade quickly, with little or no memory remaining of the infection. Is COVID-19 different in this respect from the common cold coronaviruses? This month researchers from England reported that it is not – the transient neutralizing antibody response "*is a feature shared by both the COVID-19 infection that causes low disease severity and the circulating seasonal coronaviruses that are associated with common colds*." Essentially, the more time that passes, the fewer antibodies a person retains. Why? This is not well-studied. Are there fewer memory cells? Not known. Are other aspects of the immune system failing us? We just don't know – yet.

The point is, our coming vaccines may work very well in triggering initial production of neutralizing antibodies without providing T cell defenses or long-term protection. I do not mean to be a Cassandra predicting doom and gloom. Quite the contrary. I am very optimistic, long term. We are trying many different approaches in developing a COVID-19 vaccine, and they can be expected to differ quite a lot not only in B and T cell neutralizing ability but also in the degree of long-term protection they provide. We are going to get the right answer, I do not doubt – but perhaps not immediately. That is why we test vaccines. It will take time. Not warp speed, but, if we follow the science and not politics, a sure destination.

Our Family

What does all this mean for our family? We should wait a bit, I think, as the first vaccines are announced triumphantly, and examine the phase-three trial results carefully before selecting a vaccine to take. These results will reveal if the primary response is effective at neutralizing COVID-19 infections – so long as the data are not kept from the public. How do we judge if the

primary response is effective? I would look for evidence of strong production of both neutralizing antibodies and activated T cells, and insist on 70% protection from COVID-19 infection, rather than the low-bar 50% protection that the FDA says will be its national standard (I bet they will release even 25% protective vaccines as "emergency treatments" that do no harm and some good, although they today swear they will not).

The secondary response? We can't know for some months after widespread vaccinations start. If long-lasting, COVID-19 will, within a year of today, be history. If not, COVID-19 vaccination will become a recurrent necessity – just as it is with the flu. We will see. As we wait, we are looking at another year of social distancing. Then, with a little luck, that too will be history.

Can We Fly?

One question you girls have asked me about these COVID-19 times: If we must wait until next Spring for the safety of a vaccine, can we somehow visit each other in safety while we await that day? Spread between Missouri, New Mexico, Georgia and soon New York, a lot of miles separate us. How to get together?

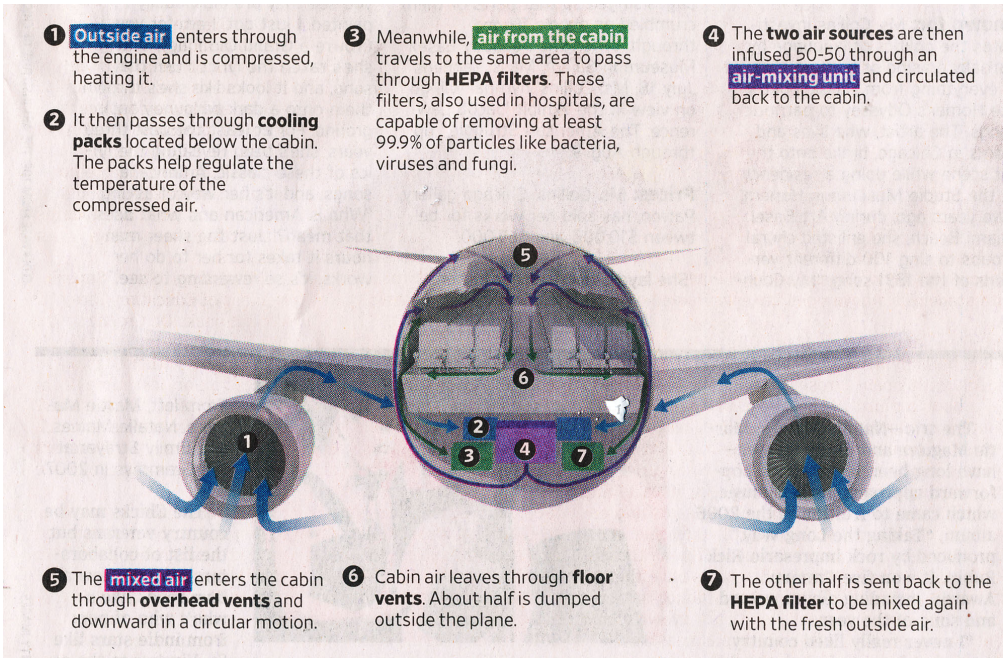
1. **Hike.** Well, it's too far to walk.
2. **Drive.** Driving is not an appetizing alternative, either. It would require a long day on the road (550 miles -- about 8 hours of driving) for mom and I to travel to Atlanta to visit Sue, with pit stops and restaurants where infection would be a very real danger. Visiting Caitlin in Santa Fe (1,000 miles over some 16 hours) would be a two-day trip, with the added hazards of staying overnight at a motel. Driving to New York City (980 miles and 15 hours) would be another two-day expedition. I don't see us driving.
3. **Train.** Taking a train (or bus) puts us in close contact with other passengers for protracted periods. Would you believe it takes a train 26 hours to get you from St Louis to NYC? And going to Atlanta takes even longer! This presents way too much risk.
4. **Airplane.** Flying also puts us in a closed space with other passengers, but takes only a few hours. I last hugged my granddaughter when she was a few weeks old, and if I want to do it again before her first birthday, mom and I are going to have to fly to Atlanta. The same goes for visiting Santa Fe and NYC – flying is the only practical way to get there.

Is flying safe enough in this age of coronavirus? It's hard to get hard data. While it is clear COVID-19 *can* be transmitted on an airplane, there are very few reports of this actually happening. A survey of 18 major airlines I unearthed identified only a few COVID-19 episodes. However, respiratory viruses like SARS and flu have spread on aircraft, much of the risk coming in flights longer than 8 hours.

So I don't know how to measure "safe enough." What I can do is suggest ways we can make it *safer*. The key to reducing risk is to avoid close contact with other passengers. There are lots of things we can do to minimize contact. For starters, we should check in and get our baggage stickers ahead of time, so the bags can be rapidly deposited at the airline check-in counter. Of course, no shopping for Starbucks or dad's candy bars as we walk quickly through the airport to our gate. There, the lines entering and leaving the aircraft offer the biggest danger to our family, with people often crowded together. A three-foot distance between individuals should be maintained (if our family travels business class, we can board last and leave first, which will further minimize this problem). As we enter and leave the aircraft, it will be critical

that each of us wear a face mask. Our trying not to use the in-flight toilet will eliminate another source of potential contact with others. At the other end of our flight, we should wait for others to depart the area before we pick up our bags at the baggage carousel. Simple stuff, but these measures will eliminate much of the risk of flying in commercial aircraft.

How about the danger of becoming infected while on the airplane? How much risk do other potentially COVID-infected passengers pose? Not a lot, in my view. In modern airplanes, cabin air is a 50-50 mix of sterile outside air and recirculated cabin air that's been filtered through HEPA filters which capture particles even as small as a virus:



With such efficient air exchange and filtration, I don't see much risk of transmission of COVID-19 from aerosols in the cabin air. Large droplets ejected by coughing or sneezing, however, are too big to be efficiently sucked away through the floor vents, so the real danger is the person sitting next to you. The best we can do -- wear our face masks all during the flight. That's what the stewardesses do, and airlines report that flight attendants spending many hours on airplanes have rates of infection little different from desk-bound employees.

Bottom line: It's time to make plans to see each other. Jed, prepare for a hug.

Dad