For my daughters: November 13, 2020

The Coronavirus Pandemic

There's Bad News and There's Good News

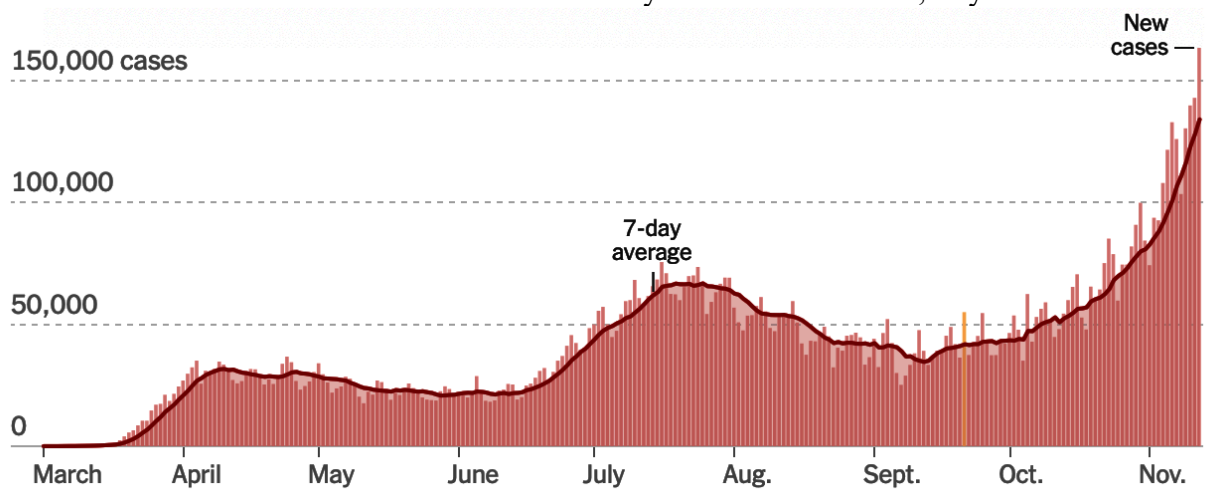
Your mother and I have been back from Atlanta for twelve days and it seems a month, so much has happened in the last week. We have a new president-elect, who is moving rapidly to properly address the COVID-19 pandemic (it exploded past 100 million cases in our country yesterday). He will push for far more rapid testing and contact tracing when he assumes command January 20, Biden said today, and in the meantime he pleads with state governors to mandate the wearing of face masks. Spot on, if you ask me.

In the meantime your mother and I have completed the battery of health tests we started before our Atlanta jaunt. My colonoscopy was clear, as was your mother's last month. My kidney doctors tell me I am stable ("*solid as a rock*") – while my filtration rate is far below normal, it is stable and not worsening, which seemed to please the docs no end. Me too. I am allowed grapefruit juice (hot damn!) and encouraged to exercise. As you all no doubt know, I continue my many-years-long workout program (over 25 years!) with Suzy Madden, one hour in the afternoon, three days a week. Of course I don't drive to her studio in these COVID times. Instead, we ZOOM-ercise, she in her studio and me in our basement:

Seems a little bazaar, but actually works out quite well.

The Bad News: Skyrocketing Infections Continue

In my letter last week I told you that the United States had begun a steep upward curve in daily new COVID-19 infections, with 100,000 cases a day. I suggested that the sharp rise in infections was due to the arrival of fall weather, and pointed to a similar sharp rise in Europe coinciding with the arrival of cool fall weather there. That scary trend has continued, as you can see:



Yesterday we had 163,405 cases in one day. It doesn't take a genius to see where the curve is going if nothing is done to slow community transmission in the United States – just take a ruler and draw a line up along the 7-day average line into December and look at the case numbers you cross as the weeks go by. You are looking at 200,000 cases a day by Thanksgiving, and over 300,000 cases a day by Christmas. And these numbers are no exaggerated "scary tale" – they are the numbers Europe (with the same size population as our country) has been seeing. Europe's daily new case number before clamping back down this week went as high as 337,389. Yesterday they were 290,372, still a scary number.

This is why Fauci's and now Biden's efforts to encourage the wearing of face masks by everyone are so important. However promising the vaccine news being reported this week, there is no way an appreciable number of Americans can be vaccinated before Spring, and the virus is exploding NOW. We must survive the winter to benefit from vaccination in the Spring.

More Bad News: Animals May Become Virus Reservoirs

And if this wave of coronavirus infections within United States communities isn't enough to get your attention, recent data suggest animals may become reservoirs for the coronavirus to resurface at any time. Many mammals can be infected with the coronavirus, which easily passes to them from humans. Dogs, cats, tigers, hamsters, monkeys, ferrets and lab mice have all been reported infected with human strains of COVID-19. As I have said to you girls before, I don't let other people pet Paddington. There are no masks for puppies, but she is very socially distanced.

In Denmark the COVID-19 virus has been transmitted from humans to mink. They raise mink for fur in Denmark, a major cottage industry in a country of small farms. In my days as a visiting scholar at Aarhus University (forty five years ago!), one of the faculty with whom I shared a lab lived on such a farm, and raised mink along with the farm's major focus, lambs. I visited the farm many times. It had been in her family for generations, although the mink were her addition to the farm's livestock.

Mink are seen at a farm in Gjol, Denmark.

This fall the coronavirus seems to have passed from Danish farmers to mink, and then back to humans again, the virus having mutated in the process. One of the new variants, found in 12 people so far, may have become more dangerous. When studied in the laboratory, this variant altered the virus spike protein in such a way that infected lab animals were less responsive to antibodies than mice infected with the common strain. Because this suggests that people infected with the mink variant of COVID-19 may be harder to treat, Denmark is culling (polite for killing) ALL of the mink in the country, some 17 million animals!

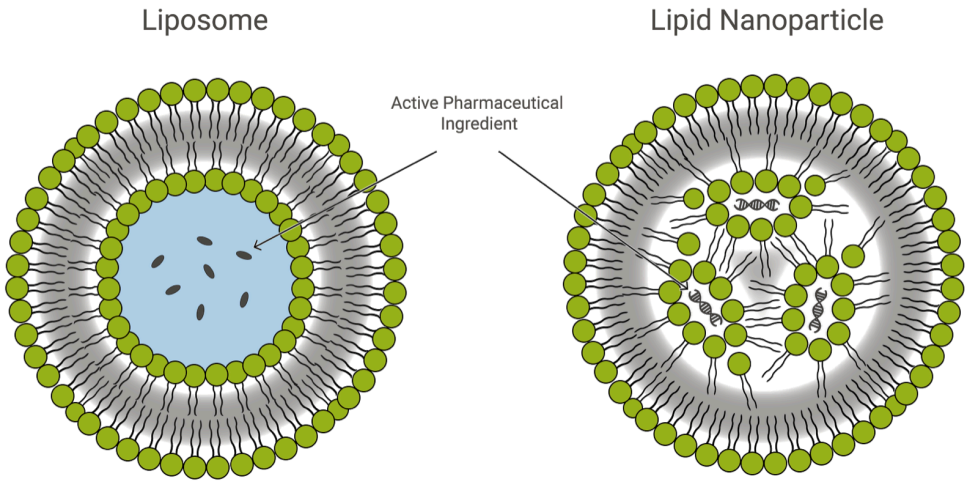
The Good News: An Effective Vaccine Is Near

The good news is very good indeed: a vaccine against COVID-19 seems to work, and work very well. In my letter to you girls last May 16, I outlined five approaches being used to develop a vaccine, two of which were the focus of USA and European efforts. Both of these approaches sought to introduce into patients the virus gene encoding the COVID-19 spike protein, the idea being that if the patient's cells could be induced to manufacture the spike protein, the patient's immune system would respond by producing antibodies and T cells directed against the spike protein. These antibodies and T cells would then protect the patient against any future infection by the COVID-19 virus. Simple, clear, and likely to work. The two approaches differ in how they introduce the virus gene into human cells:

1. **Piggyback.** Vaccines developed in the United States by Johnson & Johnson and in England by Oxford (Astro Zeneca) introduce a DNA version of the coronavirus spike gene into human cells as a passenger carried in by another harmless virus. For the harmless virus, both developers chose adenovirus, which is very good at getting into cells. The researchers first removed one of the adenovirus genes, so the adenovirus cannot replicate and thus is safe. Then they added the COVID-19 spike protein gene in its place. Once the adenovirus introduces the COVID-19 gene into human cells, these cells can proceed to manufacture spike proteins and trigger a protective immune response. This "recombinant vector" approach has been employed successfully recently against Ebola. Both the Johnson & Johnson vaccine and the Astro Zeneca vaccine are now in late-stage testing.

2. **In Fat Bubbles.** Two other vaccines have taken a radically different approach. One was developed in the United States by Moderna (Cambridge, Mass) working with the National Institute of Allergy and Infectious Diseases (NIAID), and the other in Germany by BioNTech, which has partnered with American pharma giant Pfizer. Both of these vaccines take advantage of a technology developed to fight cancer with small bits of RNA. Called RNA interference, this technology won the Nobel Prize in 2006.

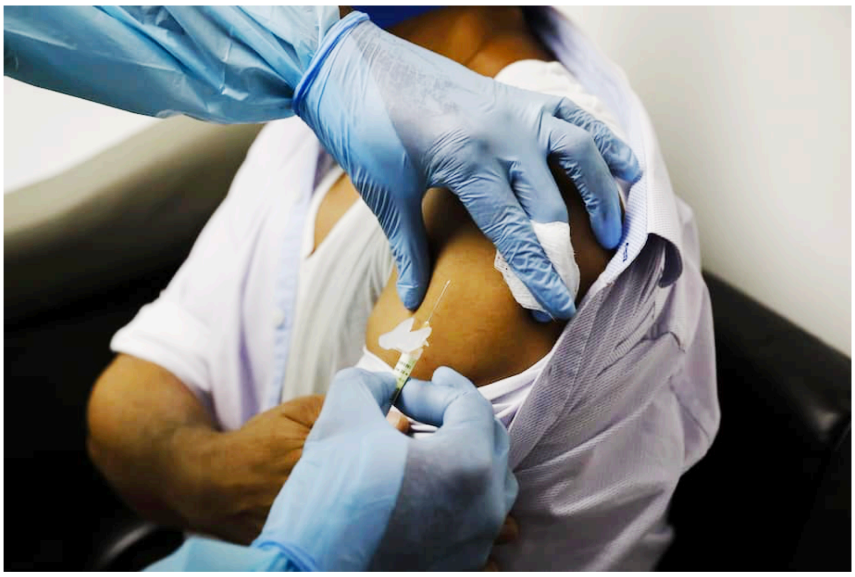
   To introduce the bits of RNA into human cells where they can shut down cancer-causing genes, researchers had created a really neat delivery vehicle, the lipid nanoparticle (LNP). You may remember from your biology classes that human membranes are made of lipid molecules, each with a polar (water loving) head and two nonpolar (water hating) tails – think of two snakes sharing one head. Left alone in water, a bunch of these lipids will spontaneously form a sphere, with the polar head facing outward towards the water and the tails facing inward where there is no water. The sphere is called a liposome. A lipid nanoparticle is a liposome in which a small bit of RNA is added to the interior of the liposome. This both protects the RNA from injury and insures that a patient's immune system doesn't attack it before it can enter the relative safety of a human cell. Each pharma company develops its own closely-held procedures for coating the LNP to stabilize its cargo and target it towards particular human cell types.



Testing the BioNTech Vaccine

The first of the four vaccines to report results is the LNP vaccine developed in Germany by BioNTech. Accepted no funding from America's Operation Warp Speed, the German company was free to adopt a very aggressive testing protocol. Partnering with Pfizer, they conducted phase one and two trials on two different RNA molecules targeting different parts of the COVID-19 spike protein, then selected the one with the fewer side effects for phase three trials. For phase three, they enrolled 30,000 subjects in the United States and other countries, and later expanded the trial to 44,000. Half of the subjects were given the vaccine (two doses) and half a saline placebo. Then the trial waited for people to get sick. You get the idea: if the vaccine is no good, then as many sick people will occur in the test (vaccine) group as in the control (placebo) group. If the vaccine is effective, then fewer of the sick people will be in the test group.

An outside panel of independent experts called a "data safety monitoring committee" has the only access to the data as the trial proceeds. The BioNTech trial was initially set up with a COVID-19 infection target of 164, which meant that when 164 cases of COVID-19 occur, the trial is complete. At that point, the monitoring committee informs BioNTech and Pfizer how many of the 164 COVID-19 cases were in the test group and how many in the placebo group.



Pfizer coronavirus vaccine trials take place in Hollywood, Fla., in September. (Eva Marie Uzcategui/Bloomberg)

For a variety of reasons, vaccine developer BioNTech/Pfizer wanted to know in October if they were backing a winner. They had invested over 2 billion dollars of their own money, and investors were getting nervous. They requested a "peek" after 32 people in the trial developed COVID-19, but regulators at the F.D.A. urged the developer to wait for 64 cases, when a more reliable initial assessment could be made. By the time the paperwork for this was completed last Saturday, 94 cases had accrued (the fall spike in USA coronavirus cases!). The independent board met immediately to look at the data. At 1PM Sunday the board informed BioNTech/Pfizer of a stupendous result: the vaccine was 90% effective! 50% would have been considered a success; this was a home run. Dr. Fauci called the trial's preliminary result "*Extraordinary*!"

When Can We Get It??

It is important to keep in mind that the BioNTech phase three trial is not over. We are only just over half-way there. With the soaring number of COVID-19 infections, a few more weeks should see us to the 164 cases. Then with the trial completed we can begin to access a number of serious questions: Is there a difference between asymptomatic, slightly ill, and quite ill patients? BioNTech designed their trial limiting subjects to those in good health. What about those with pre-existing conditions? How much of the 90% protection is short term (antibodies – as short as a few months) and how much long term (T cells – as long as several years)?

A big problem with this particular vaccine is that the LNP used is not temperature stable. Even a slight warming destroys its effectiveness. It must be kept ultra-cold, at negative 94 degrees F. So with this vaccine we are not going to be able to go down to the local pharmacy for a COVID-19 shot. Centers will have to be set up with the proper vaccine storage facilities and

the capability of rapid thru-put. Here in Saint Louis, professors I know at Washington University and UMSL have already been contacted by the government about their labs potentially having cryogenic capability (ultra-low freezers). Shipping the vaccine to locations around the country will require special freezer capacity. So while widespread use of the BioNTech vaccine will certainly be doable, the problems it presents are not trivial. Careful planning will be the key.

Today the European Union contracted with Pfizer/BioNTech to purchase 300 million doses of this LNP vaccine. In this country, the Pfizer plant in Michigan has already manufactured 100 million doses purchased last July by the U.S. Dept of Health & Human Services and the Dept of Defense. The vaccine is being stored in 3560 ultra-cold freezers awaiting FDA approval before distribution begins. If all goes well, the July agreement allows the U.S. government to acquire an additional 500 million doses. Health care workers are likely to be the first to get shots, and this alone could take several months. Dr Fauci said today that shots will likely be available for most Americans who want them by April. My best guess is July.

The Other LNP Vaccine

And then there is the other LNP vaccine in late-stage testing. Manufactured by Moderna/NIAD, it employs almost exactly the same COVID-19 spike gene as the BioNTech vaccine, but uses a different formulation of LNP. This formulation, while perhaps a little less infective, is more temperature-stable. The vaccine can be stored at negative 5 degrees F, not ultra-cold like the BioNTech vaccine requires, but still a bit colder than your household freezer.

The phase three clinical trial of the Moderna LNP vaccine is not yet complete. It involves 30,000 participants, with half receiving the vaccine and the rest a saline placebo. The target for the trial has been set at 53 of the participants becoming ill with COVID-19 (much less than the 164 cases required for the BioNTech clinical trial). As the trial hit that mark yesterday, the independent Data Safety Monitoring Board is expected to soon announce a preliminary assessment of the vaccine's effectiveness. Dr. Fauci is hopeful. "*Moderna has an almost identical mRNA*", Fauci told the Financial Times Wednesday. "*I would really be surprised if we did not see a high degree of efficacy. I'm fairly certain it's going to be up there*."

And the Other Guys?

Do not forget the piggyback vaccines also in phase three trials. While requiring refrigeration, they will not have the difficult ultra-low temperature requirements of the LNP vaccines. The furthest along is an adenovirus recombinant vector vaccine being developed at the Gamaleya Institute in Moscow, Russia. Dubbed the Sputnik V vaccine, it is just emerging from a 20,000 subject phase three clinical trial. We are told by the Russians that an initial peek at the data after 20 COVID-19 cases suggests 92% effectivity, although with such a small sample it is difficult to place much confidence in this estimate.

And the two other piggyback vaccines in late stage trials? Both are similar to the Russian Sputnik V vaccine in design, using an adenovirus vector to transport a COVID-19 spike gene into human cells. For both the Johnson & Johnson vaccine and the Oxford (Astra Zenica) vaccine, we are expecting to see results of their clinical trials within a month or so.

Until that day. Much love.

Dad