

For my daughters:

November 21, 2020

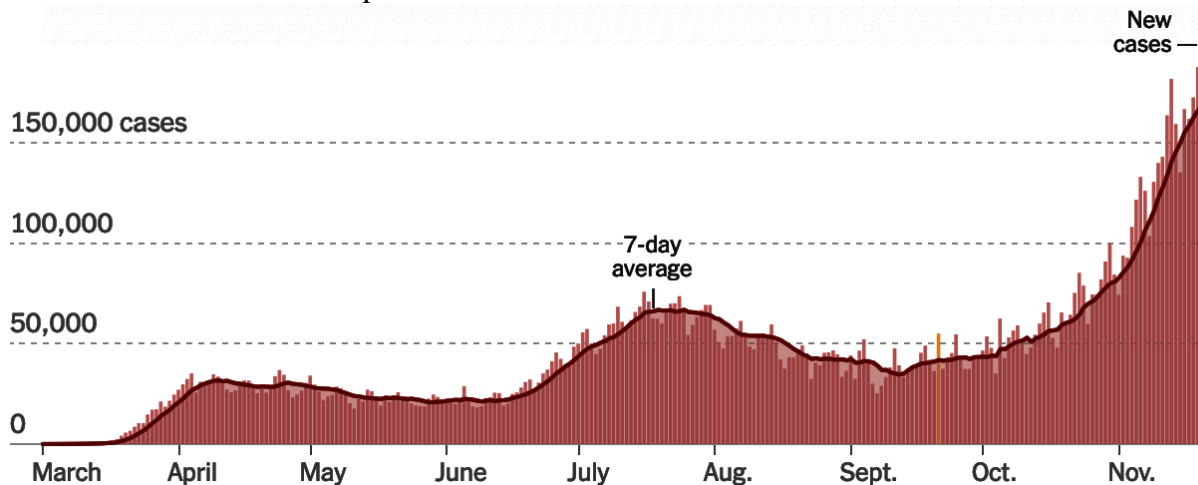
The Coronavirus Pandemic

There's Much to be Thankful For

With Thanksgiving fast approaching, our family has much to be thankful for. While your mother and I have friends afflicted by COVID-19 and I'm sure each of you do too, we can be grateful that none of us have been infected. We will not share a turkey dinner together this year, all clustered together with relatives and friends along a long table, but with luck and care there will be many turkey dinners in our family's future. In this letter I will hit you with the bad news first, then move on to the good stuff. In these black times there is bright promise, if we can just hang on.

The Bad News

Today marks 302 days since the first case of COVID-19 was reported in this country. There have been 12 million since that day. Back in March, when the danger posed by the pandemic was first becoming clear, Dr. Fauci predicted that as many as 240,000 might be killed. Few took this prediction seriously then, but this week we passed 250,000 COVID-19 dead, and recent weeks have seen an explosion of new cases:



One of every 11 coronavirus infections in the United States this year was recorded in the past week! Today alone we saw 198,537 new cases. In some states in the upper Midwest, the pandemic's grip is tightening fiercely. This is particularly true in states like Iowa with low virus regulation. Yesterday in Iowa there were 4,337 new cases, and the positivity rate (the proportion of tests that are positive) was an alarming 50%. Among the Iowans infected this last week were my McGraw Hill publisher and her husband, who live in Dubuque. They are raising a fine crop of Cubs fans, and I wish her and her family all the best in what must be a terrible week for them.

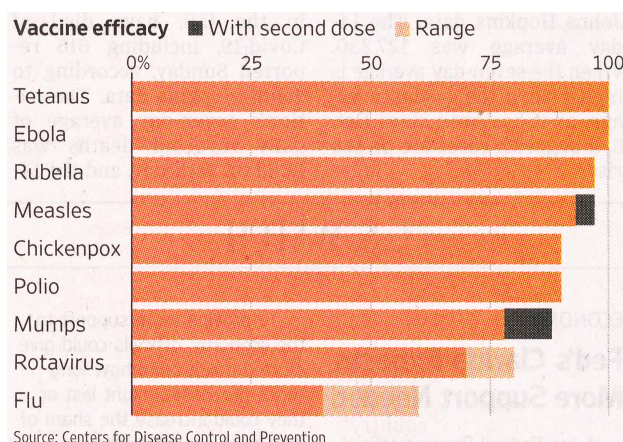
And a lot of people are dying. 1,947 Americans died of COVID-19 today – more than one every minute. This horrible death count will only increase as the flood of people infected in the last two weeks begin to add to the daily death total. We are looking at 3,000 deaths a day by Christmas.

The Good News

The good news, of course, is that the long-promised vaccines are starting to arrive – and they work very, very well. The Phase Three clinical trials of the Pfizer vaccine are now complete, and the results couldn't be nicer. Among 170 cases of COVID-19, fully 162 were in the placebo group and eight were in the vaccinated group. That's 95% efficacy. There were 10 cases of severe illness in the trial, all but one of them in the placebo group. The Phase Three clinical trials of the similar Moderna vaccine look just as nice: Of the 95 cases of COVID-19 reported to date, 90 were in the group that received the placebo. Again, 95% efficacy. There were 11 severe cases reported – all in people who received the placebo. This person is getting the Moderna vaccine:



It doesn't get any better than this. Many vaccines are far less effective:



And these are just the first vaccines to reach the finish line. Nine others are in Phase Three trials, some of them very promising. On the next page I have built you a scorecard so you can keep track as these other candidates finish development. We won't have to select one for ourselves till Spring, I suspect. By then we should know quite a bit more to guide our choice.

A VACCINE SCORECARD

There are five general ways to present COVID-19 antigen (bits of the virus) to a patient so as to invoke an immune defense. All are being tried in attempts to develop an effective vaccine. These are the dozen COVID-19 vaccines in late-stage clinical trials:

1. **Recombinant Vector Vaccines.**

Insert the COVID-19 gene for spike protein into a harmless virus and infect patient with it. This is the approach taken recently against Ebola, with 100% efficacy.

- *Gamaleya (Russia)* Reported to be 92% effective in as-yet incomplete Phase Three clinical trials, but estimate of effectiveness is from a very small sample.
- *Johnson & Johnson* Phase Three clinical trials, delayed for a month after illness in a participant, now nearly complete; no preliminary results reported.
- *Oxford/AstraZenica* Phase Three clinical trials, delayed for a month after illness in a participant, now nearly complete; no preliminary results reported.
- *CanSino (China)* Phase three clinical trials just beginning (in Russia).

2. **Live Attenuated Vaccines.**

Infect patient with COVID-19 virus particles damaged in a way that renders them harmless without killing them. This is the approach taken in the past with many commonly-used vaccines such as those directed against chickenpox, measles, mumps and rubella.

- *Sinovac (China)*. Phase Two trials were disappointing, with antibody levels lower than those seen in recovered patients. Phase Three trials incomplete. This vaccine already adopted by Indonesia.

3. **Inactivated Virus Vaccines.**

Simply “kill” the virus and inject it into patient. This is the way the Salk polio vaccine was produced. Your seasonal flu shots are another example of this very direct approach.

- *Sinopharm (China state owned)*. Two vaccines in Phase Three clinical trials, one of them also informally administered to 100,000 patients, reportedly successfully.

4. **Subunit Vaccines.**

Inject actual COVID-19 proteins into patient. This is the approach used to make the vaccine for hepatitis B.

- *Novavax*. Antigen is the virus spike protein. Just entering Phase Three clinical trials. Phase Two trials produced markedly more antibodies than any other vaccine.
- *Sanofi/GlaxoSmithKline*. Antigen is a recombinant virus protein. Still in Phase Two clinical trials.

5. **Nucleic Acid Vaccines.**

Inject a solution containing spike-gene mRNA molecules into patient. This approach has never been used before, anywhere in the world.

- *Pfizer/BioNTech*. Proven 95% effective in completed Phase Three clinical trials. Emergency approval by FDA pending. Potential problem are that the vaccine must be kept ultra-cold, and efficacy requires two doses.
- *Moderna/NIAID*. Proven 94% effective in as-yet-incomplete Phase Three clinical trials. Also requires two doses, but Moderna says it can be stored in a refrigerator.
- *Sanofi/TranslateBio*. Still in Phase Two clinical trials; induced high levels of antibodies in Phase One clinical trials.

A Quick and Easy COVID-19 Test

Remember last August when I wrote to you girls of a new COVID-19 test? I was so excited that I added a long appendix to my letter describing in detail the chemistry behind the new approach. I did --- and do -- think the underlying chemistry is beautiful. The gold standard test for COVID-19 looks for the virus genetic material using a DNA-multiplying technique called polymerase chain reaction, or P.C.R. The P.C.R. test involves an uncomfortable nasal swab and typically takes two or more days to yield results, as samples must be sent to a centralized lab and analyzed by lab techs using a complex procedure. The new COVID-19 test that so excited me in August was a much simpler at-home test that yields results within 30 minutes!

The new test also relies on amplification of the virus genetic material, but uses a different method called loop-mediated amplification, or LAMP. LAMP recognizes COVID-19 genetic material and copies it, ignoring any other non-virus stuff – and the copies it makes then loop out and themselves get copied, and these copies loop out... until the amount reaches detectable levels revealed by a simple pH dye (remember, genes are made of nucleic acids, which are acidic). This powerful amplification, which only occurs if COVID-19 genes are present, makes it possible to identify the virus even when present at only very low levels in the respiratory tract.

People can take the battery-powered LAMP test at home. They first swirl a swab in their nostrils, then dip and stir the swab into a vial of chemicals. The vial is then plugged into a test cartridge that processes the sample. In less than half an hour, the test cartridge will light up as “positive” or “negative.”

How well does the LAMP test work? According to its manufacturer, Lucira Health Inc., this LAMP test was able to accurately detect 94 percent of the infections found by the standard P.C.R. test., and correctly identified 98% of healthy people found to be uninfected by the P.C.R. test. What Lucira doesn't tell you is that this “testing” of the Lucira test was carried out only on people with COVID-19 symptoms or known to be healthy. What we really need to know is how it compares with P.C.R. when testing asymptomatic patients. A double-blind test such as we are seeing in Phase Three vaccine trials would quickly sort this out.



The Food and Drug Administration authorized limited use of the Lucira COVID-19 test this week. It will cost about \$50 and deliver results in less than 30 minutes. In order to assess safety issues, use of the Lucira COVID-19 test will be strictly limited to two clinics, and be available only to those showing symptoms of COVID-19 infection. Next spring the company intends to ask the FDA to modify its emergency-use authorization to allow people anywhere to communicate with their doctors over the internet; with a doctor's prescription, the kit would be delivered overnight to the person's home.

Those Minks In Denmark

Remember from last week's letter those mink in Denmark that had become infected with COVID-19 from humans, then passed it back to other humans in a mutated form? The Danish prime Minister had ordered all 17 million Danish minks to be killed. And a lot were:



Henrik Nordgaard Hansen and Ann-Mona Kulsoe Larsen kill their herd, which consists of 3,000 mother minks and their cubs, on their farm near Naestved, Denmark, on Nov. 6. (Mads Claus Rasmussen/Ritzau Scanpix/AP)

However, later last week, with an estimated 2.85 million minks already dead, the Prime Minister rescinded his order. Political opponents complained that the order was a threat to Danish democracy, while farmers all over the country expressed fury over their livelihoods being taken from them overnight. Imagine if in this country the federal government suddenly seized all IRA retirement accounts – it was that kind of reaction. An awful lot of Danes raise a few mink. However, the fear of COVID-19 can, if you will excuse the pun, trump anything. After days of legislative shouting, the prime minister claims he has a parliamentary majority willing to support a law reinstating the culling of the minks and suspending mink farming in Denmark for a year. A vote has not yet been held. Every mink in Denmark is holding its breath.

On that weird note I will end. Have a happy Thanksgiving. Your mother and I will spend ours giving thanks for the three of you (and associated husband, companion, and grandchild (I mean you, Jed). Stay safe.

Dad