Letter 42: Future Dangers

June 20, 2022

Dear Daughters,

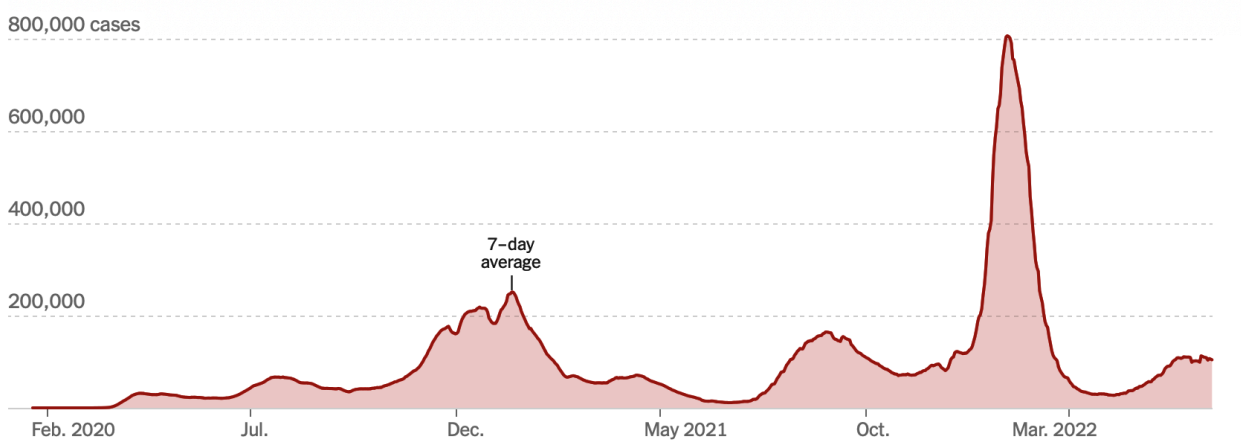
These are uncertain times. There is a major war in Europe for the first time in 75 years. I fear it may grow to be a World War. I don't see Putin backing away from his attempt to seize what he regards as rightfully part of the Russian homeland. If Putin elects next to seize the Baltic nations, also once part of Imperial Russia, he will have attacked NATO countries and we will be at war. Surely he would not take such a risk? I am not comfortable he will be rational about this – Putin styles himself another Peter the Great, who in the 17th century seized the Baltic nations and much of Sweden, incorporating them into Imperial Russia and making St. Petersburg (then considered part of Sweden) Russia's capital. Uncertain times indeed.

Here at home we listen this week and next to congressional hearings on the January Insurrection. We hear a highly-respected Republican-appointed Federal judge state in today's hearing that Donald Trump is "*a clear and present danger to Democracy in the United States of America*." I think this judge is right. What is scary about this is that, with inflation raging, there is a better than even chance Trump will be elected president in 2024. Uncertain times indeed.

Last month the COVID-19 pandemic reached a grin milestone. The first COVID-19 case was reported on December 31, 2019 in Wuhan, China. The first COVID-19 death in the United States occurred weeks later, on February 29, 2020. When I wrote my first letter to you girls a month after that, on March 28, I had no idea the grim road we were on. Total American fatalities had just passes 1,500 that day, and I envisioned future deaths as peaking at a few thousand more unfortunate souls. Last month, 2 ½ years later, the total number of Americans reported as having died of COVID-19 passed one million! And people are still catching this virus, with new more infectious variants appearing every few months. Uncertain times indeed.

The Pandemic Subsides

The good news is that the pandemic appears to be subsiding. A new subvariant of Omicron dubbed BA.5 is rapidly surpassing all earlier variants in the United States. The most contagious yet, it is not particularly dangerous, most infections being mild. Overall, things continue to improve. The seventh wave of infection, May – June, seems to have peaked at a relatively low level. While there is no way of knowing what next fall's wave will be like, there is every reason to be hopeful that new variants of Omicron will not explode as they did last winter.



The Future Pandemic Danger Is Spillover

In earlier letters I told you about spillback - the passage of COVID-19 from humans to animals - and spillover - the passage of COVID-19 from animals to humans. I reported the scary news that COVID-19 has infected by spillover many, if not most, white-tailed deer in this country. The danger, as I explained, is what might happen next. The virus may acquire many differences while evolving in animal host like deer, then reinfect humans. The future danger of COVID-19 , in a word, is spillover.

This seems to have happened once already. Chinese scientists claim that the Omicron variant originated as spillover from mice that had become infected with the Alpha strain of COVID-19. Are the spillback viruses in white-tailed deer evolving to be quite different, as Omicron did in mice?

In a word, yes. In Ontario, Canada, scientists collected nasal swabs and samples of lymph node tissue from 300 deer killed by hunters in November – December 2021. 18 of the samples (6%) tested positive for COVID-19, all from Southwestern Ontario.

The full COVID-19 genome was sequenced from five of these deer, revealing 23 mutations never before identified. Clearly, the virus is evolving quite rapidly among deer – just as Omicron did among mice.

Is spillover from these deer back to humans likely? In Ontario, a COVID-19 sequence very similar to that seen in Ontario's white-tailed deer has been isolated from a man in Ontario who had close contact with deer. Q.E.D. Yes, spillover from white-tailed deer to humans can occur.

The spillover-infected man did not then transmit the virus he had acquired from white-tailed deer to any other person, so the possibility of community spread after spillover remains unknown. But like a ticking bomb, the virus continues to evolve in wild white-tailed deer populations all over the United States. And we now know that whatever is evolving can be transmitted to humans.

Playing Vaccine Whack-a-Mole

Some 66% of the United States population has been vaccinated for COVID-19, and many Americans have been boosted, some (like your mother and I) twice. However, the Pfizer and Moderna vaccines and boosters were formulated to combat the original variants of COVID-19. While the antibodies these vaccines induce are 95% effective against the early variants, they are far less effective against the Omicron variants infecting Americans today.

While still offering some measure of protection, the Pfizer and Moderna vaccines and boosters would be FAR more effective if formulated to combat today's variants rather than ones infecting Americans two years ago.

Both Pfizer and Moderna claim to be working on vaccines targeting Omicron, but don't seem in any hurry. We know the gene sequence of Omicron, so the necessary changes to the mRNA vaccine are easy to make. Why haven't Pfizer and Moderna's vaccines and boosters already been reformulated to match the threat we face? As I see it, for three reasons:

1. *Satisfying Government Regulations*. The regulatory hurdles confronting development of a new vaccine are high. Double-blind phase three clinical trials are expensive to run and can take years. The NIH could lower the bar by accepting much-easier-to-do laboratory studies -- as they do with flu vaccines -- but has not chosen to do so.
2. *Playing Vaccine Whack-a-Mole.* Within a few months of introducing a newly formulated vaccine, another COVID-19 variant is likely to arise, requiring development and testing

of yet another vaccine formulation. Every six months for the last two years we have been confronted with a new variant, and this pattern may (probably will) repeat itself.

3. *Lack of Financial Incentive.* Vaccine manufacturers are already making an obscene amount of money selling their vaccines targeted at early COVID-19 variants. For the year 2021, Pfizer reports COVID-19 vaccine sales of $36.8 billion, and projects 2022 sales of more than $50 billion. Moderna reports COVID-19 vaccine sales of $36.7 billion in 2021, listing $12 billion of that as profit.

Seeking a Universal Vaccine

I think we face two major COVID-19 dangers in the coming months:

1. The COVID-19 virus is continuing to evolve new variants as it spreads among us. There is no way to know if future variants will stay as safe as recent ones. Far more dangerous forms are quite possible. Mutations occur at random in the coronavirus genome, and we cannot know what the future holds.
2. The spillover to humans and subsequent community spread of a radically new variant that has evolved in white-tailed deer or some other animal is a very real and immediate danger.

There is only one satisfactory way to combat these two dangers, and it is the same for both: We need to develop a universal COVID-19 vaccine.

Dr. Fauci has for some months been calling for more research into “universal coronavirus vaccines” that would work against any variant. Understand, this is not an easy task. Researchers have sought just such a universal vaccine against flu for many years with no success. However, there are promising signs that it could be possible for coronaviruses.

COVID-19’s Receptor Binding Domain May Be The Key

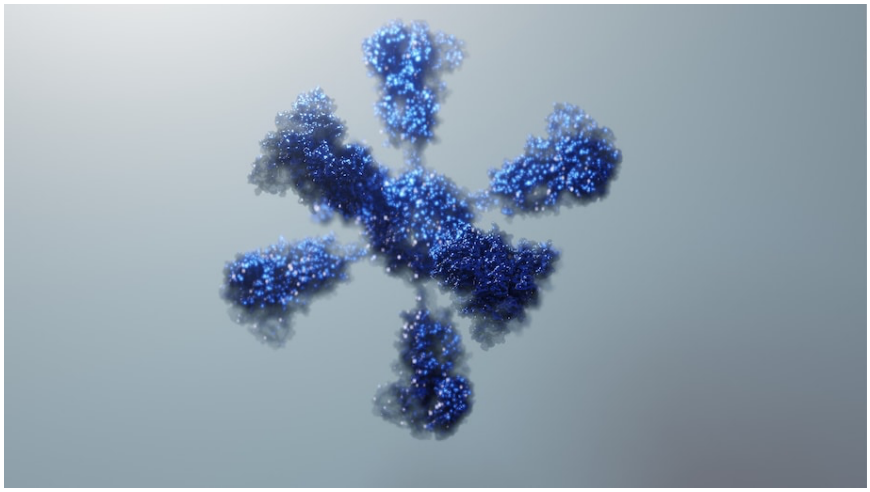
The key to a universal vaccine is to base it on parts of the virus that don’t change much or at all as the virus evolves. Because these bits are the same in every variant, a vaccine targeting them would be effective against all variants. Why would you expect to find unchanged “conserved” bits, gene sequences that are the same in whichever variant you look at? Because while a

random mutation can occur anywhere in the virus genome, any change in bits key to the virus's ability to infect human cells would be too detrimental to the virus for it to survive.

Are there such highly-conserved bits among coronaviruses? Yes! Remember COVID-19's spike protein? A portion of the COVID-19 spike protein called the receptor binding domain (RBD) is one of the "conserved" parts of the virus genome that doesn't seem to change, a part shared by all COVID-19 variants, as well as SARS, MERS, and other bat coronaviruses. RBD is the part of the virus that latches onto the host cells, and it cannot be changed much and still work. Some COVID-19 variants have small mutations in their RBD, but these mutations don't change the RBD's chemical structure.

The RBD looks like a very promising target for a universal coronavirus vaccine.

RBD-targeted vaccines will probably work best if the RBD proteins are presented to the human immune system as they would if on the surface of a virus, protruding out in clusters. Duke University labs are investigating attaching RBD portions of COVID-19 spike proteins to the iron-storing protein ferritin. This combination of RBD proteins to ferritin produces tiny nanoparticles studded with many copies of the RBD projecting outward – sort of a molecular porcupine.



The Duke RBD vaccine protects macaque monkeys against both SARS and COVID-19, and generates a good immune response against the Delta and Omicron variants too. The Duke research team hope to start human clinical trials at the end of 2022.

Let's hope their trials succeed.

I'm Not Dead Yet

Last week I celebrated my 80th birthday, and all three of you were there to help me do it! I cannot tell you the joy it gave me to have my family clustered around me, loving me fiercely and ignoring my many foibles. Thanks to weeks of Barb's efforts, (she put up the banner you can see in the photo), I had piles of wonderful presents and a fantastic dinner – standing rib roast!

I am of course not getting any younger. I look to the future with some trepidation – 80 is a large number – but am cheered by considering the friends I made among the faculty when I first became a scientist at Stanford over fifty years ago. My good friend Paul Ehrlich (age 90) and my best friend Peter Raven (age 86) are both alive and kicking, as intellectually involved as ever, and both still busy trying to help our planet survive. With less hair than I used to have, I at age 80 also hope to keep on doing what I do, trying to teach college kids and a public audience about biology and how it affects our lives. And for both your mother and I, there is the matter of grandchildren. We are going to love watching them grow, just as we loved watching you three grow. You girls can have every confidence that your dad and mom are going to enjoy the coming years very much, however uncertain the times.

Dad