

For my daughters:

January 1, 2020

The Coronavirus Pandemic *End of a A Pandemic Year*

Today we start a new year, which hopefully will see the end of the coronavirus pandemic. The year we are leaving could hardly have been worse. Today we passed 20 million COVID-19 cases in the United States (1 in 16 Americans!). Fully 346,000 of them have died of the infection, 65,000 of them in the last month alone. Worldwide, we surpassed 80 million COVID-19 cases last month, with 1.7 million deaths. With the height of the pandemic surging around us, our family has nestled in tight over these grim holidays, but as a parent I find it impossible to escape worry. Your mother and I are careful to watch who we see up close, restrict our shopping to curbside pickup -- and cross our fingers.

But on the bright side, Santa Claus was good to our family this holiday season, especially to daddy:



Best of all, everyone in the family, in Saint Louis and far away, is healthy. We have three or four rough months to get through, girls, and during this long winter every one of us in the family must remain careful -- face masks and social distancing more important than ever. The hardest part is having to keep away from friends who are being less careful. Still -- Spring is coming.

Vaccines Are Here – Sort Of

Of the dozen or more vaccines being developed to combat COVID-19, five are likely to become available in this country sometime in this new year. Two (*Pfizer & Moderna*) are FDA-approved and have begun distribution. Another (*Oxford/AstraZenica*) has been approved in the UK and is being distributed there, although the FDA has requested its USA Phase Three clinical trials be extended to clarify the data. The other two vaccines (*Johnson & Johnson, Novavax*) will complete clinical trials within a few months. That we have come so far so fast in vaccine development is a major scientific accomplishment.

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.

- *Johnson & Johnson* Phase Three clinical trials to complete in January; no preliminary results reported. The only vaccine requiring a single shot.
- *Oxford/AstraZenica* 62% effective at blocking infection (90% effective when given with a low initial dose). Very stable, and cheap to make.

2. Subunit Vaccines.

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

- *Novavax*. Injects virus spike proteins, manufactured in moth cells and then attached like studs to a synthetic nanoparticle. Phase Three clinical trials started in U.S. on December 27. Phase Two trials produced markedly more antibodies than any other vaccine.

3. 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*. 95% effective at blocking sickness; granted FDA authorization December 10. A potential problem is that the vaccine must be kept ultra-cold. Requires two shots a month apart. USA purchased 100 million doses.
- *Moderna/NIAD*. 94% effective at blocking sickness & 100% at preventing severe illness. Can be stored in a refrigerator. USA purchase 200 million doses.

Company	Effectiveness	# doses	Approval	Availability
<i>Johnson & Johnson</i>	not yet known	one	February ?	Spring
<i>Oxford/AstraZenica</i>	62%	two	Spring	Summer
<i>Novavax</i>	not yet known	two	Summer	Fall
<i>Pfizer/BioNTech</i>	95%	two	yes	some in December more in July
<i>Moderna/NIAD</i>	94%	two	yes	first quarter 2021

The New Variant

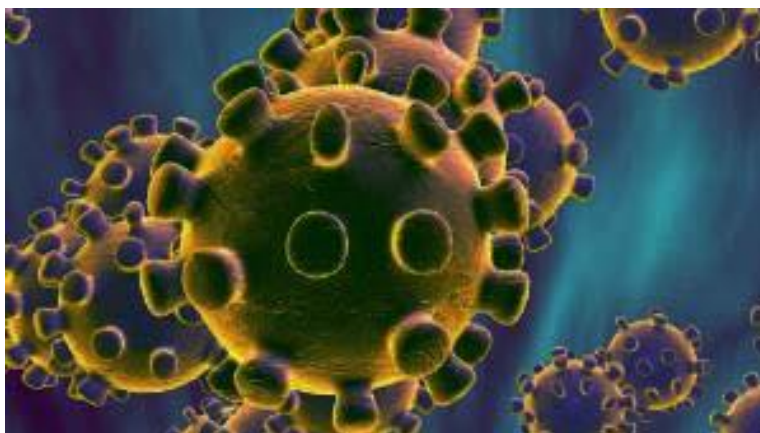
In the rush to develop a vaccine directed against COVID-19, essentially all the efforts focused on introducing the virus spike protein into patient's bodies, either by injecting it directly or by injecting the virus spike protein gene (so the patient would manufacture the virus spike protein). The patient's immune system would then react by producing antibodies and T cells directed against the spike and so protect the patient from future infection by the virus. Simple, straightforward, and effective.

BUT these approaches all depend on the spike protein of COVID-19 not changing. The vaccine-induced antibodies must be able to recognize the infecting virus particles. Coronavirus vaccine developers were encouraged by the fact that the COVID-19 virus seemed to mutate only slowly, far less than the influenza virus. We have to get a new flu vaccination every year because the influenza virus mutates at a rapid clip, changing enough in a year that the old vaccine is no longer effective.

Well, "facts" sometimes get a little fuzzy. There has been no systematic federal effort in the United States to sequence the genes of the COVID-19 virus collected from infected individuals. The only data we have is sporadic tests done in university research labs. So we have been flying blind, assuming the early inference of a low mutation rate was correct. It wasn't. There are currently some 4000 mutations that have been reported in the COVID-19 spike protein gene.

Most of these mutations seem to have little or no effect, and do not become common. An exception was the D614G variant, which increased the ability of the virus to be transmitted and is now the most common type circulating in Europe and the USA.

A new variant that has been recently reported in the UK may also speed transmission. A consortium of the UK's four public health agencies and 12 academic institutions has been conducting gene sequencing of COVID-19 collected from 140,000 infected people. It uses the data to screen for variant viruses. In December the consortium reported that it had identified a new variant, named B.1.1.7. Surprisingly, this variant had 17 changes (mutation from the basic sequence common in the UK). One very disturbing change is a mutation dubbed N501Y affecting the part of the spike protein that binds to the human ACE2 receptor to gain entrance to human cells. This B.1.1.7 variant doesn't worsen the illness, but does seem to facilitate ACE2 receptor binding, making the virus more infectious. B.1.1.7 are the swollen tips you see in the spikes of the viruses in the drawing. Leading scientists agree it is more infectious, including Dr Anthony Fauci, my gold standard. Estimates of how much more infectious are still vague, ranging from 56% to 70% more transmissible.

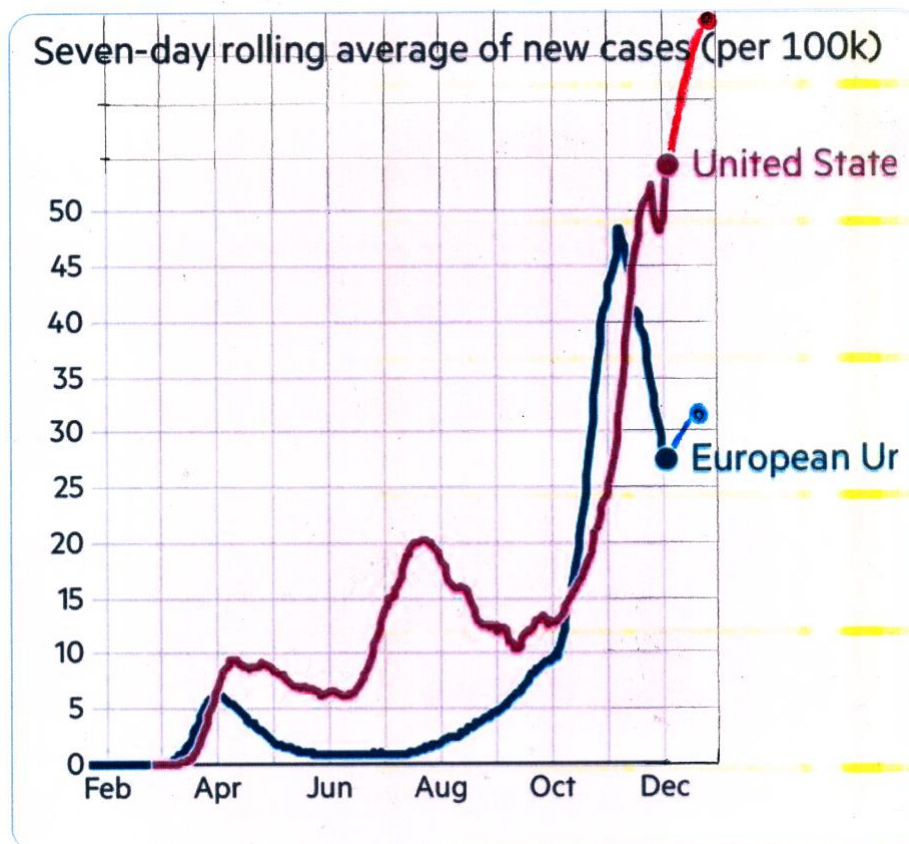


First spotted in the UK in late September, the mutation has spread quickly. By mid-December, 1108 cases of the variant had been identified in some 60 different localities throughout England, Wales and Scotland. It has been reported in Denmark, the Netherlands, Australia, Finland, Vietnam, South Korea – and the United States. There is little doubt it is spreading worldwide, and quickly. Cases recently reported in Colorado, California and Florida were individuals who had not travelled recently or associated with people who had, suggesting that many other Americans have the new variant without anyone knowing as yet. Unlike the UK, the United States doesn't keep track of COVID-19 genome changes, ranking 43rd in gene sequencing to check for variants among countries with more than 100 infections. Australia ranks first, having sequenced the COVID-19 genomes of 58.6% of its coronavirus cases!

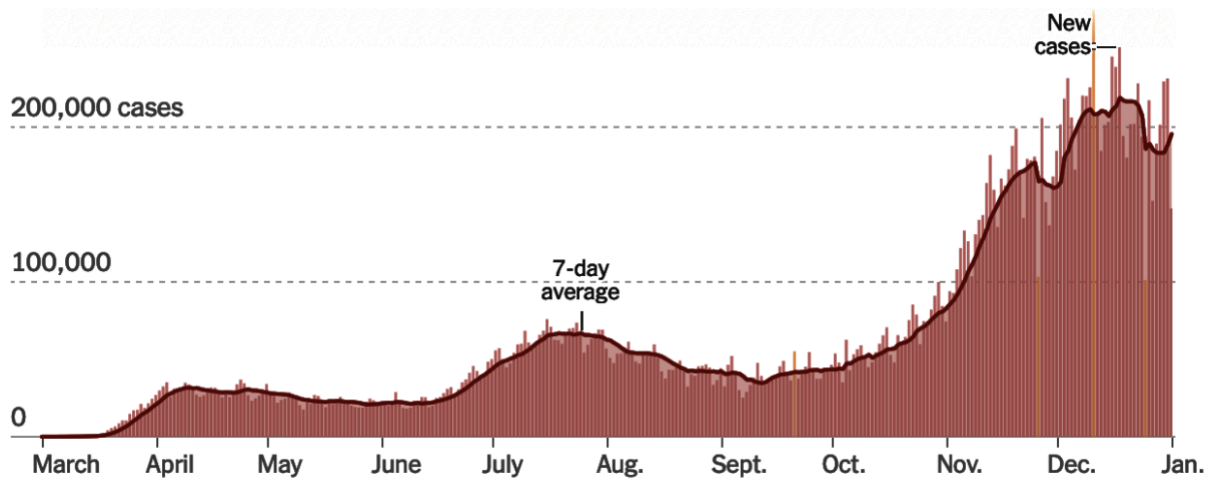
Will the vaccines we have developed against COVID-19 be effective against this new B.1.1.7 variant? A lot of labs are madly trying to get data, but for now it is impossible to be certain. Best guess? The vaccines will still work well. Antibodies are directed against many parts of a virus particle besides the tip of the spike, and these parts are unchanged in the B.1.1.7 variant. Still, it will be good to see hard data. We have been surprised by this virus before.

A January Conundrum

So the pandemic continues as we enter the new year. As I pointed out to you girls last month, an explosive spike in new cases of coronavirus has come with fall weather, affecting both Europe and, a few weeks later, the United States. Over the last months, Europe locked down in response, bringing their surge to a halt. We did not.



Even worse, the beginnings of a vaccine rollout has dampened the American fear of infection. Thanksgiving and Christmas holiday travel set records, and innumerable small parties brought people together from all over the country. Experts like Dr. Fauci warn that this easing of social distancing will surely bring a further surge in new COVID-19 cases, on top of the 200,000 new cases already being reported each day in the United States. Because testing for covid-19 slows over holidays (staff take a break and people seek to avoid the long waits at testing sites) you see dips in the numbers of new infections reported on Thanksgiving, Christmas, and New Year's days. With these dips, the graph of number of daily new cases is peaking at a few over 200,000 a day. Will the rate of infection surge once again a few weeks after the holidays are over as Dr. Fauci predicts, or will the rate remain steady about where it is? A January conundrum.



So On We Go...

So Happy New Year, girls. We have much to be thankful for, and not a little bit to fear, as we march into these cold January days. For ten months we have been careful to wear face masks, stay well away from those we don't live with, and carefully clean surfaces we use. We have not gone to the Rep theater as we usually do, or out to dinner. Shopping is by phone, online, and with curbside pickup. Damn, but I am tired of this, as I'm sure you all are. This is the 24th pandemic report letter I have written you girls, and in several of these letters I have told you *"Hang in there, the end is in sight, only a few more months..."* As this year starts, I find myself doing it again: Four more months, girls, and we should be vaccinated and in the clear.

Until that happier time, keep safe, stick to your pod, cook lots of healthy food, and think kindly of your father gleefully roasting helpless sticks of wood in his new firepit.

Dad