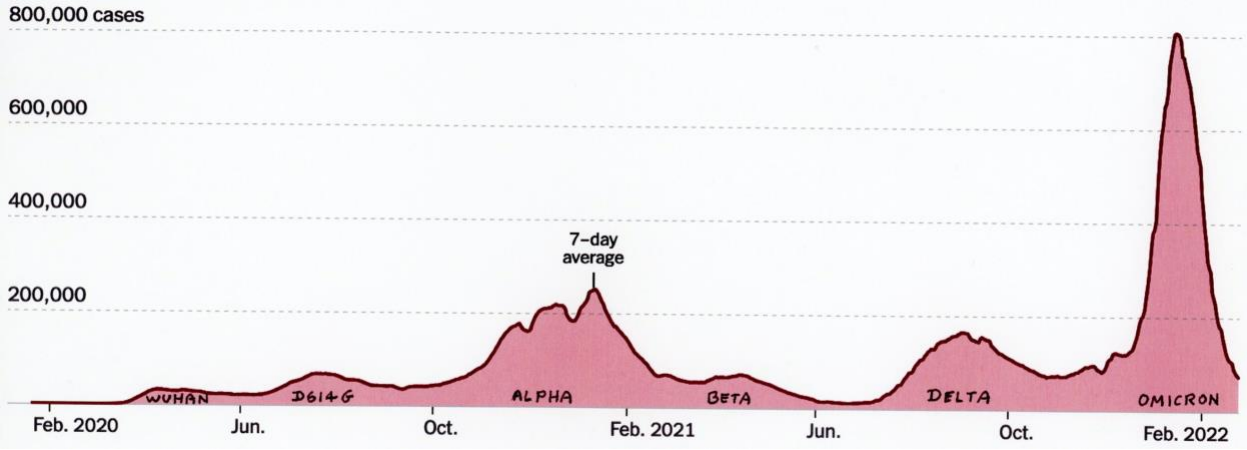
Letter 40: Is the Pandemic Over?

March 1, 2022

Dear Daughters,

With war beginning in Europe, these cold winter months cannot be considered a happy time, but at least the Covid-19 news is quite good news. All over the country, the number of daily new cases continues to fall. Daily new cases have fallen more than 90% from their January peak, as low as they have been since before the Omicron Variant took hold. It seems clear that the Omicron surge is bottoming out, and no new variant has yet arisen to take its place. Good news indeed.



The pandemic is certainly not over. In Missouri and many other states mask mandates are being cancelled. People are just fed up, and unwilling to take it anymore. Even St Louis County, which has fiercely defended its mandate requiring everyone to wear masks in stores and other commercial enterprises, is dropping its mandates. The CDC is lifting its mandate for indoor association, except for high-risk counties – over 70% of Americas can now discard their masks. Please pay no attention, and continue to wear N-95 face masks whenever around others. As I have said, our family should wait until daily new case numbers fall below 10,000 nationally. With luck, by April.

However, please note what the history of the pandemic seen in the graph above is telling us: every six months, like clockwork, a new variant produces another surge. It is hard not to suspect that next fall we will be looking at another surge by another variant. That danger is what I want to explain to you today.

A Closer Look At The Omicron Variant

To get some idea of what sort of new Covid-19 variant might arise, we need to look carefully at the last one, the Omicron variant. Omicron is quite different from the five variants that preceeded it. To see this, we can compare each new variant to the previous one, to see what mutations have accumulated:

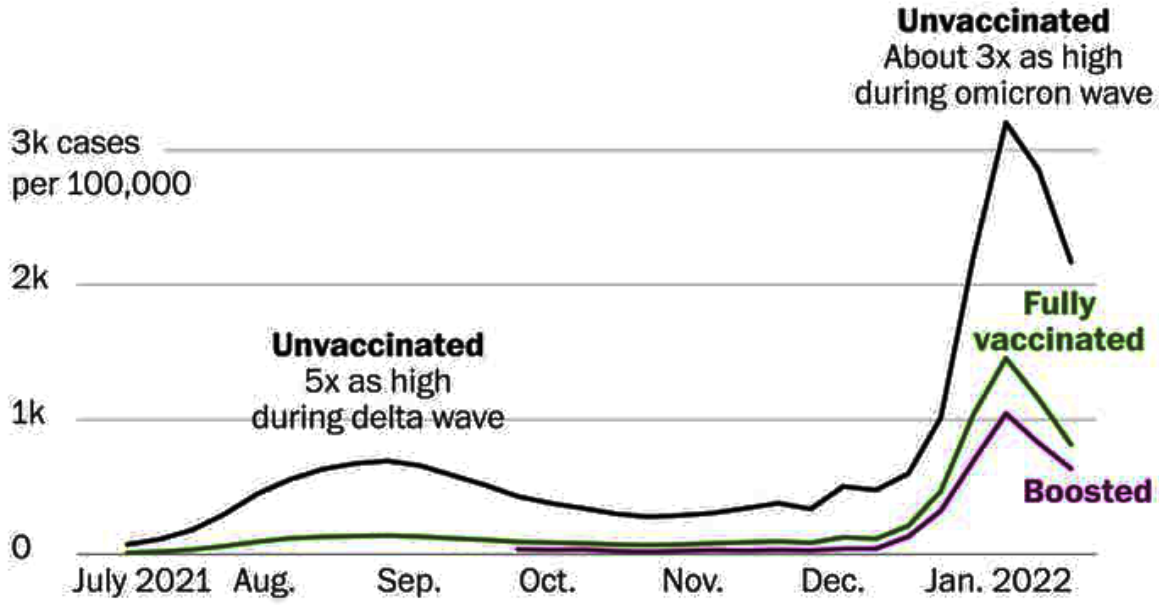
- D614G has a few key mutations that allowed it to outcompete and quickly replace the original Wuhan strain.
- In their turn, Alpha and then Beta acquired a few novel mutations that increased their transmissibility and led to their surge.
- Delta added key mutations that both allowed it to partially escape our immune defenses and also made it more deadly. By last fall, all new Covid-19 cases in the United States were the Delta variant.
- Then came Omicron, first seen in India in September and quickly at least 77 other countries, including our own. Omicron was a different kettle of fish entirely. Omicron does not have a few novel new mutations – it has more than 50, most in the spike protein used to infect human cells. Fully 50 mutations! I will come back to this point in a moment, as it is very important.

As you might expect from such a different gene makeup, Omicron's behavior is quite different in at least three major ways:

1. *It is much more transmissible than Delta or any other prior variant*. Apparently it infects the nasal passageway nearer the nose, making it easier to spread in tiny droplets expelled when exhaling.

2. *It is less deadly than Delta*. This may be related to the fact that Omicron infects tissues further from the lungs. Many do get quite ill and must be hospitalized, but far fewer.
3. *Omicron is even better at evading our immune system than Delta*. The mRNA vaccines widely used in this country, formulated against the earliest variants, work pretty well against the Delta variant, although not as well as they do against the Alpha variant they were designed to combat. However, these mRNA vaccines are even less effective against Omicron.

Even fully vaccinated people get infected by Omicron. A third "booster" shot of the mRNA vaccine helps, but not a lot. In the graph below, compare the unvaccinated to the vaccinated during the Delta wave last September (left portion of the graph) and during the Omicron wave this January (right portion of the graph): Fully vaccinated people were pretty well protected against the Delta variant on the left – some vaccinated people became infected (about 150 per 100,000), but five times fewer than unvaccinated people (some 750 per 100,000). Come the Omicron variant, on the right, many more vaccinated people became infected (1,500 vaccinated per 100,000 + 1,050 boosted per 100,000 for a total of 2,550 per 100,000).



Why Is the Omicron Variant So Different?

Sequencing information suggests that the Omicron variant began to diverge from the straight evolution of Wuhan -D614G-Alpha-Beta-Delta sometime in mid-2020. Omicron contains some of the Alpha mutations but not all, and none of the mutations unique to Beta or Delta. Evolving independently for over a year, it accumulated many novel mutations.

Researchers have proposed three explanations of how Omicron came to independently evolve for what seems to have been several years:

1. *It evolved undetected in an isolated population*. The virus may have been circulating for years in a remote population of people in southern Africa where no testing was being done. I don't buy this. I doubt there is any place in Africa that is isolated enough for the virus to transmit among people for that length of time without it emerging elsewhere.
2. *It evolved in a person with a weakened immune system*. Living in an immune-compromised patient, where the immune system defenses cannot combat it, the virus might persist as long as six months, all that time accumulating mutations. All this time, generation after virus generation, there would be strong selection to evade immune defenses. But I don't buy this either. Viruses in people with HIV-weakened immune defenses do indeed evolve over time, but they in every instance studied evolve to <u>reduce</u> the ability to transmit from person-to-person, just the opposite of what is seen with Omicron.
3. *It evolved in an animal host and jumped back*. Perhaps there was a transfer of Alpha from humans into an animal host (a spillback), where it evolved into Omicron. This might have been followed later by a reinfection back into humans (a spillover). This "spillback/spillover" is the explanation I buy. The coronavirus might have experienced a totally different set of evolutionary pressures in a new animal host, leading to the accumulation over time of the large array of unique mutations found in Omicron.

There is no consensus in the scientific literature I am reading as to which of these three explanations is correct, although there are a lot of strong opinions. Not to be left out, I too have a strong opinion. I feel sure explanation #3 is correct, that we are looking at spillback/spillover.

We have seen just this circle of re-infection in commercial minks last year. Minks being raised in in Denmark acquired Covid-19 from their human handlers (spillback). Circulating among the mink, the virus spread like wildfire on fur farms across Europe, evolving several new mutations. Then the virus re-infected several of the humans working on a mink farm in Holland (spillover). The Omicron variant may have undergone exactly this same sort of spillback – spillover cycle.

Did Omicron Come From a Mouse?

Researchers at the Chinese Academy of Science in Beijing recently published a paper identifying *Mus Musculus*, the common house mouse, as the animal species from which the Omicron variant originated. Looking at 45 point mutations unique to Omicron, they found the relative frequency of key DNA base substitutions very different from what is seen in viruses evolving in human patients. However, they were quite like the relative frequencies of base substitutions among mutations in viruses evolving in mice. Also, Omicron's mutations increased the spike protein's binding affinity to the mouse ACE2 receptor, just what you would expect if the virus was evolving in mice, with a strong selection for changes conductive to infecting the cells of the mice hosts. "*Collectively, our results suggest that the progenitor of Omicron jumped from humans to mice, rapidly accumulated mutations conductive to infecting that host, then jumped back into humans*," the researchers concluded.

The arguments are indirect, so not totally convincing. I would be more convinced if Omicron were to be found, with various levels of new mutations, in wild mice populations. This is an important point to settle. If spillover from an animal gave us Omicron, it may (will) happen again with a new and yet to be discovered variant.

Red Fox

White Tailed Deer

Cotton Tailed Rabbit

Grey Squirrel

Raccoon

Feral Cat

Future Spillover Candidates. These six animals, like mice, all have natural free-living populations, all are known or suspected to be spillback-infected with Covid-19 from humans, and all live in close everyday contact with us, roaming freely.

Long COVID Maintains its Grip on Our Family

Nikki continues her protracted battle with long COVID. In this she is not alone. Estimates of the number of people who develop long covid range from 10% to as high as 50% of cases. Why do we call their disease "long COVD?" Because long after these patients recover from the immediate respiratory illness of COVID-19, they continue to experience a large number of other lingering symptoms. Some report long-lasting heart issues, others damage to taste and smell, fatigue, and shortness of breath. That means that millions of people continue to wrestle with the aftermath of COVID-19 infection, just as Nikki does. Thankfully, for Nikki things do seem to be getting slowly better.

Looking Forward

In these uncertain times, the only sure exit from the COVID-19 pandemic is a universal vaccine, one targeted at all coronaviruses. When we succeed in developing this, we will be protected from any variant, even one due to spillover. Until that day, the danger will persist. Researchers are working like beavers on this problem. Happy chewing! The speed of our remarkable success with engineering vaccines and understanding the virus give me hope we will solve this problem too!

Stay healthy.

Dad