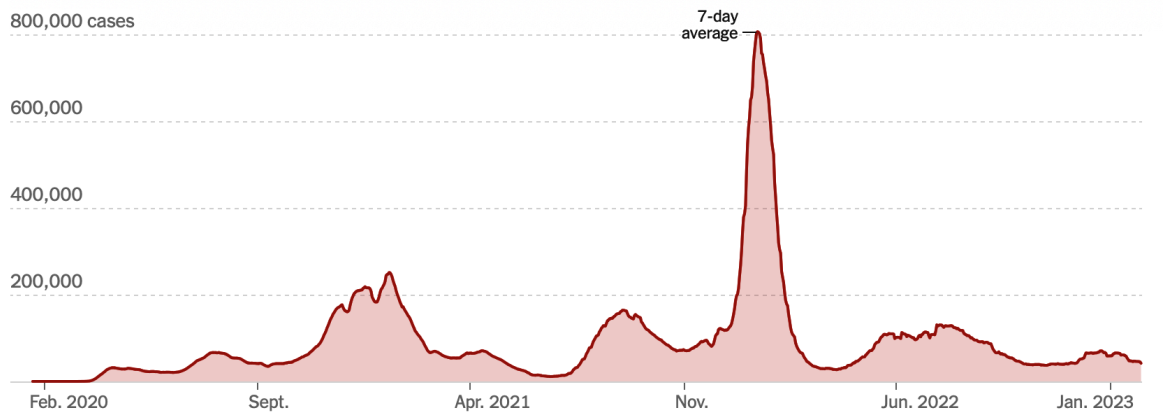
Letter 44: Breakthrough

February 1, 2023

Dear Daughters:

I last wrote in the fall, as the COVID pandemic seemed to be waning. Daily new cases in our country had fallen from summer's 128,000 to below 60,000, and people had begun to reassume their normal "before COVID" lives. While your mother and I still wore masks when in public and still refrained from theater and restaurants, we were in the decided minority. To most folk, the pandemic had past. I remained worried that we might face a new outbreak if humans were to be reinfected by a strain of COVID infecting white-tailed deer or some other animal, but that hasn't happened. In the four months since I last wrote, national levels of COVID-19 infection did not peak in winter weather as I and many others had feared. For members of our family, there no longer seemed to be much to worry about.



Nikki Gets COVID

This week I learned in a way I could not ignore that I was being too optimistic. Nikki telephones that she has just tested positive for COVID! Nikki, you have already had COVID (and a lingering Long COVID illness), have been fully vaccinated, and have had all your booster shots including the new bivalent one. I have told you that you were as safe as could be, and to get about your life. But it turns out, safe as could be wasn't safe enough from COVID for you, Nikki. This letter is to ask why.

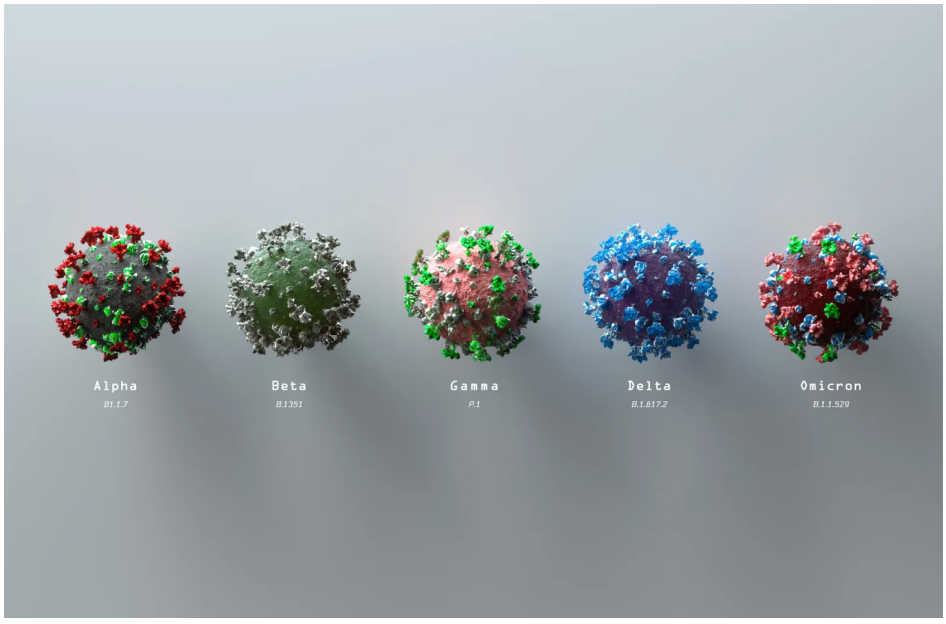
Reasons Why You Weren't Safe Enough From Covid

I have thought about this quite a bit since your phone call, Nikki, and can think of three possible explanations why the bivalent COVID vaccine you received last September didn't protect you: ***1***. *Your vaccine lost its efficacy.* ***2.*** *A new variant infected you.* ***3.*** *Earlier vaccinations limit booster protection.* It seems to me likely that all three played a role. Let's look at each.

Explanation 1. Your Vaccine Lost Its Efficacy

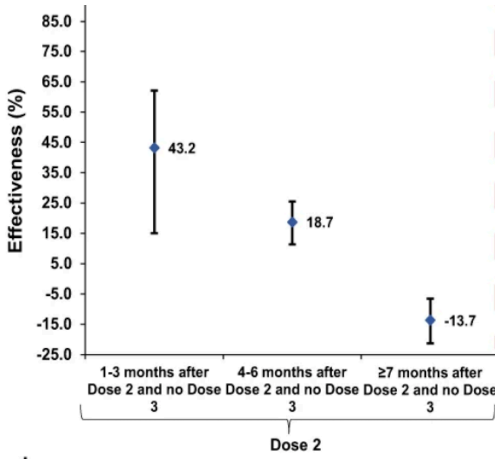
How long should you expect the immunity you get from your vaccine shots to last? Well, mRNA vaccines like the ones you have been getting are a new development, never used before. Because of their novelty, there is no hard data from years of use to tell us how long they would be expected to protect you from infection. It is clear they do offer substantial protection in the first few months, although the protection has fallen as variants have evolved that are better able to evade your body's immune defenses.

We saw greater than 90% protection during the pre-Delta variant era. Delta when it arose was a lot better at evading antibodies than earlier variants, causing protection to drop into the 70% range. Then came Omicron, a genius at evading antibodies. For Omicron we saw protection drop even lower, to the 50% range. For subvariants of Omicron like BA.5 and XBB.1.5, data are limited, but protection seems even lower, in the 40% range.



Protection Wanes

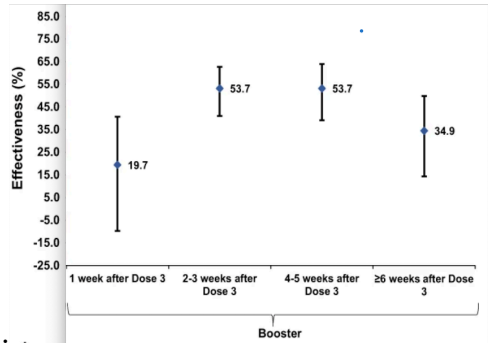
A few months after vaccination, protection begins to fade. Numbers vary, depending on which study I look at, but on average COVID-19 mRNA vaccine efficacy decreased by about 20% over the first five months. That's a big decrease. If our starting point for BA.5 and XBB.1.5 has already fallen to a protection range of around 40%, then the decrease starts from there, not 100%. Most studies seem sketchy, with limited samples and no blind controls. The only really top-notch study I have found presents an even bleaker picture:



As you can see in the graph, seven months after the two-shot vaccination program was completed protection has all but vanished.

Boosters Help For a While

This fading of vaccine efficacy is why we take booster shots. You (along with all the rest of our family) had a "bivalent" booster five months ago last September. Your booster would be expected to add protection on top of whatever protection you had left after previous vaccine doses. How much? The one thorough study I have found paints this picture:



What this graph tells us is that having a COVID-19 booster will give you some additional protection against infection, probably cutting your risk of getting sick by about 50%. But that protection doesn't last long – less than eight weeks in this study. After that, you would still be expected to be vulnerable to breakthrough infection. Nikki, you like the rest of our family had the bivalent booster twenty weeks ago.

Explanation 2. A New Variant Infected You

Considering all that has happened over the last three years, it's hard to believe so many people still don't believe in evolution. Evolution has been a major feature of the COVID-19 pandemic. Natural selection has favored forms of the virus better able to infect, or to evade antibodies. This has given us a parade of variants, leading eventually to the Omicron variant that a year ago became the dominant form seen in the United States, infecting up to 800,000 Americans a day.

The evolution of COVID-19 did not stop with the Omicron variant. Mutations within Omicron have produced a series of subvariants, each becoming in turn the dominant form in this country. The modest wave of daily new cases we saw last April was due to a variant called BA.2.

XBB

Sometime in the summer of 2022, two descendants of BA.2 containing many new mutations infected one person, and by a process called genetic recombination swapped pieces of their genetic code. Imagine a hot dog lying beside a polish sausage. Cut both in two, then stick one end of the hot dog onto the other end of the sausage, and you can get a dog/sausage. This sort of new combination can have surprising properties. The two BA.2 descendants had their new mutations clustered at different ends of the spike protein gene, and combining the two mutation-rich ends resulted in a new sub-lineage called XBB containing most of the new mutations from BOTH descendant -- 14 new mutations to the virus' spike proteins compared with BA.2.

XBB never gained much ground in the US, where it had to compete with a slew of co-circulating subvariants which had independently evolved many of the same mutations as XBB. XBB's one great advantage over these other variants was a greatly increased ability to evade antibodies. Its great disadvantage was that XBB does not bind well to the ACE2 receptor the virus uses to invade human cells. Said simply, XBB can't infect as well as other co-circulating variants.

The Kraken Variant

Then, in late 2022, the hammer struck. In October, researchers in New York noticed a new form of XBB with a rarely seen mutation called F486P in the spike protein. This change greatly improved XBB's ability to attach to the human ACE2 receptor, while not lessening its considerable ability to evade antibodies. These changes make it both much more transmissible and much better able to evade vaccines.

This variant, formally named XBB.1.5, was given the nickname "Kraken" by the scientists studying it, because of the rapid way XBB.1.5 seems to spread out in all directions. The Kraken is an enormous mythical multi-tentacled sea monster (like a giant squid or octopus) in Scandinavian lore. Kraken has spread like wild fire in the New England area, where infections quickly rose to more than 84% of daily new cases by the end of the third week of January 2023. The CDC estimates that levels in NYC are even higher. Nationwide, Kraken cases rose from less than 2% of all new cases at the beginning of December to 49% by the end of the third week of January. Nikki, Kraken is very likely the variant you contracted last week in NYC.

Unfortunately for you, Nikki, Kraken is particularly easy to catch, even if you are immunized.

Explanation 3. Earlier Vaccinations Limited Your Booster Protection

The bivalent booster you received last September contained two sorts of mRNA -- one the same as your previous vaccinations (the original Wuhan variant), the other a recent Omicron variant, BA.5. The idea was to protect you from infection by either variant. While this "bivalent" approach seemed to me a good idea when I last wrote you, it turns out not to be.

Why not? The answer lies in an observation made decades ago, about people exposed to influenza (flu) each year. The immune systems of these people responded to a new circulating strain by producing antibodies tailored to their first flu encounter! This tendency of your immune system to remember initial infections is called immune imprinting. Remembering the look of an invader helps your immune system to prepare for future battles, enabling a lightning-fast response should the same invader reappear.

The key players in immune imprinting are memory B cells, generated in your lymph nodes during your body's first exposure to a virus. Circulating in your bloodstream, these memory B cells keep watch for the invader, ready to develop into plasma cells that churn out antibodies directed against that invader. When a similar but not identical strain of the virus appears, those on-guard memory B cells react to their encounter with it, jumping into "time to defend!" mode. The only problem: your immune system does not generate new memory B cells keyed to the new variant. Instead, the existing memory B cell defense kicks in, producing antibodies directed at the original virus. Which is not the virus in you. So your defense system is ready for an enemy who is not there.

Immune imprinting defeats the ability of vaccine makers to update their mRNA vaccines to match new strains. A vaccine altered to match a new COVID will not produce antibodies protecting you from the new variant. It will just keep on trying to fight the infection with the antibodies it already uses, just making more of them. Studies published this summer and fall of breakthrough Omicron infections (people that contracted Omicron after being fully vaccinated) show that vaccinated people infected with Omicron produced antibodies better matched to the original strain against which they had been vaccinated (the old Wuhan strain), than to Omicron. Their bodies were primed to fight COVID by the prior vaccine targeted to the original Wuhan strain, loading their bloodstream with memory B cells keyed to this strain. In contrast, people without a previous vaccination made antibodies that specifically matched Omicron.

So you see the problem with the bivalent booster you took last September: It adds no protection against infection by BA.5. Nor would it have, had the booster been directed only at BA.5. Your body would produce antibodies against the Wuhan variant in either case – the version of COVID-19 you have been pre-wired to respond to by previous vaccinations. In one study published in the *New England Journal of Medicine* last month, antibody levels after the bivalent booster were 11 times as high against the Wuhan variant as against BA.5.

So Nikki, your booster didn't boost your protection against the virus variant you were being exposed to.

So How Do We Solve This Problem?

Nikki, you did everything right: vaccinations, booster shots and even the latest bivalent booster and still you have a breakthrough COVID-19 infection to deal with. As I read the scientific literature in an attempt to understand what is going on, everything seems very confused, with scientific studies lacking proper blind controls and riddled with gaps. The newspapers are also full of conflicting reports, with one expert panel unanimously advising the Food and Drug Administration to adopt an annual bivalent vaccine, another panel of research scientists advising that all future boosters be aimed solely at the most common variant that year, and still other scientists worrying that an annual booster may not be frequent enough. A frustrating picture.

All I can say is that we are clearly not out of the woods yet. The evolution of new variants of COVID-19 will continue, and vaccines will continue to focus on past experiences with COVID-19 rather than recent ones. The key to beating the virus at this game is to find a vulnerability shared by ALL variants, and target our vaccines there. New variants would not present a problem if our vaccines were targeting a part of the virus so essential to being a virus that it could not be altered, and so would be the same for all variants. How do we identify such a target? By looking for places in the genome that are always the same in any COVID-19 variant, and are also unchanged in other kinds of coronavirus like those that cause the common cold.

Are there gene sequences that are shared by all coronaviruses, implying the sequences can't be changed ? That appears to be the case. A lot of research labs are working on this challenging problem. We will get there, of that I am confident. In the meantime, we must continue to wear N-95 masks whenever around others indooors. It is the sure path to a safe future.

Have Mask, Will Travel

Which doesn't mean that life can't be simply wonderful. Nikki is marrying her marvelous Australian Matt this summer. Susie is raising her second child, a tiny beautiful daughter named Grace. With a very active and ever-curious elder sister, 3 year old Cindy, Susie has her hands full, with sleep a distant memory. Caitlin continues to publish exciting work, deep in snow in Santa Fe. Barb and I are trying to age gracefully, playing with grandchildren as grandparents do.

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I have been writing these pandemic letters for three years now (!), and it doesn't look like I will see the end of this story any time soon. But there is lots of fun to be had in our mask-wearing future, and much of interest to do. So, like Paddington, keep your ears up and your tail wagging.

Dad