

Letter 27: *Winter's End*

March 3, 2021

Dear daughters,

This last week your mother got her first vaccine shot (Moderna) and I got my second (Pfizer). Your mother had signed up for vaccination at seven different places with no sign of an appointment until she stumbled onto a small clinic right here in the city that gave her a shot within a few days! No ill effects other than sore arms for either of us on first injection; on my second, I had brief chills but no fever. I must say, COVID-19 vaccination has done wonders for our dispositions. What a relief.

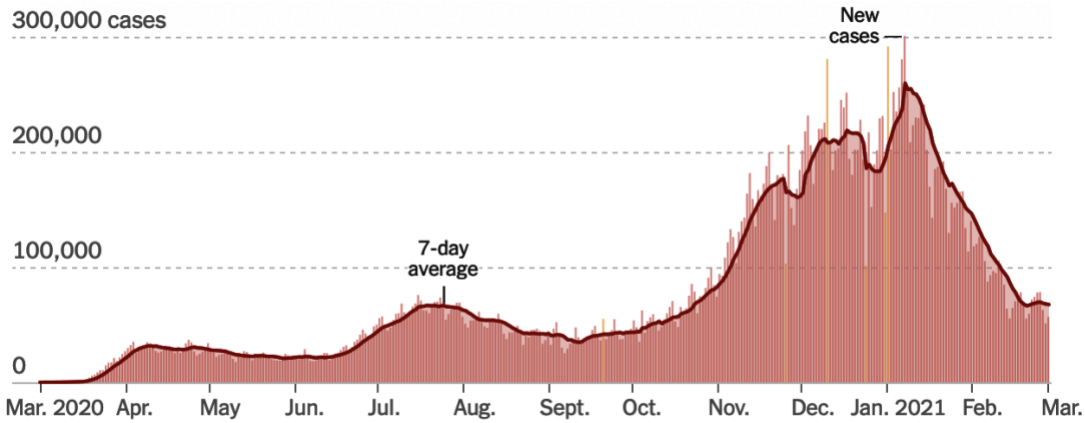
A Bleak Year

While it looks more likely now that your mother and I will survive this long winter, many have not. Last week our nation passed a horrifying milestone: half a million dead of COVID-19. A year ago on this date, the total number of deaths attributed to COVID-19 in the United States was two. If I had predicted to you girls then that we would see 500,000 dead within 12 months, you would have thought me demented.

A grim milestone indeed. If you do the arithmetic, this last year has seen an average of 1,424 COVID-19 deaths per day. That's almost exactly one very individual person dying of COVID-19 in the United States every minute! Each one leaves a particular void. Each of those 500,000 who died of Coronavirus infection was a person, an individual with a life just as particular as yours or mine – a person with a dog, a love of steaks and peanut butter, loved ones who grieved.

New Cases Are Way Down

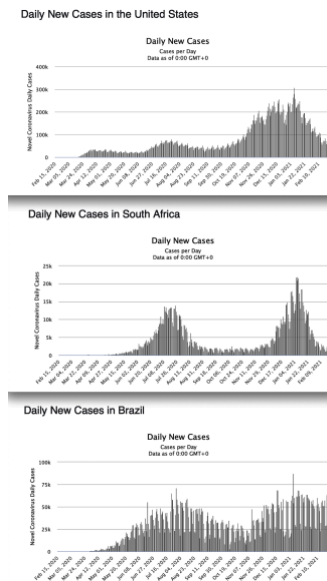
I do think we are leaving the worst behind us. The number of new COVID-19 cases being reported each day in the United States has been falling precipitously for weeks, and has finally settled at a level not seen since last July, before the dread November increase:



Why The Sudden Decrease?

What is going on? Why did the COVID numbers, which jumped so high this winter, then fall like a rock over the last few weeks? It's important that we try to answer this question, because whatever caused the drop, we want more of it!

When faced with an open question like this, my first instinct is to look around at other countries. Whatever is going on, it should affect them too. Do they show the same “winter peak” of infection?



In a word, yes. Indeed, the countries of Europe and South America also show the same general pattern. Differences in the timing and severity of economic lock downs have a country-specific impact.

So this rise and fall is happening globally. But why would infections fall from their peak levels so rapidly, in country after country? Do mitigation measures work? Or are we just running out of people to infect?

Could Herd Immunity Be the Reason?

The idea of herd immunity – that so many Americans have antibodies to COVID-19 that a virus particle emitted by one infected person is unlikely to encounter an unprotected individual – would certainly explain the mid-winter infection drop off.

In a such a herd, protected individuals would be of three sorts:

1. Those who have been diagnosed with COVID-19 and survived the illness, as their bodies would now possess antibodies directed against the virus
2. Those infected with COVID-19 who did not become ill, as their bodies would still possess antibodies directed against the virus
3. Those vaccinated against COVID-19, as the vaccine would cause their bodies to manufacture antibodies directed against the virus.

Could herd immunity explain what has been happening in our country? Unfortunately, the math doesn't add up:

- 23 million people had recovered from COVID-19 by January 15, when the steep decline in infections began, which is 7.2% of the U.S. population of 320 million.
- Add in asymptomatic cases, those people infected but not counted as being so because they had no symptoms. This fraction is usually cited as 30% or so – very roughly, for every two reported COVID-19 infections, there is another unreported. That adds 11 million more with antibodies, 3.4% of the U.S. population.
- 12 million people were vaccinated by January 15, another 3.8% of the U.S. population producing antibodies directed against COVID-19.

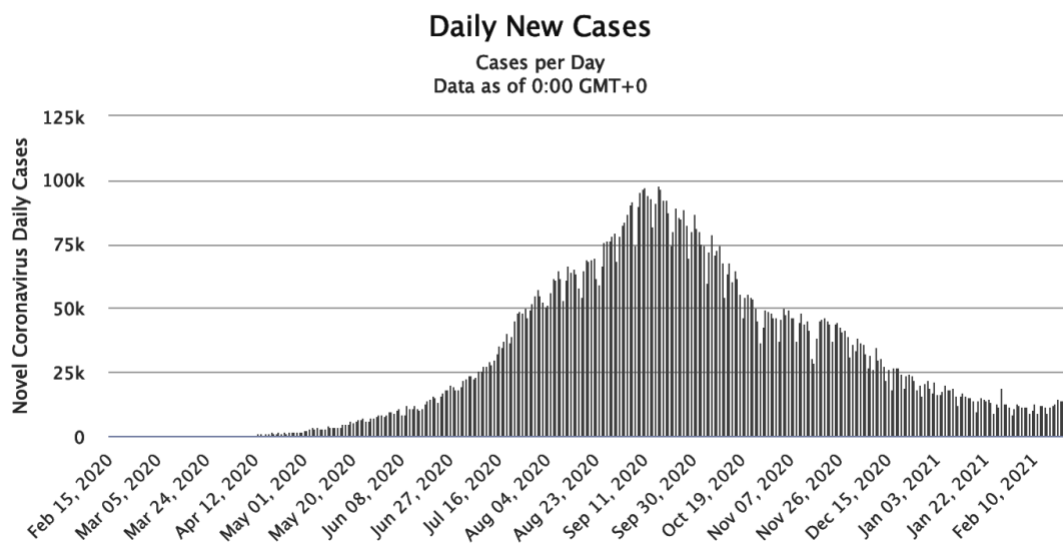
Add up the three sources of protection and you get 14.4% of the U.S. population protected from COVID-19 infection by January 15, when the steep decline in infection began. That's just not enough for herd immunity.

Most experts in this sort of stuff say we will need something like 80% protection before herd immunity can take off. For herd immunity to provide an explanation of our winter infection drop off, a lot more Americans would have to have had been infected with coronavirus without knowing it.

Herd Immunity in India?

In recent days there has been considerable discussion in India about the possibility that country is approaching herd immunity. Like the United States, India is a big, diverse country in the Northern hemisphere, and it has experienced the same massive flux of COVID-19 infection, with the same rapid fall off - but in mid-summer, not winter!

Daily New Cases in India



Last September, India was confirming nearly 100,000 new COVID-19 cases a day. But by the end of January the number had fallen to under 10,000 new daily cases – in a country of nearly 1.4 billion people! The fall in new cases was every bit as steep as in the United States, although in India infections rose in the summer and fell in the fall.

What has raised the issue of possible herd immunity is the report that a surprisingly large number of the people living in India seem to have antibodies to COVID-19!

Like most industrialized countries except the United States, India carries out extensive routine serological surveys – random tests for antibodies. A survey last week of 28,000 residents of India’s capital New Delhi showed that 56% had antibodies directed at COVID-19. In the Mumbai slums, the number was 57%. This is way more people than reported COVID-19 cases. It seems that most of the COVID-19-infected people in India had no symptoms.

Still, even if you buy the serological argument that so many people contracted the disease without knowing it (and the data seem thin), 57% protected by antibodies in India still seems a bit short for herd immunity.

And here?

Serological studies in the United States, while limited, hint (the data are very scanty) that as many as half of infected Americans may be asymptomatic. This would suggest that as many as 20% of the United States population might have been infected by the middle of January, when the great decline in infections began. Thus, counting vaccinations, recoveries, and asymptomatic infections, we get at most 25% protected in the United States by January 15, way south of the 80% needed for herd immunity.

So it’s not herd immunity causing our steep drop in infections.

What, then?

It may just be that mitigation works – all that social distancing and mask-wearing cuts r_0 down well below 1.0, causing the number of new cases to drop. Mitigation has been extensive in both India and the United States. Not a novel explanation, but I don’t know of any better hypothesis.

A Third Vaccine Is Approved

This week the FDA approved a third vaccine for widespread use in the United States, a viral vector vaccine developed by Johnson & Johnson. Long awaited, this vaccine is cheap to make, is administered as a single shot, and is easy to store and transport. 20 million doses will be available this month. Compared to traditional vaccines, it is quite effective, although it does not reach the sky-high effectiveness of the Pfizer and Moderna mRNA vaccines:

	Pfizer	Moderna	Johnson & Johnson
<i>Number of doses</i>	2	2	1
<i>Overall efficacy</i>	95.0%	94.1%	66.1%
<i>Efficacy against severe disease</i>	100%	100%	85.4%
<i>Efficacy against hospital/death</i>	100%	100%	100%

The J&J vaccine efficacy is actually 72% when measured in the United States, quite a respectable number. Its lower overall efficacy reflects the fact that a significant proportion of the J&J clinical trial was carried out in South Africa, where the J&J vaccine proved to be only 57% effective – that lower rate due to its inability to protect against the E484K variant of COVID-19 which had become common in South Africa by the time the clinical trial was underway.

Should you girls take the J&J vaccine if you can get it?

Sure! It offers quite good protection against serious illness in the United States. Most importantly, it is totally protective against hospitalization and death, which is the core issue. Fauci strongly recommends the J&J vaccine, as being “*well within the cushion of effectiveness.*” Of course, given a free choice you would pick either of the mRNA vaccines (Pfizer & Moderna), but I doubt very much you will have such a choice. Get protection from serious illness, girls, any way you can. As your father, I think it wonderful that such protection will be available for my daughters.

What About the Variants?

Last week I wrote about how the COVID-19 coronavirus has changed over the course of the pandemic. A coronavirus copies its genes when it multiplies within human cells, and sometimes in the copying mistakes are made. These mistakes create a new version of the virus called a variant. Most mistakes are harmful to the virus in which they occur, but sometimes a variant is changed in a way that improves its probability of transmission from one person to another. The variants D614G and N501Y were examples. As the pandemic progresses, the virus continues to

change. Some of the most important new variants are being generated right here in the United States. These new homegrown variants should come as no surprise. The United States has by far the greatest number of COVID-19 cases in the world, and so of course would be expected to generate the greatest number of variants. And of course those variants that transmit better will become more common:

- Newly arisen variant **L452R** in California (the amino acid leucine is replaced with arginine at position 452) affects the spike protein in a way that improves its binding to the human ACE2 receptor, enabling the virus to dock more efficiently with the ACE2 receptors on the cells of the human respiratory tract. This makes the virus more infectious.
- Another new variant **Q667P** is becoming common in the Southwest (the amino acid glutamine is replaced with proline at position 667). Q667P affects the spike protein outside the ACE2 binding pocket, but introduces a kink in the spike that facilitates the triggering of endocytosis and in this way promotes ease of transmission.

Should you girls be concerned about your own exposure to these new variants? Of course.

Will vaccination protect you from a more transmissible variant? Yes.

A mutation that improves the probability that a virus particle will be transmitted from one person to another does nothing to change how that virus particle is recognized by the anti-coronavirus antibody proteins a vaccine will add to your body's defenses.

A Variant to Fear

However, improved infectivity is not the only change in a variant that can cause it to become more common in a population or country. Another change that can cause a variant to explode within a community is defense avoidance – the ability of a coronavirus variant to better defeat our body's immune defenses. Here is how: In a population where many people have already been infected with COVID-19, most of the people a virus might infect will already possess antibodies directed against it, and as a result there will be very strong selection favoring any variant

mutation that allows the coronavirus to avoid being recognized by antibodies. Such a variant could happily infect everyone in the population, even the vaccinated.

Is such an antibody-avoiding variant possible? Unfortunately, yes.

We discussed one such variant in last week's letter: E484K.

The E484K change in the *s* gene of COVID-19 blocks antibody binding to the spike protein. This *s* gene mutation has occurred repeatedly over the course of the pandemic, and has been strongly selected for in countries where COVID-19 has struck heavily: South Africa, Brazil, the United Kingdom, and more recently here in the U.S. in New York City.

Because E484K blocks antibody recognition, vaccines developed to combat the usual strains of COVID-19 will not be as effective against E484K variant strains. We have already seen this in the South African clinical trial of the J&J vaccine: high levels of E484K infection in the South African population, and low J&J vaccine efficacy. Nor do the two mRNA vaccines of Pfizer and Moderna work effectively against E484K.

Obviously we will need to tweak our vaccines. Are we doing so? No and yes:

- Pfizer announced last Friday that it had begun a small study to see whether a third “booster” dose of their authorized vaccine would augment protection against E484K variants. To find out, Pfizer is offering a third dose of their vaccine to 144 people who were part of their clinical trial and had their second dose six months ago. In essence, Pfizer is proposing to simply give patients more of the ineffective vaccine.
- Moderna said last Wednesday that it has crafted a new vaccine targeted at E484K variants and is shipping doses to U.S. government agencies for testing. Needless to say, this is the right way to go. In a rational world, Pfizer will soon follow Moderna's example.
- Johnson & Johnson say, without releasing details, that they are also moving to improve their vaccine's performance against E484K variants.

So we wait and see. I have no doubt all three vaccines will be offered with E484K boosters by fall. In the meantime, it will be important to keep better track of where the E484K variant arises in the United States and how it spreads. This means we will need to do a great deal more virus genome sequencing. The new legislation coming out of Washington has funds to greatly increase genome sequencing of COVID-19 cases. We currently generate about 15,000 genome sequences a week from confirmed COVID-19 patients, which is way up from last month. Experts say we need to be doing 50,000 a week. Until that bright day, we should all keep our heads down, even your vaccinated parents.

The COVAX Global Initiative

While much effort is being expended by our federal government to obtain vaccination for every American, it is a great mistake to think that the pandemic will respect our national borders. Variants will continue to arise in other countries, so long as their populations remain unvaccinated. I have no doubt that some future variant will be potentially dangerous, able like E484K to evade our vaccines.

How do we address this very real danger? By vaccinating ALL countries, of course.

The United Nations tells us that 10 countries account for 75% of all vaccinations to date – and that more than 130 countries have not received a single dose. That's some 2.5 billion people who do not yet have access to a COVID-19 vaccine.

How do we get vaccines to these other countries, many with limited resources and affected by conflict and political instability? The World Health Organization has set up a global initiative called COVAX to help that happen. More than 190 countries have agreed to participate, although the United States opted out (the last U. S. administration has feuded with WHO for years).

COVAX first buys vaccine from the manufacturer and then distributes it to low-income and middle-income countries. A total of 600,000 doses of the AstraZeneca vaccine was delivered to Accra (the capital of Ghana) last week. COVAX plans to deliver 237 million doses to people in 147 countries by May of this year.

There are two problems:

1. The most obvious problem, of course, is paying for all that vaccine. COVAX has raised \$6 billion so far, and two weeks ago the current U.S. administration pledged \$2 billion more, with an additional \$2 billion to be released over two years if other countries make good on their pledges.
2. Then there is finding vaccine to buy. COVAX has penned deals with Novax, Pfizer, AstraZeneca, Sanofi, and Johnson & Johnson, but much of the world's vaccine has already been purchased. The U.K. has offered all of its excess, and France has pledged 5% of what it has on hand. The United States has not yet addressed this issue.

Our Family's Immediate Future Involves Kale

While we cautiously travel towards fall, when your mother and I plan to invade Maine, I leave you with this photo of me gathering foodstuffs at a Maine farm two years ago, with no thought of pandemic. May that day come again soon.



Love,
Dad