## Letter 36: The View Ahead

November 9, 2021

Dear Daughters,

Last week I watched a Zoom workshop of the Papal Academy of Science devoted to *COVID-19 Today*. Peter Raven, a Papal Academy member, had kindly asked that I be invited as a "nonspeaking" participant – a fly on the wall, if you will. 14 researchers, clinicians and government officials from around the world were invited to speak, spaced over two days, starting at 8AM St Louis time (early for your dad!). Some of the talks were very fine, especially that given by Francis Collins, the head of the NIH. A few were awful. The 20 Academy members listening to these experts asked questions after each presentation.


Much of what I heard dovetailed with what I have been pondering as I read the scientific literature. In a few instances, I found myself surprised. After swishing this all around in my brain for a few days, I would like to share with you my own views on where the COVID-19 pandemic is going. There is much that I would like you three to think about in coming months.

**Exciting New Vaccines**

I have been writing you girls about COVID-19 vaccination and boosters as if there were only two vaccines (Pfizer & Moderna), with an occasional mention of a third (Johnson & Johnson). Actually, the New York Times *COVID-19 Vaccine Tracker* web site lists 22 approved vaccines, with researchers currently testing 105 additional vaccines in clinical trials, with 75 more under active investigation in animals. That's 202 different vaccines! Fully 41 of the vaccines in clinical trials have reached the final stages of testing and will be presented to the CDC for approval within the next few months. Wow.

It's easy to get confused, with so many vaccines making their appearance. However, all vaccines act by stimulating an immune response, and basically there are only four ways to do it. All the 202 vaccines under development are variations of these four approaches. To elicit an immune response of a person to COVID-19, you can administer

1. enfeebled or dead COVID-19 **virus particles**.
2. harmless adenovirus containing COVID-19 **DNA** ( a letter in an envelope).
3. **mRNA** of the COVID-19 spike protein, within a protective lipid envelope.
4. COVID-19 spike **proteins**, attached in clusters to nanoparticles.

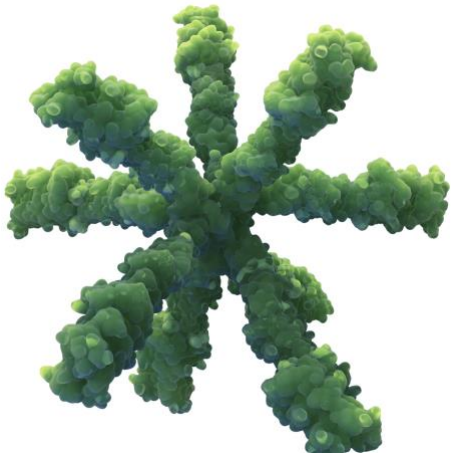
The first approach is used in four of the dozen leading vaccines, the second in four more, while the third and fourth approaches are used in two vaccines each. Our family is a third-approach family, getting our vaccinations and boosters from Pfizer and Moderna, both mRNA vaccines.

But it is the fourth approach that has me excited today. Approach-4 vaccines latch a bunch of spike proteins onto a nano-particle, presenting the spike proteins to our immune system much as if they were on the surface of a virus particle. The other three approaches all induce the vaccinated person to create a lot of individual spike proteins floating in the patient's bloodstream like logs in a river.

This fourth approach is the approach used to develop the rather mysterious Russian Vektor vaccine approved for use in Russia in October 2020. I have not been able to learn much about it,

except that it uses chemically synthesized virus proteins. I suspect the Russians have had production problems.

A small U.S. company, Novavax, also tested this approach in animals last year. Rather than chemically synthesizing the spike proteins like the Russians did, Novavax harvested naturally-made spike proteins from infected insect cells growing in culture. When tested in animals, the Novavax vaccine yielded extremely high levels of antibodies! However, it has proven difficult to upscale the manufacture of this promising vaccine. Only after a year of ironing out wrinkles has Novavax been able to manufacture enough to complete clinical testing. It has recently been approved for use in Indonesia and will be soon presented to the FDA for approval of use here.



I lit up like a candle when Francis Collins in his Papal Academy workshop talk described an approach-4 vaccine currently under development the U.S. Army at its Walter Reed Institute of Research. Collins hinted that the Army's version (24 spike proteins per nano-particle, arranged in small bouquets of three) was effective not only against COVID-19, but also against other coronaviruses like MERS and SARS! Remember that 20% of common colds are caused by other coronaviruses, and you see what Collins is hinting at: a pan-coronavirus vaccine that protects against ANY coronavirus!

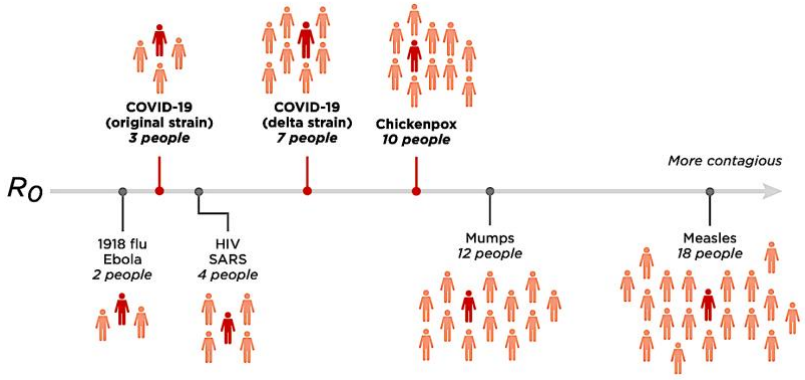
Experiments administering the Army's vaccine to monkeys showed that a two-dose vaccine delivered extremely high levels of antibodies. Phase 1 clinical trials began on April 5, so we are looking at next year to see just how effective it will be, and how broad its protection against variants like Beta or Delta.

**Herd Immunity**

As of today, 192 million Americans are fully vaccinated against COVID-19, 58% of the entire population. Isn't that enough for the United States to be approaching herd immunity?

No.

This is a very important question, greatly misunderstood, so I want to explain to you why I make this harsh judgement. The key to understanding what is going on in the COVID-19 pandemic today is our old friend $r_0$, how many people an infected person can be expected to infect. The greater $r_0$, the more infectious a disease. Relative to most diseases, the Delta variant of COVID-19 is pretty infectious, with an $r_0$ value of about 7:

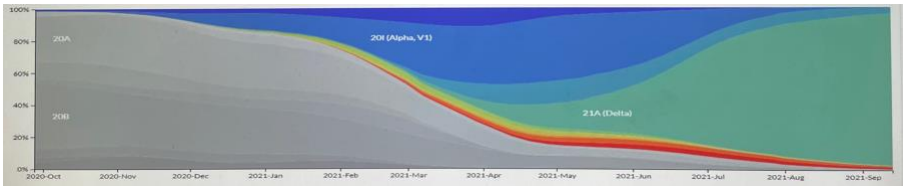



Now consider the seven people a person infected with the Delta variant might infect. If one becomes resistant to infection, you can see that this would reduce the effective value of $r_0$. As more of the seven potential "*infectees*" become resistant, the value of $r_0$ falls further and further. If $r_0$ falls below 1.0, the virus will not spread. At that point, the population has achieved herd immunity.

The goal of massive vaccination in this country, the reason President Biden and Dr. Fauci urge all Americans to "get the shot, " is to lower $r_0$ to below 1.0. It is that simple. How many Americans will need to become vaccinated? Most estimates fall in the range of 60-70%, with recent estimates by Dr. Fauci of perhaps 80%.

However, there are four big problems with these estimates:

1. **Declining Efficacy.** The basic assumption of all these herd immunity calculations is that someone who has been vaccinated will not become infected, and so cannot transmit the virus to others. Recent data tell us this assumption is flat wrong. Over some six months the efficacy of the Pfizer and Moderna vaccines has fallen off significantly (that's why your mother and I got booster shots). Over the course of a year, declining vaccine efficacies will cause the $r_0$ of the American "herd" to rise again.
2. **Waning Immunity.** How about the 45 million Americans who have been infected with COVID-19 and recovered? Aren't they now immune from future infection? Yep, but not indefinitely. Immunity wanes as the months pass. While the data are skimpy, about 1% of infected individuals become reinfected within 6-8 months. Over the course of a year, that's almost a million Americans subject to reinfection, driving $r_0$ further up.
3. **New Variants.** The initial COVID-19 variant that spread widely in this country was D614G, with an $r_0$ value of about 2. This was followed by the Alpha & Beta variants, with an $r_0$ value more like 3 – the virus was becoming more infectious. Then came the Delta variant, with an $r_0$ value of 7, far more infectious. The Delta variant simply thrived better in the human body, with patients typically having a1000-times-higher viral load. You hit more targets when you shoot more bullets. It is difficult not to fear that a new variant may arise with an even higher $r_0$ than Delta.




4. **Vaccine Hesitancy.** In his talk to the Papal Academy Workshop, Dr. Collins said that as the head of the NIH, the greatest surprise to him about the pandemic was the hesitancy of many Americans to receive COVID-19 vaccination. With fantastically effective vaccines now readily available and FREE (the federal government picks up the cost), he had expected everybody to welcome vaccination. However, resistance to "mandates" has become a political issue in the United States, coupling misinformation about vaccine

safety to concerns about government overreach. States where vaccination has lagged are clustered in the South, creating zones where $r_0$ is far higher than in the rest of the country.

For all of these reasons, I don't think there is a ghost of a chance that our country will ever reach herd immunity. It is, unfortunately, a pipe dream.

Widespread vaccination is still a key priority, for the simple reason that it saves lives. I am all in favor of vaccination mandates for the military, large corporations, health workers, and professional football quarterbacks. What vaccination will NOT do, however, is create a world where the unvaccinated are safe from infection.

I think it highly unlikely $r_0$ for COVID-19 will ever fall below 1.0 in this country, and as a direct result of this the coronavirus pandemic will persist here indefinitely. We live with the flu in just this way, an endemic disease always with us. Not negligible, but manageable.

**Taking a Pill for COVID-19**

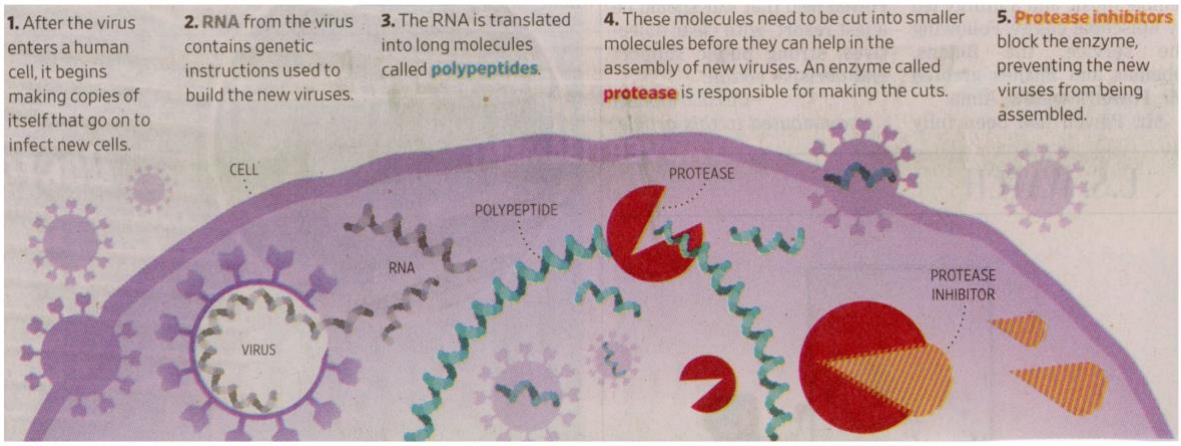
Good news from an unexpected quarter this week. Biomedical researchers have found a way to tweak drugs originally developed to treat AIDS so that they can be used to fight COVID-19.

The drug maker Merck was the first to do this. Their anti-COVID-19 drug, molnupirvir, was approved last Thursday for use in Great Britain, and has been submitted to the FDA for sale in this country. It is a slightly altered form of a drug Merck had developed to successfully manage AIDS. The anti-virus pills act to block replication of the H.I.V. virus by inserting errors into the virus's genetic code. Unfortunately, molnupirvir is only 50% effective, and only when given within five days of the onset of symptoms (40 pills over five days).

The anti-COVID-19 drug announced by Pfizer this week appears to be much more effective. Its clinical trial involved unvaccinated adults at high risk (age, obesity, diabetes). Three out of 389 patients who received the drug required hospitalization, compared to 27 out of 385 who got placebos. An independent group of medical experts monitoring the trial stopped it midway

through the trial because results were showing such a clear benefit: an 85% reduction in the risk of hospitalization or death from COVID-19!

The Pfizer drug, called paxlovid, works by inhibiting a virus enzyme called a protease. The COVOD-19 virus uses this enzyme to slice up the gene copies it makes of itself so those sliced-up bits can be packaged into newly-made virus particles. When paxlovid inhibits the protease from slicing, new virus particles cannot be assembled and infection fails.




The origin of Pfizer's drug goes back 19 years, to the SARS epidemic of 2003, when researchers first used AIDS and hepatitis C treatments to fight that deadly coronavirus. Early last year, Pfizer began modifying the SARS drug's design so it could be used to fight COVID-19, a coronavirus very similar to SARS. Because the new formulation of the protease inhibitor can be taken as a pill (actually a lot of pills, 30 over 5 days) rather than intravenously, it can be taken at home as soon as symptoms appear, long before a person gets sick enough to go to the hospital.

Pfizer has already begun manufacturing paxlovid and plans to produce more than 180,000 pill packs by the end of the year. Rapidly upscaling, they plan 21 million packs in the first half of next year, and 50 million by year's end. They have not disclosed the price.

Enough. Stay safe.

Dad