

For my daughters:

May 16, 2020

## **The Coronavirus Pandemic** *A Long and Bumpy Road*

After two months of shelter-in place lockdown, and seven letters to you girls telling a story with ever-blacker edges, my memories of you are what keep me upright and hopeful of a brighter future. This photo, not recent but alive in my memory, is what I mean.



With over 300,000 dead worldwide from COVID-19 and our government response muddled and ineffective, we could use some good news. It's not that the issue is complex. COVID-19 is a respiratory virus, passing from one person to another in air droplets we expel with each breath we take. This photo tells you all you really need to know about the virus:

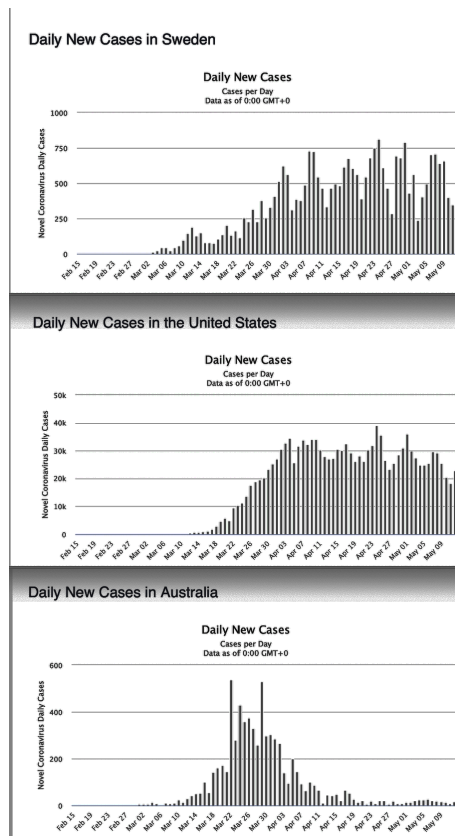


## What You Need To Beat the Virus

To combat infection by a virus spread in this way, we need to do only two things, both equally necessary:

1. keep people apart, so the virus cannot bridge the distance between them.
2. identify and isolate infected individuals, so they're not near anyone else.

Simple, right? How effective are these two strategies? As you can see in my diagram below, we can answer this question by comparing countries that have adopted just #2 (Sweden), just #1 (United States), and both #1 and #2 (Australia):



**JUST #2: Sweden** has ignored social distancing, keeping its shops, restaurants and schools open while carrying out extensive testing and contact tracing to identify and isolate infected individuals. Its daily COVID-19 infection rate has remained at a  $r_0=1.0$  constant rate, not getting worse and not getting better.

**JUST #1: The United States** has (until recently) imposed strict social distancing, closing down business and schools and insisting on shelter-in-place, while not carrying out extensive testing or contact tracing. Its daily COVID-19 infection rate has remained fairly constant at an  $r_0$  of nearly 1.0, like Sweden yielding a plateau rather than a mountain peak.

**BOTH #2 and #1: Australia** has both closed down its economy and carried out extensive testing with contact tracing. Its daily COVID-19 infection rate after rising rapidly has fallen dramatically to near-zero, the mountain peak every country seeks.

## A Bleak Outlook

In my letters of the past few weeks I have been quite pessimistic about our federal government's recent encouragement of relaxing social distancing guidelines. With 40 million unemployed, many are understandably eager to get back to work. Other, like the people crowded onto the Christopher St Pier in NYC on May 3, just want to get out of the house or apartment. In this



photo, there is only one person with a face mask! Try a “Where’s Waldo” and find him or her...*(hint: she is dead-center in the photo)*. You can see why I have been so gloomy in my past letters to you. In the analysis I just gave you, our country’s new approach to the pandemic would be to adopt NEITHER #2 nor #1 -- not an encouraging direction for our, or any, country.

## Whistling in the Wind

What our federal government IS doing is promoting development of a coronavirus vaccine. This is exactly what we should be doing, so I have no criticism of this policy. It is the marketing of the policy that is misleading and dangerous. The white house has labelled the effort “Project Warp Speed” and has promised a vaccine before the end of the year -- more than a full year earlier than vaccine experts like Fauci say is possible. Appointing an Army General to plan a quick ramp-up of production and distribution makes great sense to me; again it is exactly the right thing to do, and timely. Promising the vaccine a year early, however, is just politics - the November election looms in the fall. Today the White House promised 100 million doses of the vaccine will be available by November, 200 million by December, and 300 million by January (the population of the United States is 331 million). We can expect to hear similar loud promises of a coming vaccine repeated often in the summer months to come.



## Inventing A Vaccine

With all the talk of coming vaccines, I think it worthwhile for me to step back a bit into my Professor mode and explain to you girls a few things about vaccines, so you can get a sense of why it is difficult to develop a COVID-19 vaccine at warp speed. The record for developing an entirely new vaccine is four years, so how might we hope to improve on this?

First, we have to manufacture a vaccine. At the heart of every vaccine is an antigen, a molecule which provokes the body's immune system to generate antibodies against the virus – like poking a sleeping wasp nest with a stick. There are five general ways to present COVID-19 antigen to a patient, four that have been used successfully in the past and a new approach:

1. **Recombinant Vector Vaccines.** One way to present a COVID-19 antigen to a human immune system is to insert the COVID-19 gene for spike protein into a harmless virus. A common choice is adenovirus, which is very good at getting into cells. Scientists remove one of its genes, so it cannot replicate and so is safe. When injected into a person, this so-called “recombinant vector” virus will induce the cells it infects to make COVID-19 spike proteins, which these cells will then display as antigens on their surfaces, waving them around like little flags to draw the attention of the immune system. The immune system responds to this warning by making antibodies directed against COVID-19 spike proteins, and so protects the vaccinated person against the virus. This is the approach taken recently against Ebola.
2. **Live Attenuated Vaccines.** Another way to expose a patient to COVID-19 antigens is to damage COVID-19 virus particles in a way that renders them harmless without killing them (the virus is said to have been “attenuated”), and then inject this live but hobbled virus into people. The spike proteins are still present on the attenuated virus, so antibodies to COVID-19 are produced, but the vaccinated person doesn't get sick because the virus has been disabled. This is the approach taken in the past with many commonly-used vaccines such as those directed against chickenpox, measles, mumps and rubella.
3. **Inactivated Virus Vaccines.** A third way is to simply “kill” the virus and inject it. All you have to do is heat the virus solution. The spike proteins on the heat-inactivated virus can still induce antibody formation. This is the way the Salk polio vaccine was produced. Your seasonal flu shots are another example of this very direct approach.
4. **Subunit Vaccines.** In a fourth kind of vaccine, the patient may be presented with the antigen itself, spike proteins harvested from the blood of those infected. This activates the patient's immune system to produce antibodies against COVID-19 spike proteins. This approach is the one taken to make the HPV vaccine. Yeasts can be engineered to carry a DNA version of the virus S gene and manufacture large amounts of the virus spike protein. This is the approach used to make the vaccine for hepatitis B.
5. **Nucleic Acid Vaccines.** In principle, it should be possible to simply make jillions of copies of the COVID-19 gene encoding the spike protein using PCR (remember? Polymerase Chain Reaction), and inject a solution containing spike-gene RNA molecules directly into patients. Their cells would be expected to take up the RNA and begin producing the spike proteins, inducing the patient to manufacture antibodies directed against it. To date, no RNA vaccine has been licensed for use anywhere in the world, but several labs are working on this one, and preliminary results are promising.

## **Testing Is the Bottle Neck**

Vaccine testing usually begins with testing animals to see if the vaccine harms them and lessens their susceptibility to infection. This is an important step, as there is nothing guaranteed in vaccine development. Some vaccines developed with approaches like attenuation or inactivation that have worked for past diseases prove to be harmful to animals you are attempting to protect from a new disease – called “antibody dependent enhancement,” some vaccines (including a vaccine directed against cold-causing coronaviruses) actually turn out to promote the infection! The only way to know for sure if a vaccine is safe is to try it out, usually starting with mice or rabbits, then moving up to monkeys, which are a lot more expensive but much more like us.

Vaccine trials in humans can begin if the animals testing is successful. There are usually three phases, increasingly more intensive:

1. The first phase involves injecting the candidate vaccine into a small group of people to assess its safety.
2. If it proves safe, the second phase ramps up the number of people to a few hundred at risk, and is conducted as a randomized trial in which some people get the vaccine and others get a placebo (a “dummy” dose of plasma fluid). No one, not even the investigators, knows who is who until the results are in, so the test is guaranteed to yield an unbiased answer to the question “Does it work?”
3. If the results are promising, the testing moves to a phase three randomized clinical trial for efficacy and safety involving tens of thousands of people.

How long does all of this take? Sanofi, a French biopharma company, has begun phase three clinical trials of a vaccine it has repurposed from a SARS vaccine that has already passed phase two trials. It says that, if successful, its COVID-19 vaccine could be ready by late 2021. Note: the date ends in the number “1,” not “0.” It is hard not to feel the White House promise of a vaccine by November is a bit silly.

There are short cuts, of course. One way to shorten the time required for clinical trials is to drastically reduce the number of people being tested. How? By deliberately infecting test subjects with COVID-19 after vaccination. Wildly unethical, this “challenge” approach is being promoted on the website “1 Day Sooner” – more than 16,000 people have volunteered.

## **But Summer Is Coming**

Do any of you three play bridge? I used to be a fanatic in grad school. Well, in a bridge hand of cards, certain ones are winners against any others, no matter the other card’s face value. Called “trump” cards, if you slap one of them down on top of your competitors’ cards, you automatically win (Shouting “Trump!”). Well, in the COVID-19 game, it seems that there is going to be a trump card: summertime. Summer is fast approaching, and coronaviruses are seasonal, so we might expect the number of COVID-19 infections to drop as the weather warms, no matter the lack of social distancing. We shall see. There is nothing wrong with hope.

Till then, love you lots and lots.

Dad