"We'll get through it": A venture capitalist and medical doctor reflects on COVID-19

Laurence B. Siegel
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In this article, I interview Dr. Drew Senyei, a medical doctor who has spent much of his life starting and growing biotechnology companies. He is a member of a discussion group to which I also belong, and his wide-ranging accomplishments and interdisciplinary knowledge are widely respected. Please see his biography in the sidebar.

ANDREW ("Drew") SENYEI, M.D., is a venture capitalist and inventor with more than 30 years of experience in the building of emerging technology and healthcare companies. For 25 years, he served as managing director of Enterprise Partners Venture Capital, which has $1.1 billion under management. He has served on the boards of more than 30 private and public companies and was named one of the top 100 venture capitalists in the U.S. on *Forbes* magazine's 2006 Midas Touch List. He was the founding investor in Nuvasive (NASDAQ: NUVA), one of the largest minimally non-invasive orthopedic companies in the U.S today with revenues of more than $1 billion. Currently, Dr. Senyei is Executive Chairman of, NeoSeq Ltd, a company focused on advanced genetic testing of cancer and other diseases with primary operations in mainland China.

Dr. Senyei is credited with 30 patents and more than 45 publications in peer-reviewed journals, including the *New England Journal of Medicine* and *Proceedings of the National Academy of Science.* He was an inventor of the first and currently only FDA approved test to predict and help manage pre-term birth, as well as the use of RF chips for new chemical compound synthesis and single cell isolation technologies for medical diagnostics.

Drew currently serves on the board of trustees of Northwestern University. He is a former chair of the UCSD Jacobs School of Engineering Advisory Council and member of the UCSD Foundation Board. Currently, he is co-chair of the advisory board of the California Institute for Telecommunications and Information Technology. He received his M.D. from Northwestern University and completed his residency training at the University of California, Irvine, where he served on the faculty prior to becoming active full-time with venture capital funding of early stage technology companies.

Larry Siegel: I'd like to start by just asking you to give me a rundown on your thinking about the novel coronavirus or COVID-19 situation. We have heard every possible point of view ranging from, on one extreme, just letting it happen so that we develop herd immunity to, on the other extreme, taking draconian measures that lock people down and stop the economy to inhibit the spread of the disease or "flatten the curve." By the way, you asked me to mention that your answers reflect your own views and not those of any institution, so I'm doing that.

Dr. Drew Senyei: Let me begin by saying that our knowledge of this particular virus is about 13 weeks old. We sequenced it, we know some of the proteins in it, but its biology – how it behaves in humans, who gets sick, who doesn't, can we make a vaccine or not – all those things are unknowns. We have lived with various coronaviruses for a long time, but what is now clear is that this coronavirus is very different from the previous coronaviruses that became epidemics, such as SARS and MERS. But we don't know how different, either quantitatively or qualitatively, so we're dealing with projections and guesses on a variety of major parameters.

The most immediate unknown is how lethal this is. That is related to something called the case fatality rate (CFR). That's simply the number of people who die of the disease, expressed as a percentage of the number of people who have it. The problem is that the denominator is very poorly estimated, for multiple reasons. One is that we haven't tested everyone, especially asymptomatic patients. This virus is particularly infectious because many people who have it and can transmit it are asymptomatic, and we really have no idea how many of them there are.

In addition, the reporting of deaths in this country is not perfect, in that some people who died from this also have other causes of death. They often have cancer or heart disease, so the question is: did the virus kill them or did the cancer or heart disease kill them? That can be difficult to ascertain. They're usually coded in the medical record as viral pneumonias or acute respiratory distress. So the

data are noisy.

The CFR helps us decide, is this like the regular flu, with a CFR of 0.02%, or is it something worse? The best guesses right now are that this is not the ordinary flu. But it's not SARS with a CFR of 9.6% or MERS with a catastrophic rate of 35% either. Also, the measured CFRs for SARS and MERS were much, much higher in the early part of the pandemics than they were after the pandemic subsided. So we're kind of building a plane as we're flying it. We just don't know the numbers. When you don't know something, you overreact in an abundance of caution. Right now the best estimate of case fatality I've seen was in an unfortunate Petri dish experiment called "The Diamond Princess."

Larry: What is that?

Drew: It is a cruise ship that had 3711 people onboard. Apparently only one person had the virus until they got on the ship, then a very large number of them contracted it – 705 tested positive – so we have a controlled experiment. The result was that no one under 70 died. When you consider that there were actually in a confined condition and how contagious this virus is -- it survives on surfaces sometimes for days…

Larry: That sounds like a pretty good outcome, very good actually.

Drew: Of those 705, half were asymptomatic. We know that we're not testing all the asymptomatic patients here in the United States or anywhere else. So the denominator of the CFR is much, much larger than the count of people with active disease.

Larry: So that means that the actual CFR is much lower than the measured CFR, doesn't it?

Drew: Yes, but you have to go a little deeper than just an average CFR. You have to go to both age-adjusted and health-care-system adjusted CFRs because this virus is clearly much more lethal in people over 70 than in people under 70.

Larry: Okay, but before you do that, can you explain how this virus works and why it can be so lethal?

Drew: The lining in our lungs and intestines is composed of epithelial cells that block many harmful pathogens from entering the body. The new virus (SARS-Co-V2) evolved a special spike protein (think of it like a key) that attaches to a receptor on these cells (think of it like a lock) that allows it access to our body. If a virus does not have the right key it cannot get in. Once inside, it replicates itself many times by hijacking our cell's normal machinery. It then bursts out to infect many other cells, causing our immune sytem to go into overdrive to try and combat it. Normally, our immune response stays in check and only kills the invader. However, in this case our body overreacts and starts harming our normal cells. The inflammation injures primarily our lungs but also other organs including our heart, leading these patients to become very sick with multiorgan failure very quickly.

Once the lungs become flooded with inflammatory products, they cannot exchange oxygen very well and require advanced mechanical ventilation. This is called Acute Respiratory Distress Syndrome (ARDS) and requires very skilled doctors and nurses in ICUs to manage these patients. The ventilators support the patients and allow the lungs time to heal. Unfortunately, once a patient is intubated and on a ventilator the death rate is very high, but we do not yet know why. Even those that survive stay in the ICU much longer than other critical patients. The ICU bed turnover for these patients is a lot longer so it is not just the number of beds available, but also the length of stay that strains health care resources and personnel.

Let's look at Italy and South Korea, where hopefully you can believe the numbers. (Italy and

South Korea have about the same number of positive patients.) Italy's case fatality rate was something like 6.6% at one time, and South Korea's 0.2%. you go down one more layer and ask what the case fatality rate was for people over age 80, and Italy's is 19.0% and South Korea's is 3.0%. But if you looked at the 20- to 29-year-olds, the case fatality in South Korea is 29.0% and 3.7% in Italy. So it's exactly backwards from what it is for people over 80.

Larry: The Italy-South Korea CFRs span a range of 33 to one! What good is this measure with numbers like this? And, a CFR of 29% for people in their twenties is huge, how can that be?

Drew: Again, these are incomplete statistics, because you don't know the denominator. You don't how many of the 20 to 29-year-olds got tested. There are probably a lot more of them out there with COVID-19 than the ones who got sick enough to get tested. The way that various countries test is different too. Some, like South Korea, test everybody and some only test symptomatic patients. So the bias of your sampling is really a function of the health care system, the reporting and resources, access to testing, and so forth.

In past epidemics or pandemics like SARS and MERS, we saw a high initial CFR, and then it dropped considerably. No one knows, but the numbers I'm seeing indicate a CFR of 0.5% to 1.0%. But this can change as more testing is done.

Larry: Considering how many people need to be infected to achieve herd immunity, that's still a lot of deaths unless you mean simply the accelerated deaths of the very old and very sick. Let me go through a few numbers. If it takes 50% of the U.S. population, which is 50% of 330 million or 165 million people, to achieve herd immunity (that is, where everyone you're likely to meet is either recovered or immune in the first place), and you then multiply by your low CFR number of 0.5%, that's 825,000 deaths.

Am I in the right ballpark doing the calculation this way? Are these incremental deaths (on top of the roughly 3 million people who die each year in the U.S. anyway), or are many of them really a reclassification of the deaths of the old and sick to COVID who would die from some other cause, including the flu? An incremental 825,000 deaths would be a catastrophe. "Only" 58,000 people, mostly young, died in the Vietnam War over a period of years and it turned the country upside down and changed our foreign policy forever.

Drew: Your calculations are mathematically correct but are relevant only if your starting assumption of CFR is correct and social distancing has zero impact. But social distancing is having a very positive impact!

My bet is that the CFR will fall below what we are guessing now, but we do not know how far below. It will be determined by how well we prevent overwhelming our healthcare facilities and personnel and how rapidly we develop a treatment. The seasonal influenza CFR is around 0.1% and 20,000 to 60,000 people die in a given year, yet we do not close the economy down because of it. However, because COVID-19 has already spread to so many places, we want the density of new cases presenting in any geographic area at any given time to be as low as possible and over as long a time period as possible to prevent a surge on the healthcare system.

I want to mention testing because that's what I've been doing most of my life. There was a lot of mishandling in the early part of this by the government. The CDC would not accept the World Health Organization (WHO) test, which was developed in Germany, because they didn't feel it was accurate enough. That might be true and it might have been the right thing, but doing the right thing meant that we delayed testing significantly. So we couldn't estimate the denominator very easily. And we're still behind. That's point 1.

Point 2 is that the FDA issued what's called Emergency Use Authorization, which means labs

could develop their own home-brewed tests, so we're getting a wide variety of different equipment and tests. I predict there will be more testing in the U.S. in the next month than there was in the world in the last month**,** because of the number of manufacturers who are coming up a range of tests.

Larry: Good!

Drew: And they all have what's called *analytical validity*, which the FDA requires. This means that if you do the test in your lab on a specimen 100 times, then you get the same results 100 times.

But we don't know what the *clinical validity* is – which is, how does this test behave in the real world? So for example, when you sample your nose and the back of your mouth, how is that sample done by different individuals? Some go higher, some go lower. How long is that sample sitting around before it's shipped to the lab? Does it go somewhere where it gets frozen, then heated? How much degradation of the RNA virus takes place before it is analyzed?

Then we have to know that the patient you took it from is a true positive. The third problem is that reporting differs across states. Some states report positives only, some report positives and negatives. We have a patchwork of information systems - the National Influenza Database, CDC/NIH, private tracking of these things. So we don't have a single uniform national standard that everyone is adhering to.

Larry: Why is it considered acceptable to report positives and not negatives? In any investigative field, if you if you look for something and don't find it, you're supposed to report that to save other people the trouble of going down the same dead end. Whether your report ever gets published is, of course, another matter…

Drew: Welcome to the real world. There is a lot of point-of-care testing going on, using many different systems. There are over 100 companies now started for testing for coronavirus. We may not need all of these 100 companies, but we'll probably need 20 – because we're going to need to continually test. Not just for this virus, but for all the respiratory viruses because it's so hard to discriminate between a regular flu and COVID-19 on initial presentation.. The symptoms overlap. So you have to test for influenza A/B, parainfluenza, all the respiratory viruses out there, ideally at the same time so we can help with the differential diagnosis of COVID-19 versus other respiratory viruses.

If we actually were able to do that, it would be the most useful way to test because you could then attribute the incremental fatality that's due only to COVID-19. The problem with that is co-infections: you can get both the regular flu and COVID, and then, to complicate it more, there are secondary bacterial infections. You're compromised to fight a bacterium, so people often die of bacterial sepsis instead of the virus. So we need better testing and more testing, primarily for triage purposes. We need to know how much of the disease is out there so we can have the health care resources and physicians to respond to that surge, where and if it occurs.

Larry: The concern that keeps me up at night is not getting the disease, but the social costs of the "cure." Opinion seems to have crystallized into two camps. One says that we have to prevent or slow the spread of the disease at all costs. But I want to know, what *are* the costs? The other camp focuses on the economy, mental health, morbidity, longevity, and the money available for solving long-term problems. This second camp argues that we should ease up relatively quickly on policies that discourage work and income and social interaction, otherwise we will severely injure the economic life that provides the resources to fight disasters like this, as well as the everyday needs that people have.

The problem is that in any dichotomy like this, it seems to me to poorly framed. There's an optimum or balance somewhere between the two extremes. You need to balance your responsibility to the patient in front of you and the health of the society including future patients (or helping people in

the future not become patients). If you were in charge of this, what would you do? And why?

Drew: OK, so I'm king for a day? First, because of all the unknowns, I would try to err more on the side of caution rather than what England tried to do initially, which was to keep a stiff upper lip and get to herd immunity; as quickly as possible. That policy changed rapidly once they realized the surge it would produce on healthcare resources. So I think I agree, there's a rational middle ground and that is: we have to first understand if this is peaking. And remember when you look at new case rates, you're actually lagging by 2 weeks…

Larry: I'm aware of that.

Drew: I would look at those [new case rates], and then at hospitalizations and intensive care utilization, and see if that's peaking because that is the most pressing problem. Then I would look at the rates by population density and see where the wave is happening more locally and usher resources there. New York is a canary in the coal mine. But there are other places; New Orleans, Washington's kind of coming up. So I would, first of all, mandate a standardized test, looking at everyone's serum to see if they have antibodies against COVID-19. That means testing everyone, which would be impractical but...

Larry: To get a stratified sample, couldn't you test a tenth of the population or even one one-hundredth of the population, selected to be representative of the entire population?

Drew: Yes, I would do a power calculation to determine sample size. This is an estimate of how accurate your test is and determines the minimum required sample size needed to achieve statistical significance.

I would do that with one standardized test so we know who's already had the infection and who hasn't. That gives you immediate triage for who could go to work and who can't. This is especially critical for health care providers because, once you get one doctor infected, it becomes a "care multiplier," decreasing the number of people who can attend to those who are sick. So health care providers are really not a great population to infect….

Larry: Please continue describing what you would do.

Drew: I would, first, get serology testing on a representative population in a standardized test. There are some complicating factors, but this would get you a better sense of who's had the infection, who's over it, and who's protected at least for a while. We don't know about reinfection because the biology of this disease is only 13 weeks old but at least those data give you a starting point.

So the first priority is triage. You would need serology testing (that is, a test relying on a blood sample to identify neutralizing antibodies to the new coronavirus) to prove that an individual is already immune and not likely to get infected or infect others. Such people could go back to work. The second is to look at the density of the elderly and make sure resources are adequate for that particular region – not just equipment and supplies, but personnel. Finally, I would invest really heavily in the basic biology and in vaccine development which is two years out. I think you're going to need a vaccine and you'll probably need a new vaccine like you do for the flu every year. This virus will mutate. Now all that takes money, time, and coordination – but people are working on it and I think, if we did that, we could sort of get back to the economy being an economy. Otherwise we're going to be in the dark ages.

Larry: Yes – we're going to become very poor very quickly. I was wondering: is there some sort of last word you'd like to add?

Drew: This is just another chapter in the viral wars on the human race. We have had many attacks in past eons. Today fortunately we have the tools to better characterize them at the molecular level. In the future, we need to be earlier in becoming aware of their arrival, to prevent them from getting out of control. We have already eliminated other some viruses from the world, including smallpox and polio, which are virtually gone. We now have vaccines for influenza, though they could be better. Given the advances in medical knowledge and molecular biology, especially in the last decade and with the full focus of the world on this one challenge—we will get through this.

Larry: Thank you.

Laurence B. Siegel is the Gary P. Brinson director of research at the CFA Institute Research Foundation and an independent consultant, writer, and speaker specializing in investment management. Previously, he worked at the Ford Foundation for fifteen years, most recently as director of research in the investment division. Prior to that, he spent fifteen years with investment research and statistics firm Ibbotson Associates, the last seven of those years as Managing Director. His book, *Fewer, Richer, Greener: Prospects for Humanity in an Age of Abundance,* was published by Wiley in 2019 and is available at https://www.amazon.com/dp/1119526892/. His web site is http://www.larrysiegel.org and he may be reached at lbsiegel@uchicago.edu.