



COVID-19: What we Know, What we Don't Know and What that Means

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These are unprecedented times, both from a human health and welfare perspective and a market perspective. Things are moving quickly and there is a lot of misinformation and partial information circulating. It is often difficult to keep things in perspective, so data about things like the supposed Korean re-infections or the implications of a positive antibody test are often taken out of context and blown out of proportion.

The point of this note is to lay out what we do and what we don't know about SARS-Cov2 (the virus) and COVID-19 (the disease), how we as a society and humanity really are dealing with that from a health policy perspective.

This is what we DO know about the situation we are in right now:

This is the most significant public health crisis most of us will have ever faced in our lifetimes – and it's not going anywhere until we have a vaccine, or everyone has natural immunity. But importantly, we are in a lot better position to deal with this from a scientific and clinical perspective than we ever have been in human history. The knowledge about genetics, molecular biology and medicine are much farther advanced than they were 5-10 years ago, much less 100 years ago. Given the technology, knowledge and resources being directed toward COVID-19, there are many reasons for optimism.

This is what we DON'T we know about our current situation:

We don't know when things will be "normal again" and ultimately that's what we all really want to know. As a grandparent, you want to know when you can hug your grandkids again; if you are someone dealing with working from home with a 10 and 7 year old, you want to know when you can get back to the office, many people want to know when they can just take their next trip.

Functionally, that's what the market wants to know too – when the economy is going to be back on a stable track. The other big unknown – what the cost of the cure is going to be economically – will have to be priced in by the market.

Just over a month ago, we at Signature thought the market was being far too pessimistic based on what we believed about the disease, now we think the pendulum may have swung a bit too far the other way. We think we still have some volatility ahead as we see how well the virus can be contained.



SARS-Cov2 (the virus)

It’s important to start with the virus, because the virus informs what we know about the disease, which informs how we must implement health policies to get us through this, which will ultimately inform the economic impact and the subsequent market reaction.

What we know	What we don’t know
A member of the coronavirus family of viruses that likely jumped from bats to humans last fall. Similar to SARS.	How to stop the virus from infecting human cells and replicating.
Less fatal than SARS or MERS, but more easily spread (significant pre-symptomatic transmission).	Exactly how it spreads, by who and in which environments.
Genetically stable -- not expected to mutate, so new vaccines would not be frequently required	How our immune systems will react to the virus over time -- will humans gain lifetime immunity, or something more short term?
	How close we are to herd immunity (requires 50-70% of the population to have immunity).

Our immune response to SARS-Cov2 is critically important, because for the pandemic to be completely behind us, enough people must become immune so that the virus can’t be spread and burns out. There are only two ways this can happen: 1) either a vaccine is developed, and everyone can get it – which is likely more than a year away; or 2) enough people get infected and recover and we get to “herd immunity.”

We won’t really know how close we are to herd immunity until we have tested enough people to know how widespread the virus is. Current best estimates are that between 1% (in areas relatively unscathed by the virus) to 20% (in areas hit particularly hard) of the population may have antibodies.

COVID-19 (the disease)

Unlike the virus, where there was already a reasonable base of knowledge given the close relation of SARS-Cov2 to SARS, there is a lot that is still unknown about the disease itself.



What we know

What we don't know

Significantly worse symptoms and fatality rates than influenza.	What the actual fatality rates are for the broader population (lack of testing; testing focussed on those most ill).
More severe impact on the elderly and those with underlying health conditions such as COPD, diabetes, obesity and cardiovascular disease.	All the ways that COVID-19 causes damage to the human body. The focus has been on respiratory issues, but it can have a more complicated effect.
Treatments to date have been largely ineffective at altering the course of the disease.	How to treat the disease, although there are hundreds of treatments and vaccines in development.

The first drugs we are getting results from are repurposed from other viruses or other conditions – these have already started to generate clinical data. The first, and the most famous, of these are repurposed anti-viral agents, such as hydroxychloroquine (a malaria drug) and Gilead's remdesivir (originally unsuccessfully developed for Ebola). Based on early data, both offer modest benefits, but neither is a panacea.

We are also starting to see data from more sophisticated approved biologic drugs (including Roche's Actemra and Sanofi's Kevzara) aimed at treating some of the more severe consequences of the disease, such as lung inflammation and damage. As with the anti-virals, we have started to see some data showing these drugs should be more useful in the more severe and critical cases of COVID-19, but not enough to really feel comfortable that we have a handle on things.

Possibly the most interesting approach (at least to us), and one we do have a fair bit of hope for, involves the generation of recombinant antibodies to the virus. With administration of these, it should be possible to functionally provide immunity by proxy, with the manufactured antibodies essentially providing the protection that your immune system would do naturally, once you had been vaccinated or had been infected and recovered. We think this could have a large impact, particularly for people in high-risk populations (e.g. health care workers, vulnerable seniors) and could serve as a bridge to a vaccine.

Another possibility is that medical treatments will advance to the point that the impact of the



disease is decreased. As an example, there is data emerging that suggests that significant portion of the respiratory damage is done because infected people are “silently hypoxic” (have low blood oxygen before they are symptomatic). By the time they seek treatment, lung damage has progressed too far for treatments to be useful, which is potentially one reason that ventilators haven’t seemed to be useful. This raises the intriguing possibility of monitoring blood oxygen levels early (pulse oximetry is easy and inexpensive) and treating with supplemental oxygen to stave off damage before it occurs.

Public health policy responses

Health policy decisions are currently aimed at trying to balance the near-term impact to human health against the longer-term impact to the economy (and the longer-term impacts to human health and well-being). This is an extremely difficult exercise as governments are all dealing with imperfect information and cost decisions which can be massive.

In the early stages, policy responses were all directed at the necessity to get the virus under control, before we could move on to the next phase of dealing with it. There is a very good article, which we have referenced prior, called the [Hammer and the Dance](#) which outlines this very eloquently. In this vernacular, the Hammer is getting the virus under control and the Dance is dealing with it until a vaccine is available. Many countries have successfully deployed that Hammer and now the Dance begins.

It is worthwhile remembering that efforts to “flatten the curve” were never intended to get rid of the virus completely. We did it for two major reasons: 1) so health care systems weren’t completely overwhelmed (this has been successful so far other than in places like Northern Italy and New York); and 2) to buy time to be prepared for the Dance.

What we know

What we don’t know

Physical distancing works.	Which re-opening approaches will be right, and which will be wrong? The path of the virus from here depends on each country’s individual approach to removing restrictions.
Most countries and health care systems were not adequately prepared.	If the testing and contract tracing infrastructure are sufficient to prevent further outbreaks. What happens next -- a



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	slow burn of cases, smaller manageable flare-ups or a second major wave of outbreaks?
The most aggressive responses have been most effective in limiting the spread of the virus.	How countries will make the decision on the balance between human health (conservative re-openings) vs limiting economic damage (less restrictive measures).

Leading epidemiologists believe the most logical path forward is gradual re-opening focused on protecting at risk populations, coupled with extensive testing to quickly quell new outbreaks.

Some countries are headed toward this, but we don't have all the information we need to do that intelligently yet, which is our biggest concern about the countries being aggressive with re-openings. It seems likely some countries will open too fast and there will be outbreaks and some countries will likely go too slow and inflict more economic damage than they need to – but those stories are still to be written.

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