

The Viral War: COVID-19, a Formidable Foe

Many government and health care leaders have compared the COVID-19 pandemic to a war against an invisible enemy. Healthcare workers are the frontline soldiers in this war. Like other conflicts, COVID-19 has its own fog of war. We are discovering new information about this novel coronavirus, SARS-CoV-2, on a frantic basis. Unfortunately, the quality of the information is generally poor and unreliable. Governments around the world are taking drastic steps to limit the damage this disease is having on its population and economies. COVID-19 has no current therapeutic options, therefore, governments have implemented various defensive and controversial strategies, such as total economic lockdowns and involuntary quarantines. As a global society, we are conducting hundreds of clinical trials to find therapeutic options to attack COVID-19, and take the war to the virus. Winston Churchill's quote about World War II is aptly appropriate about the present state of our war against COVID-19. "Now



this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

We have watched in horror and astonishment at the speed and devastation that COVID-19, the disease, has brought to the world. SARS-COV-2 literally traveled around the world in 80 days resulting in massive worldwide lockdowns and unprecedented layoffs. Countries that were seasoned by SARS in 2003 and H1N1 in 2009 (like South Korea, Taiwan and Germany) were prepared and well-organized. It appears to have paid off as they have managed the COVID19 outbreak reasonably well. Those countries that did not or could not prepare properly are paying an enormous price in terms of lives lost and economic hardship in the coming days, weeks and months.

As value-focused investment analysts, one of our job mandates is to determine a company's intrinsic value. To perform any investment analysis, it is crucial to have a good model predicting the future cash flows of industries, sectors and companies. However, COVID19 has thrown the proverbial monkey wrench into the world's economic machinery. There are unprecedented levels of uncertainty concerning whether the post-COVID world will be similar or vastly different than pre-COVID one and when our lives will go back to 'normal', if ever.

This is the first of a two part blog on COVID-19 and how to manage our investment decisions through this crisis.

Part 1: Framing the Problem and Solution for COVID-19, provides a synopsis on our current predicament. We review our understanding of COVID-19 and its health care impact. We summarize why and how COVID-19 is a devastating disease. We review possible therapeutic targets and highlight the key variables that a therapeutic option would require to become widely successful. While we are waiting for tools to fight



the virus, governments around the world are using various defensive approaches to tackle this pandemic. Do we try to flatten the curve or should we let the natural disease progression of COVID-19 make its impact? We also will review the rationale why governments have used lockdowns and how governments may phase in a return to work strategy. The outcome of governments defensive strategies to minimize the impact of COVID-19 is arguably the most significant social experiment in the past half century.

Part 2: Scenario Analysis and Our Thoughts, we create possible outcomes to this crisis, provide a tool to screen your investments and provide our thoughts and opinions. Please note that this blog article is not meant to provide in depth review of COVID-19 nor provide definitive analysis of the economic impact COVID-19 will have on the world economies. We are physicians and investment analysts with a good understanding of both. We believe our readers might be interested in our decision making process and some of our thoughts.



Part 1: Framing the COVID-19 Crisis and Possible Solutions

SARS-COV-2: A Novel Coronavirus

Origin

In December 2019, local health professionals in Wuhan tried to warn fellow physicians to inform their family and friends to take protective measures against a new 'SARS coronavirus' that came from Huanan Seafood Wholesale Market, a 'wet market'. At the time, no one understood how this novel coronavirus was transmitted, but cases resulted in severe pneumonia and respiratory distress in patients and many healthcare workers. Almost a month later, once human-to-human spread had been established, China imposed a total lockdown in Wuhan and the rest of Hubei province. Wuhan is considered the manufacturing capital of China and is visited by many foreigners. Unfortunately, some foreigners were able to fly out of Wuhan and became the new index cases to countries all over the world, most notably in Iran and Italy.

The Perfect Storm: For a Viral Pandemic

For decades, healthcare and government experts have warned that a global pandemic would occur. The question that was unknowable was when. The investment markets outside of China were roaring to all time highs (S&P 500 reached its highest point on February 19, 2020), despite knowing China was in the midst of a lockdown in Wuhan. In part, the lack of investor concern was due to historical precedent that previous epidemics had only limited economic impact. Now two months since the all time market highs, we are in the midst of a worldwide pandemic with global government imposed lockdowns and investment markets experiencing significant corrections.



What makes SARS-COV-2 dangerous is the combination that it is 'novel' which means no one has developed an immunity to this virus through prior exposure. The virus is highly contagious with a reproduction rate, R_0 , in excess of 2. Most importantly, there is evidence of asymptomatic spreaders which could be the source of a large number of unwitting superspreaders. This would explain why the virus has been able to transmit around the world so efficiently. In addition, 5% of those that are infected have disease that require critical care and a death rate of 1-2%. The great fear from COVID-19 is the combination of a high transmission rate (often from minimally symptomatic people) and its potential lethality, and the distinct possibility that in a single year the whole world is at risk of contracting this illness. A simple back of the envelope calculation produces truly mind blowing estimates. 7.6 billion world population multiplied by % infected multiplied by % death rate: Assuming 20% infection rate and death rate of 1% that would produce 15 million deaths (current total is 177k as of April 20, 2020). This number does not even begin to reflect total lives lost: because of overwhelmed resources many other patients who do not have a viral illness will certainly die from potentially treatable diseases. There is no convenient way to measure the indirect effects of COVID, but there's little doubt they are enormous.

COVID-19: Efficient Transmission and Replication

The virus gains entry through the mucous membranes of the nose, throat or eyes by way of air droplets. Early reports were that the most common routes of transmissions are through fomites and aerosolization procedures (like intubation). However, more recent reports suggest that asymptomatic spreaders can transmit by simply talking too closely to other people, or even shouting or singing over 3 meters away inside a building such as a church. After the virus gains entry into humans, it binds onto the



angiotensin-converting enzyme 2 (ACE2) receptors (present in type 2 pneumocytes in the lung, as well as in the gut, neural tissue and kidneys) and begins the process of replication.

The replication process and rapid spread to surrounding tissue induces common, non-distinct viral symptomatology in patients. For the majority (current estimate of 80%) of infected patients, COVID-19 symptoms range from no symptoms to what feels like a mild cold to a bad case of Influenza-Like-Illness (ILI). Recent reports that a significant number of patients also have difficulty with taste and smell and sometimes this is their only symptom. Due to its lack of distinguishing symptomatology, along with the fact that over 50% of patients do not even have a fever, a COVID-19 diagnosis is very difficult by clinical exam alone. Other disturbing facts are that once infected, patients suffering from severe illness may take up to 12 days before presenting to an ICU and the average ICU patient spends up to 2 weeks utilizing the ICU's expensive, scarce resource.

The mechanism by which SARS-CoV2 infection causes death in patients despite receiving aggressive supportive care is not entirely clear; however, there are several hypotheses.

The first scenario is the frail, elderly patient with multiple comorbidities, often a resident in a nursing home. This patient is infected, develops COVID-19 associated pneumonia which leads to hypoxic respiratory failure. Because of the patients previously expressed wishes or due to the expectation of a short lifespan with or without COVID-19, the patient is not supported with mechanical ventilation and they die from hypoxia. Hypoxia eventually leads to bioenergetic failure at the subcellular level, multiorgan failure and death.



The second scenario is seen in healthy patients who are usually under 60. They contract COVID-19 and endure flu-like symptoms for 7-10 days. They then often improve for a few days and then rapidly deteriorate with high fever, profound hypoxia out of keeping with the severity of their pneumonia, kidney failure, circulatory shock, and an odd thrombophilic variation of DIC, a clotting disorder. Their lab tests demonstrate remarkably dysregulated systemic inflammation and activation of clotting throughout the body: this situation is often referred to as cytokine storm. Many organs fail in a cascade, despite supportive therapies such as invasive ventilation, anticoagulation, vasopressors, ECMO, and dialysis. This process escalates to unresuscitatable cardiac arrest.

A final, more rare, cause of mortality is primary cardiac arrest. The cause for this is even less well understood, but a rhythm disturbance induced by the virus is suspected in some patients, whereas myocarditis leading to cardiogenic has been reported in others.

Demographics: Targeting the Most Vulnerable

The data has been fairly consistent that COVID-19 is more fatal in patients that are over 70 and those with comorbidities, such as diabetes, hypertension, smokers, and autoimmune conditions. Experts believe that the COVID-19 death rate is in the 1-2% range, but data from the number of people who have died and the number of people who have been infected with COVID-19 is still a matter of great debate. We believe that the numerator (number of deaths) is more accurate than the denominator (total number of COVID-19 patients). If you look at official data, the Italian and UK death rate is at around 13% and the US death rate is 5.4%.



From John Hopkins University: <https://coronavirus.jhu.edu/map.html>

Covid-19 Testing

A positive PCR test is currently the only method to confirm a case of COVID-19. There has been a shortage of available PCR testing resulting in many countries placing restrictions on whom to test. In Canada, the priorities have been to test healthcare professionals, nursing home and hospital patients. Alberta recently expanded its testing to the general public to anyone meeting their online screening assessment.

Diagnostic testing is crucial to Public Health's containment and mitigation strategies. With sufficient testing, it is possible to contain COVID-19 infection clusters before they result in community spreading. Testing is not without its challenges. Depending on the quality of the PCR test used, the sensitivity rate ranges from a low of 65% to a high of 95%. The world wide demand for PCR reagents has created repeated shortages and disruption in testing capability.



Another available test is a serology test used to detect COVID-19 antibodies. A positive serology test would signify that a patient had been infected and has developed some immunoprotection. Serology testing will be useful in deriving a better estimate on the total number of people infected COVID-19. In addition, people testing positive with serology could be immune protected from another COVID-19 infection and thus be ideal candidates to go back to work less encumbered.

Other Possible Diagnostics that are still not mainstream

CRISPR- a non PCR method is being researched as an alternative in the diagnosis of COVID-19 patients.

Lateral Flow- Canadia firm Sona Nanotech is trying to find biomarkers that would highly correlate with a COVID-19 infection. This would be analogous to detecting Beta-Hcg in urine pregnancy test.

Viral Load- COVID-19 viral loads are measured in some centers. There is research to detect if viral load corresponds to infectiousness or disease severity.

Possible Other Markers- We measure CD4 count in HIV patients to check for the immune status. We may find markers from COVID-19 patients that help with patient care, especially in the hospital setting.

COVID19 Therapeutic Options

There is currently no approved treatment for COVID-19. COVID-19 patients requiring hospitalization are managed with basic and advanced



supportive measures. The current goal is to stabilize the patient and allow the patient's own immune system to fight off the illness.

Scientists, hospitals and companies from around the world are conducting hundreds of clinical trials. Repurposing existing drugs, like hydroxychloroquine and colchicine, would be the quickest, easiest and cheapest to introduce into widespread use if effective. [More recent data](#) on Gilead's Remdesivir is encouraging. Remdesivir is an IV drug used to prevent the replication of SARS-CoV-2. The study looked at 53 severely ill COVID-19 patients. 68% of the patients had improvement in oxygen-support status and the overall mortality rate was 13% over a median follow-up of 18 days. The mortality rate compared favourably to data from China 66% and UK ~50%. Although encouraging initial results, the small number of patients and the lack of control arm should temper our expectations. Nevertheless, there is also the possibility that further studies may demonstrate that Remdesivir is more effective in less ill patients or when it is given early in the disease process. (We are ALL desperately searching to find positive developments.)

COVID-19 is a worldwide problem. Remdesivir, even if proven effective, will not be a worldwide solution. The drug will be too expensive for many countries, the manufacturing process is difficult and time consuming and the fact it must be given intravenously makes the treatment logistically awkward, particularly in austere settings. The variables that are important to wide adoption include the therapy's efficacy, tolerability, scalability and cost. This is a very high hurdle to achieve. On the positive side is that if the disease severity can be reduced by a treatment, herd immunity will theoretically be accelerated because the risk of contracting the illness will be more acceptable and the critical care resources will be less likely to be overwhelmed. In other words, a treatment that isn't a cure but changes the



disease into a nuisance rather than life-threatening would be enough to be a game-changer.

Vaccination has been the best solution to prevent pandemics. It is scalable, effective, inexpensive and tolerable, in most cases. The CDC has stated that it would take a minimum of 18 months, if everything went well. Historically, the quickest vaccine that was developed was the Mumps vaccination and that took four years to complete. There are added challenges in a COVID-19 vaccine: First, no coronavirus vaccine has been developed despite prior research and disease outbreaks. Second, there is the possibility of antibody-dependent enhancement (also called Vaccine-induced enhancement). In a prior coronavirus vaccine trial, vaccinated test subjects (rhesus monkeys) had more severe illness with future infections. Vaccine production is very expensive, time consuming and fraught with logistic obstacles (ie. availability of millions of fresh eggs!).

Breaking News: Sinovac Biotech, a Chinese company, released a scientific article announcing results of their purified inactivated SARS-CoV-2 virus vaccine candidate (PiCOVacc). The vaccine was able to confer complete protection in non-human primates against SARS-CoV-2 strains circulating worldwide by eliciting potent humoral responses devoid of immunopathology.



How We Think About It

COVID-19 Therapeutic Options

Approved							
Class	Type/Name	Mechanism of Action	Setting	Cost	Tolerability	Scalability	Efficacy
Supportive	Basic	oxygen, nasal canulae, IV	hospital	moderate	good	Moderate	moderate
Supportive	Advanced	ventilator, ECMO	ICU	High	Low	Low	moderate
Investigational							
Class	Type/Name	Mechanism of Action	Setting	Cost	Tolerability	Scalability	Efficacy
Block Viral Entry	Monoclonal Ab	Block Viral Entry	unknown	unknown	unknown	moderate	unknown
	Covaescent Plasma	Supplements patients with antibodies from previously infected patients	hospital	high	good	low	unknown
Block Viral Replication	Remdesivir	Inhibits viral replication	hospital	\$500 per IV	good	moderate	unknown
Viral Replication Disruption	Lopinavir-Ritonavir	Protease inhibitor					fail
Immunoprotection	Vaccination	Allows patient to create an innate immune response	community	low	unknown	High	unknown
Disease Modification	Colchine	anti-inflammatory	community	low	unknown	High	unknown

Government Response: Finding our Churchill

Governments are making difficult decisions based on imperfect information. Wrong decisions are inevitable. Nevertheless, our leaders must take deliberate, rational and decisive actions to prevent the Covid-19 crisis from overwhelming the front line, the hospitals and its workers, while maintaining hope and reassurance and deciding on when to and how to relaunch their economies. There is an interesting global experiment that is playing out. Most western countries have implemented varying degrees of containment, mitigation and lockdowns. A few, such as Brazil, Austria and Sweden, are wagering that natural herd immunity can be developed without proactive defensive interventions. Many undeveloped countries don't have the necessary resources to provide an effective defensive strategy. Normally, the World Health Organization with the help of developed countries, will help the more vulnerable countries. But the COVID-19 war is everywhere and countries are thinking about their own battles first. The world is watching and hoping.



Operation: Hammer and the Dance

The Hammer: Rationale for Flattening the Curve

In the first wave of COVID-19 outbreaks around the world, countries have consistently found that an overwhelming number of patients presented with respiratory distress. With 5% of infected requiring critical care intervention, the rate limiting resources were hospital beds and respiratory support systems (oxygen, ventilators). The defensive strategy of containment and mitigation have proven to be effective in slowing down the total number of infections. When community spread was found, many countries chose a form of enforced lockdown, the hammer, to drive down the reproduction rate.

How We Think About It

Rationale for Flatten The Curve

Projected Number of COVID-19 Patients * % Requiring ICU * % Requiring Intubation

Vs.

Number of ICU Beds and Number of Ventilators

Ways to Flatten Curve: Containment, Mitigation and Isolation

Containment

Mitigation

Isolation

Public Health, Testing

Masks, Small Gatherings, Social Distancing

Lockdowns, self quarantine

The Dance: Phasing in Back to Work

There is an enormous economic cost with the Hammer Maneuver. It is effective but not sustainable. Simply put, at some point the number of people dying from non-covid related diseases associated with the flattening the curve strategy will outnumber those that die from COVID-19. In



addition, COVID-19 associated poverty will take its toll; the World Bank estimates that more humans may die of these indirect effects of the virus than from the disease itself! There is no proven plan on how and when to implement a return to work/normalcy strategy. Governments are forming task forces to help formulate battle plans. Implementing their own unique battle plan is the dance that governments will have to make, balancing a back to work strategy with the likelihood of further outbreaks. The goal is to avoid having to use the Hammer again.

How We Think About It

Back to Work Strategy

$$\text{Death Rate (2020)} = \text{Death Rate (Historical)} + \text{DR (COVID-19)} + \text{DR (Non-COVID)}$$

if $\text{DR (Non-Covid)} > \text{DR (COVID)}$

then favours Back to Work

Dance Strategy

Step 1

Containment

Step 2

Mitigation

Repeat

Preventing Waves of Attack: A Fire Dance

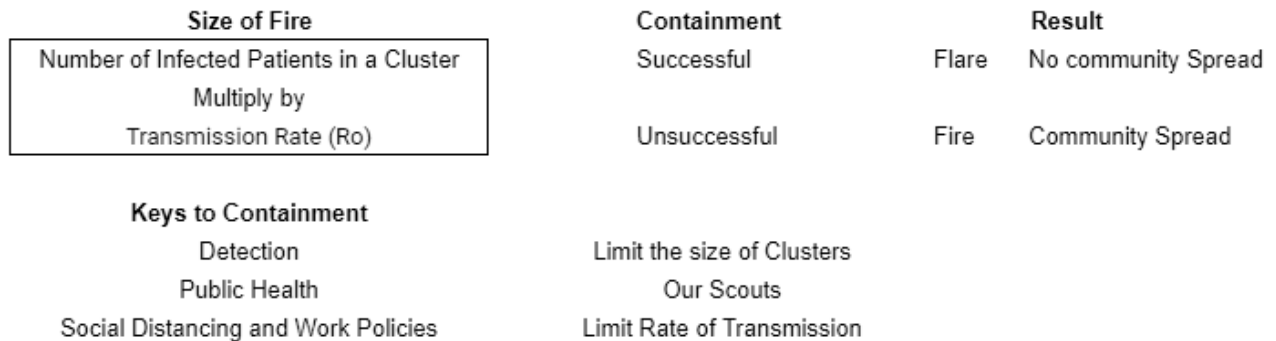
It is reasonable to assume that when the dance has started that the number of new cases of infections will rise. Think of these new cases as embers with each the potential to start a new fire. If detected early and containment is achieved through public health measures, we can limit uncontrolled community transmission. Therefore, rapid, extensive testing and a strong effective public health system will be crucial. The other variable to watch is how quickly we ramp up work without dramatically



increasing transmission. Social distancing, masks and workplace policies will be important in this respect.

How We Think About It

2nd Wave



Ending Part 1 with Hope

We tried to capture the COVID-19 crisis/war and the government's response/defense. Due to the fog of war and the unexpected strength of our foe, the world is suffering through the worst pandemic in modern history. We are very confident that we will eventually win the COVID-19 war. There is an unprecedented level of cooperation in the world today: scientists from all 6 continents are sharing data and furiously working to achieve a common goal. Software developers, engineers and architects are busy recruiting innovation and technology to help us adapt to the threat. Everyone can play a role. History has shown that humans have gone through pandemics, recovered and prospered. The pent up demand to go on holidays, go to a hockey game or see a great new movie is already building up within each one of us.



COVID-19 has disrupted the investment markets. Many companies will have significant distortions in their financials. An uncertain amount of businesses will fail and many jobs may be permanently lost. Some companies may be priced to fail but their underlying businesses are robust. These companies may represent significant investment opportunities. In our next blog, we will discuss our scenario analysis on how the COVID-19 war may come to a resolution. We will provide our thoughts on investing during both a medical and financial crisis.

How We Think About It

Sample of Variables and Issues to Monitor

<i>Characteristics</i>	How does the virus spread? What is the importance of asymptomatic spreaders? When are people most infectious?
<i>Disease Process</i>	Can we predict who will get severe illness?
<i>Diagnostics</i>	What is the sensitivity and specificity of tests Is testing limited?
<i>Therapeutics</i>	Clinical Trial results
<i>Government Response</i>	Are responses logical and decisive?
<i>Immunity</i>	How long is one protected after infection?

Please feel free to email us or place a comment. We enjoy bantering to our readers and colleagues about our blog topics. We always learn by asking and listening. Please stay safe. We can all play our part because we are all in this together.