

Update on SARS-CoV-2 / COVID-19: General Guidance

March 12th, 2020

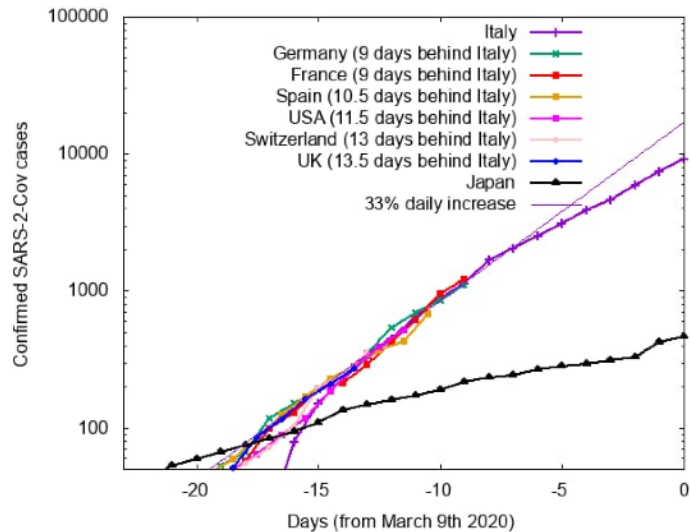
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March 12, 2020

Point of order

We **do not believe** that current reports reflect the reality of the situation on the ground. All accumulated data suggests a near term trajectory that looks much like Northern Italy, and lack of testing availability means we will not have an accurate assessment of spread for 2 to 4 weeks. We have determined the most prudent option to be immediate and significant social isolation, removal from population hubs when possible, and watchful waiting to calculate the disease trajectory over the next 2 to 4 weeks. The virus is at least an order of magnitude more lethal than seasonal influenza and severe morbidity is *not* limited to the elderly and infirm (though is concentrated in that demographic). The prospect of health system collapse is non-zero in the near term if the current case trajectory is not stymied with near-draconian containment measures.



*whether this flattens/is exponential or not is irrelevant in the near term.

This graph % Mark Handley at Univ College London. Trying to get his data for SK, China, Singapore- CONTAINMENT IS EVERYTHING

Summary

With so much uncertainty, such a lag between front lines and tabulated data, and such non-linearity and asymmetry in terms of outcomes, as of the first week of March we turned our attention to conducting interviews with experts. What follows is our best assessment of risk and our current thinking on mitigation and planning.

Given the perceived responsiveness from our government, the sluggishness of our response to the current outbreaks indicates that the U.S. may look more like Italy than South Korea or Singapore. Currently, the number of cases in Italy has pushed the healthcare system past its capacity, the death toll is rising (current virus mortality from confirmed cases at 5%) and there are knock-on effects as hospital resources are diverted almost exclusively to the virus. In other words, you may be just as likely to die in Italy from neglect as you are from COVID-19 because of how taxed the healthcare system is.

In New York, we see risks. First, the cold weather and population density point to a possible spread that mirrors China. Second, the response of the city has been suboptimal. At the time of this writing, schools remain open, there has been little effort to diminish large gatherings and there is little evidence of adequate testing.

This does not preclude the possibility for a swift and effective public health mobilization and response. In the U.K., for example, new case growth has begun to decline due to unified case tracking and containment. The current decentralized approach and past minimization of government support for public health infrastructure in the U.S. makes this somewhat less likely.

In China, from the first few cases until cases reached the tens of thousands, required only about five weeks. It is too soon to say if the U.S. will mirror this (or Italy), but we expect to have a much better sense by early April.

The best line of personal defense, until we have greater clarity around the rate of spread, the capacity of our healthcare system to manage the burden of disease, an efficacious testing system, and any further research into off-label treatments is to avoid contact with as many people as possible.

Our best recommendation at this time is based on the following decision nodes:

1. Are you in an area with community spread?
2. Are you personally, or are you in contact with, a person at high risk?¹

If you answer 'YES' to either of these questions, the people we have been speaking with suggest isolation is the safest strategy, pending further information (e.g., the rate of spread, speed of doubling).

If you answer 'NO' to both of these questions, a reasonable course of action seems to be avoiding all gatherings and being obsessive, if not maniacal, about handwashing and hygiene.

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What we are learning in real time from interviews we are conducting with virologists, immunologists, and infectious disease specialists in the U.S. and China

The following represents the result of our interviews with several leading researchers, both inside academia and industry, including people on the front lines of drug development, and on the front lines of the hospital system in the U.S., in the U.K., and Milan. Due to the speculative and predictive nature of these conversations, and the fact that many are also having ongoing discussions with governments, including ours, all have asked their quotes not be directly attributed.

"I am much more concerned with COVID19 than I was with SARS or MERS."

"This is a much bigger problem in the U.S. than most people realize."

"This coronavirus (SARS-CoV-2) will be much harder to contain than any other coronavirus we have encountered."

¹ Smoker, age over 55, high blood pressure, type 1 or type 2 diabetes, lung disease, cardiovascular disease

“There’s a chance that this is the epidemiologic event of our lifetimes.”

“I am much more worried about the inability of the U.S. to contain this virus today than I was two weeks ago”

“Being young and healthy with zero medical problems does not rule out becoming vented or dead--probably the time course to developing significant lower respiratory symptoms is about a week or longer.” (U.S. physician currently treating patients with COVID-19)

“Distribution of the emergency is extremely dishomogeneous, with the epicenter mainly localized in the north of Italy, with other regions of the country still under non-emergency operations (see map), but with growing numbers of cases. The healthcare infrastructures located in the epicenter areas are close to maximum capacity with hospital staff running turns overnights - doctors in those hospitals are working under extreme conditions (fast track for enrollment of early graduate doctors are in place). In the same regions all non-critical procedures have been postponed. Geographical reorganization of non-covered-emergency response are in place, ambulances are instructed to allocate cases accordingly. All hospitals at the national level are pre-triaged in external tents, with secure paths for suspicious cases. To overcome overcapacity, plans are in place to move patients in temporary external containers and other structures (fair pavilions, etc), and expedite releases when possible. Coordinated effort to acquire ICU, sub-ICU and responders’ protection equipment at the national level are in place. While in the first days people were running to hospitals also for non extreme cases, today the population is trying to keep away as much as possible.” - Italian hospital CEO

“Messaging from top to bottom is a clusterfuck and inconsistent.”

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Below is an attempt at organizing the insights from our discussions

- The SARS-CoV-2 virus seems to have a unique combination of lethality and transmissibility that is more concerning than previous coronaviruses.
- The virus seems especially infectious, which is reflected in the “reproductive number” (R_0) assigned to SARS-CoV-2 (the virus that causes COVID19). The R_0 is an average assessment of how many people an infected person can go on to infect. For influenza, this number is about 1.3. For SARS-CoV-2 it seems to be closer to 3.8 to 4.0, though one person we spoke with believes it is closer to 5. Another person we spoke with believes the range is 2.25 to 3.6. By comparison, the most contagious viruses (e.g., measles) have R_0 closer to 12 to 14. The point remains, this virus is highly, highly contagious and infected individuals do not know they are shedding and spreading the virus for many days.
- The SARS-CoV-2 virus seems more robust in the cold than in the heat, which may partially explain the difference between case fatality rate in China, South Korea, and Singapore.
- The virus seems to be robust enough to survive for long periods of time outside of the body, which emphasizes the need for aggressive hand-washing and social distancing. The coronavirus virus responsible for SARS was especially robust outside of its host and reports suggested it could survive up to 9 days outside of the body. We do not yet know how long SARS-CoV-2 survives in this setting, but the rate of spread on the two cruise ships suggests we should assume survival outside of the body is on the order of days, not hours.
- The latency period, the time between infection and overt symptoms, is probably closer to 2 to 6 days, based on data from the cruise ships and in-hospital infections and most people are having some symptoms, most notably fever and dry cough. There may be a delay between first symptoms and severe respiratory symptomatology that provides both an opportunity to intervene and a caution that once infected vigilance, particularly for shortness of breath, is important.

- People tend to fall into two clinical categories: (i) A mild to moderate, self-limited disease characterized mostly by high fevers, and (ii) Those who may have only moderate fevers but experience shortness of breath that takes a rapid turn for the worse at about 7 to 10 days from onset of symptoms, requiring hospitalization.
- Children seem especially shielded from the virus (versus the flu, for example) but it is not clear why. It is hypothesized that children have fewer binding receptors for the virus, but this is unclear.
- The pathology of SARS-CoV-2 seems to differ from influenza in that the latter results in an over-exaggerated immune response, followed by immune paralysis, which often renders the host susceptible to secondary infection. By contrast, SARS-CoV-2 seems to inflict damage directly to the lung, with one hypothesis focusing on damage to a particular type of cell called the Type II pneumocyte. This cell manufactures a crucial “detergent” called surfactant, which allows the tiniest air sacs of the lung to overcome the surface tension necessary to expand for gas exchange. The result of this destruction of Type II pneumocytes, and the loss of surfactant is a severe viral pneumonia, which can result in respiratory collapse.
- The virus’s affinity for the Angiotensin II Receptor in the lungs may explain why people with pre-existing conditions such as high blood pressure and cardiovascular disease are especially susceptible. Below, we describe a class of drug, angiotensin receptor blockers (ARBs), that may ameliorate these symptoms by preventing the virus from using the angiotensin receptor to access these cells or damage them. Again, this is speculation at this point and based on triangulation between animal data, autopsy data, and clinical data.
- One of our front line physicians noted that some patients are not succumbing to an inability to ventilate the lungs once intubated, or to septic shock from the infection, but instead to myocarditis or inflammation of the heart muscle. Interestingly, the same Angiotensin receptor thought to be involved as an entry point in the lungs is also significantly present in the cardiac tissue. There is data that the genome of the virus can be detected in the blood, but the significance of this is unknown. Superimposed bacterial pneumonias have also been observed in the early Chinese literature (China does have more resistant bacterial pathogens due to antibiotic overuse). (They also have an aging population and higher underlying lung disease from pollution and smoking). That said, the normal predictors of disease severity (namely age and multiple

underlying health conditions) don't seem to be telling the whole story -- there are clearly cases of otherwise healthy adults succumbing rapidly to this illness.

- There is no option to "stop" COVID-19 at this point; the goal is now to slow it down. If a month's worth of potential infections can be slowed and stretched out to 6 months, it will give the healthcare system a chance to respond appropriately.

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Likely versus worst-case long-term scenario

In China, from the first few cases until cases reached the tens of thousands, required only about five weeks. It is too soon to say if the U.S. will mirror this (or Italy), but the current trajectory looks similar. We expect to have a better sense by early April when testing has been belatedly rolled out widely and we can have more accurate accounting. In our discussions with experts who have studied other virulent coronaviruses, the causes of SARS and MERS, they point to the following developments to impact long-term scenarios:

1. *Will there be a successful treatment and/or vaccine developed, specifically for this virus?*

A vaccine seems unlikely in the nearterm for at least two reasons.

i) Unlike influenza, vaccinating against coronaviruses is more technically challenging, as there is a greater risk of harm in an effort to expose the host to enough of the protein coat of the virus to generate an immune response.

ii) Furthermore, while there are several groups working on vaccines, the bar for safety and efficacy is very high for vaccines. Most people we have spoken with think a vaccine is a year away, or more.

More likely than a vaccine is the development of one or more antiviral small molecules that would be effective in treating the virus in infected individuals. It is possible some of these molecules will be in phase I clinical trials in 6 months.

2. *What are the long-term dynamics of immunity, mutation, and spread?*

Time will tell if the virus can be shed for prolonged periods. The population dynamics of immunity and whether immunity to new infections occurs and is effective is still unknown. Finally, whether the virus can mutate fast enough to circulate in previously immune people will play a significant role in the ultimate spread.

3. *Will the virus spread to animals in large numbers and back to humans?*

This is another unknown and another determinant of how many people will ultimately be infected by COVID19 in the coming years. If the virus is able to “comfortably” take up residence in animals, as influenza does, it is likely to stick around for a long time.

4. *Will the virus have seasonal bounce back and forth between the northern and southern hemisphere?*

This is also unclear at this time, though probably less important than #2, above.

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Treatments on the Horizon

Remdesivir is a repurposed Ebola antiviral, that shows strong activity against SARS-CoV-2. It is currently in phase 3 clinical trials. It is not commercially available, though it may be available by compassionate exemption in extreme cases.

Monoclonal antibodies against highly conserved segments of the viral proteome are currently in rapid development with a target for autumn 2020 phase I testing in clinical trials.

Convalescent serum, meaning antibodies purified from the blood of someone who has recently recovered from the illness, have been suggested as a longshot but possibly viable option. It is not clear what the logistics and/or timing on this option look like.

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Contingency planning

It **cannot be overstated** that the most effective means of combating this virus is vigilant hygiene and social distancing. Full stop.

If it is possible to work from home, work from home. If you are able to isolate yourself and your family, buying time for the next 2-4 weeks while the US gets a more accurate accounting of the epidemiology will be of high utility.

We have to keep a couple of IFs/THENs in mind when making a treatment preparation algorithm.

You must make a risk assessment for yourself and your immediate family members, categorizing roughly as follows:

- Elderly relatives
- Those with underlying lung disease (smokers, asthma, COPD) or multiple medical problems (heart disease, diabetes, hypertension, cancer, immunocompromised)
- Children (seem to be lowest risk group)
- Otherwise healthy adults

Though isolation and avoidance are paramount, we must prepare for the following (2x2) scenarios:

- Self-limited, mild/moderate disease **WITH** functioning healthcare system
- Severe, complicated respiratory or cardiac failure **WITH** functioning healthcare system
- Self-limited, mild/moderate disease **WITHOUT** functioning health system
- Severe, complicated respiratory illness **WITHOUT** functioning healthcare system

Given reliable reports of health system strain and even breakdown in areas of concentrated outbreaks outside the U.S., if you must be in one of these areas (any metro area in the U.S.), we are proposing the following “emergency kit” to be used in the event that health services are inaccessible.

There are a few very important considerations to keep in mind regarding these contingencies. Significant shortness of breath should always be referred to the nearest hospital.

For moderate to severe disease, the most important care to obtain by far is *respiratory supportive care*. In absence of health system capacity, self management is going to rely on *maintaining your ability to breathe and oxygenate appropriately*. While it is unlikely that passive oxygen utilization will be of much benefit in absence of positive pressure ventilation, we are attempting to source 3rd-party oxygen concentrators for home use. If the disease process is advanced enough to cause shortness of breath, you almost certainly need a level of care that requires inpatient monitoring with physicians and nurses present. A home oxygen concentrator will only be of use in a very narrow window and set of circumstances. In the event of public health breakdown, this may provide a bridge of several hours if hospital resources are overwhelmed. We do not consider it as a core component of a treatment or prevention plan.

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