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SUBJECT: Post Pandemic Return to Normal

Introduction

When we will return to normal? The answers from experts vary but are converging on achieving notable progress in the first half of 2021 and reaching a state that could be considered normal by late 2021. By normal we mean:

- People no longer fear getting deathly ill
- The economy will be largely re-opened including travel and entertainment venues
- Routine social interactions with friends and family resume

We expect that COVID-19 will likely never disappear completely and will become endemic like influenza. If cases drop to a low enough level, we may fully return to our pre-pandemic economic and social patterns or we may continue to use masks as is common in Asia. We may require proof of vaccination or a negative test to board a plane, attend a concert, or visit a nursing home. Those who are immune from vaccine or natural infection will likely be confident in moving about society. Those who opt not to be immunized may find themselves being required to take rapid tests frequently including in order to enter the workplace.

Reaching the new normal will not be an event, but rather a gradual process. The rate and timing of that process will vary from country to country. Generally, the richer, more developed countries will progress faster than poorer, less developed countries.

Some experts have tried to project when we will reach herd immunity. We do not address this in this document. Vaccine will contribute substantially to herd immunity as will natural infection. There is also likely an element of cross-immunity from other viruses which will impact the percent of the population that will need to be vaccinated or infected to reach herd immunity. Also important is understanding how long immunity will last from either the vaccine or natural immunity and if waning immunity leaves the person fully vulnerable or if subsequent infections will be mild in most cases.

We will get to the new normal through the combined impact of:

1) Societal measures
2) Frequent and widespread testing designed to ensure that public spaces are safe
3) Herd immunity through vaccine
4) Readily available treatments which prevent severe illness or death.

We suggest that return to a new normal will be gradual over the next year. We are entering a period where the number of infections is rising exponentially. Europe has already seen the rate of new infections that equal or exceed that experienced in the spring. Cases are rising throughout the US and we expect our infections per million to exceed what is happening in Europe. We believe that the expansion of rapid tests in the first quarter of 2021 will be a driving force to allow people to feel comfortable in public settings while waiting for the vaccine. We also believe that new treatments will become available that will allay fears of severe illness for many.

Societal Measures to Facilitate a Return to Normal

The world's first coronavirus 'passports' are being launched to enable people to travel without having to quarantine. Passengers will voluntarily upload their coronavirus test results from a validated laboratory onto a digital health pass, such as the CommonPass, up to 72 hours before departure. Airlines and border officials will be able to scan the digital data on the pass to see if passengers are free of the virus, allowing them to reduce time in required quarantine. The goal of CommonPass is to create a standardized global testing system in which governments and airlines can trust passengers' results because they are from reputable laboratories and on a recognized health passport. The CommonPass is being launched by the Commons Project, a non-profit trust, and the World Economic Forum, in collaboration with government representatives from 37 countries. Continued improvement in applying public-health interventions (such as test and trace) that don't significantly limit economic and social activities will be drivers for societal and economic normalcy.

Additionally, people may voluntarily sign up to a service that tracks their movements via their phone, alerting them if they had been close to known infected people or disease hot spots. This type of advanced digital contract tracing could become a requirement to enter large venues, government buildings, airports, or public transport hubs. We know there has been a reluctance in the west to download contact tracing apps and that people are concerned that tracing their movements will impinge on personal privacy. However, if access to flights and entertainment venues is restricted to those who have downloaded the relevant app, there will be an incentive to comply. We expect that privacy protections will be built into the apps and communicated as part of the promotion campaigns.

Until 1996 it wasn't necessary to present identification when flying and travelers often flew under each other's names for frequent flyer programs. Prior to 9/11 airport screening was very lax and inconsistent. We quickly adjusted to presenting our ID's, taking off our shoes and keeping our boarding passes on our phones. Similarly, we believe behavior patterns (including adoption of CommonPass or usage of contact tracing apps) could change.

Crowded, poorly ventilated spaces are increasingly recognized as posing a risk of contagion. New facilities will be built with, and older facilities will likely be gradually retrofitted with better ventilation and air-disinfection systems where feasible.

Improved Testing Detection and Isolation

Currently, the U.S. relies on a molecular test, RT-PCR. RT-PCR testing is expensive, requires trained laboratory technicians & equipment for processing, and has a long turnaround time for results. It is not a viable test for widespread screening of asymptomatic individuals. There is a movement towards rapid antigen testing to allow more people to be tested more frequently.

The US FDA has granted Emergency Use Authorization for five antigen tests. The U.S. Department of Health and Human Services announced on August 28th that they awarded a contract to Abbott for delivery of 150 million BinaxNOW COVID-19 tests. The test which costs $5 and comes with a complimentary mobile app named NAVICA™. This app allows one to receive and store encrypted BinaxNOW test results and manage one's NAVICA Pass. The Pass via a Q.R. code is similar to an airline boarding pass that allows one to share an authenticated negative result with a NAVICA-enabled organization employers, airlines, entertainment venues and schools providing assurance to all stakeholders. This is conceptually the same as CommonPass but envisions broader applicability as well as more frequent and timely testing.

Antigen tests are less sensitive than the PCR test when the viral load is low. While this at first sounds like a down-side, it may actually be an advantage. These tests are very good at detecting clinically meaningful levels of virus (i.e., levels of virus that are present when people are infectious), however, unlike PCR, they do not find remnants of virus present at the tail end of an infection when the individual is no longer infectious.

Rapid at-home diagnostic tests have been developed but not yet approved. One example is a lateral flow test, a paper strip that works similarly to a pregnancy test. The test provides results in 10-15 minutes at the cost of

about $1-2 per test and does not require any additional equipment. A positive result would indicate the need for self-quarantine and confirmation of test results through a healthcare provider. A negative test, in the absence of symptoms would indicate that you are not ill and could interact with people without posing a meaningful risk to them. If the individuals you were interacting with also tested negative, they likewise pose little to no risk to you. While self-administered tests are quicker, cheaper, and more convenient than those intended to be administered by others such as BinaxNOW, it is not clear that they could be used with an app such as NAVICA.

A quick, easy, and inexpensive test that can be used daily, at home, or at one's school, office, social gathering, or entertainment venue would be a significant step toward achieving normalcy. Since the technology exists, the primary obstacles are regulatory approval and scaling of manufacturing. These obstacles are surmountable, and we anticipate that such testing will be available in early 2021. Currently, samples for PCR and antigen tests can be collected via nasopharyngeal swab (the very deep swab), mid and front of the nose, saliva and throat. Sample collection methods are part of the test application for FDA emergency use authorization EUA) and there is an increasing trend to request modification to EUAs to include saliva. For screening, we expect that saliva will become the preferred sample as it can be reliably self-collected and minimizes the use of PPE, swabs and viral transport media. Lower nasal swabs are also very well tolerated for regular screening.

Achieving Immunity Through COVID-19 Vaccine

As of October 20, 2020, there are currently 45 vaccines in various stages of clinical trials and over 90 more under development or in pre-clinical evaluation. Of those, 11 are in Phase 3 clinical trials (the final testing before application for use). Several vaccines, 4 developed in China and 2 in Russia are currently being used in limited circumstances despite not having yet completed clinical trials. Many health authorities and researchers predict that one or more vaccines will successfully complete Phase 3 by year-end and will be available to first responders and health care workers by the first quarter of 2021 and rolled out by priority groups throughout the remainder of 2021 with wide availability in the 2nd or 3rd quarter.

The United States and several other countries have purchased hundreds of millions of doses of various vaccines with the hope that they will successfully complete the clinical trials. If the vaccines prove safe and effective, this provides a significant jumpstart to the production of vaccines. Yet, to vaccinate everyone who will accept it across the globe will require billions of doses (some vaccines will require two doses further increasing the total number needed). Vaccine manufacturers are actively planning for mass production, but the challenge is daunting. In addition to manufacturing, distribution will be a major challenge, especially in remote, poor locations. Vaccines need to be stored and transported at a narrow window of temperature to maintain their full effectiveness. This is referred to as cold chain management. While some vaccines only need to be refrigerated or stored at temperatures of a typical household freezer, the vaccine produced by Pfizer & BioNTech needs to be stored at -94° Fahrenheit, the temperature of dry ice.

The vaccines are not likely to eliminate the risk of infection. The FDA has said that their minimum acceptable effectiveness is 50%. It is hoped and expected that most approved vaccines will prevent 70% or more cases (Dr. Fauci hopes to see 75%-80% effectiveness). For many vaccines, such as those for influenza, those who get sick despite being vaccinated tend to have a relatively mild illness. It is likely, but as yet unproven, that this would be the case for COVID-19. Furthermore, it is not clear how long immunity will last. Based on how other related viruses behave, it is likely that immunity will not be extremely long lasting. Estimates range from 3 months to 3 years. Recent studies demonstrate persistence of antibodies for up to four months which is as long as we have been running these studies. Many researchers are optimistic that we will find immunity lasts more than one year.

An important factor determining how much of an impact the vaccine will have is how many people will take it. Typically, fewer than half of the people eligible for flu vaccine take it each year in the US. Because the COVID-19 vaccines are new, there may be more reluctance to take them. On the other hand, there is (appropriately)

greater fear of COVID-19 than there is of the seasonal flu which may drive vaccine acceptance up. In addition, it is not yet clear whether there will be requirements for vaccination to attend school, work in a hospital or based on other criteria. If there are, they could drive vaccination rates higher.

If we assume that the vaccine has a 70% effectiveness and that 50% of the population gets vaccinated, approximately 35% of people will be protected from infection and another 15% may be protected from a severe case. Even if the uptake of the vaccine is greater than 50% and if Dr. Fauci's hope for a vaccine with an 80% effectiveness is realized, vaccines, while important, will not get us back to normal by themselves. We estimate the Ro (the average number of people an infected person goes on to infect) of COVID-19 at 2.5. Mathematically this means that we need to get at least 60 percent of the population immune to achieve herd immunity.

Uptake on the vaccine is dependent on confidence in its safety and effectiveness, ease of access and elimination of financial barriers. It will require a coordinated, national, public health campaign to drive up the percentage of people taking the vaccine, especially if it requires two shots.

It is possible that early vaccines may be less effective than the vaccines released later in the year. There may be individuals who choose to wait for the "better vaccine".

Because of the variables associated with the vaccine, we view it as contributing to the progress to the new normal but place significantly greater weight on rapid point of care testing and new treatments in moving us along that path.

The leading western vaccine candidates are listed in the table below. The Pfizer and Moderna vaccines are genetic vaccines which deliver one or more of the coronavirus's own genes into our cells to provoke an immune response. This is a new technology but it is very promising. We expect the initial results of the phase 3 trial to be published in November. On October 27, Pfizer announced that they still did not have enough trial participants who had been infected. We believe these will be the first two vaccines to be brought to market.

The Oxford Astra Zeneca and Johnson and Johnson are viral vector vaccines. These vaccines contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface. Johnson and Johnson report they expect to have Phase 3 data ready by the end of the 2020.

It is also important to mention the Chinese vaccines. Very little is known about the vaccines but they are being distributed broadly. Some overseas Chinese businesses such as oil and gas operations are now requiring staff to be vaccinated. The vaccines are being used on the military and essential civil servants. The manufacturers include CanSino and SinoVac. Given the extensive distribution, safety and efficacy data should be available soon but the process to date has not been transparent.

Name of Vaccine developers (Phase 3)	Vaccine Types	Dose number, Timing & Route of administration	Form. approved by Country
University of Oxford / AstraZeneca	Non-replicating Viral Vector -Use ChAdOx1 (chimpanzee adenovirus) vector that expresses S protein-	1 dose/ Intra Muscular	No
Johnson & Johnson (Janssen)	Non-replicating Viral Vector -Ad26.COV2-S an Adenovirus type 26 vector that expresses S protein-	2 doses/0,56 days/ Intra Muscular	No
BioNTech/Fosun Pharma/Pfizer	RNA (genetic instruction) -Use encapsulated mRNA that encodes stabilized S antigen-	2 doses/0,28 days/ Intra Muscular	No
Moderna Therapeutics / NIAD	RNA (genetic instruction) -Use encapsulated mRNA that encodes S protein-	2 doses/0,28 days/ Intra Muscular	No

Achieving Immunity through Natural Infection

There is a movement calling for allowing the virus to spread among the general population by resuming pre-COVID lifestyles while still trying to protect the most vulnerable (e.g., nursing home patients). The idea is that this will achieve herd immunity more quickly without impacting day-to-day life and the economy as much as measures designed to encourage social distancing. This position is articulated in The Great Barrington Declaration.

Herd immunity is achieved when enough people are immune to a disease that it does not readily spread, thus providing protection even to those who are not immune themselves. The percent of a population that needs to be immune varies from disease to disease but is generally in the range of 60-70%. Thus, for this approach to work, assuming complete and lasting immunity (neither of which are likely), ~60-70% of the population would need to contract COVID-19 infections. While it is easy to identify and theoretically possible to protect vulnerable populations in institutions such as nursing homes, it is difficult to imagine how the elderly or those with chronic medical conditions who are integrated into the broader society could be protected. In addition, many people experience symptoms of COVID infection long after the infection resolves. In most cases these persistent symptoms are mild (e.g., headache) but in other cases they are debilitating. The WHO and a growing list of public health and infectious disease experts have opined that this approach would result in many more deaths and overwhelm the healthcare system.

Treatments

Improved understanding of COVID-19 and advances in its treatment could significantly decrease related mortality. While there are not yet any proven cures for the COVID-19, substantial strides have been made in the management of serious cases, resulting in improved outcomes. These include:

- Steroids such as dexamethasone which are anti-inflammatory and decrease the risk of complications caused by an over-aggressive immune response, referred to as Cytokine Storm, which can result in disability and death
- Heparin, an anti-coagulant which decreases the risk of complications caused by the formation of numerous small clots in the bloodstream, referred to as Disseminated Intravascular Coagulation (DIC). DIC in turn can clog small blood vessels throughout the body resulting in multi-organ failure and death
- Improved respiratory management which can decrease the need for intubation and artificial ventilation. This minimizes complications directly associated with these procedures and makes ventilators more available for those who need them

There are several classes of drugs being tested for their ability to treat the viral infection directly, rather than just the complications that arise from the infection:

Antivirals are drugs that kill viruses or suppress their ability to replicate. Antivirals have been successful in managing HIV, Hepatitis C, Herpes and influenza among others. Remdesivir has received Emergency Use Authorization but currently is only available intravenously for use in patients with serious illness. In its Phase 3 trial, it was found to shorten the duration and decrease the severity of illness among hospitalized COVID-19 patients. However, a larger, albeit less rigorous study organized by the WHO found no benefit to Remdesivir. The report of this study has not yet been peer-reviewed. Based on the conflicting results of these studies, it is not yet clear whether Remdesivir provides any benefit, however, it is clearly not a game changer.

There are several other drugs under investigation that could be taken orally or inhaled as soon as symptoms begin. Molnupiravir is an antiviral originally designed to fight the flu. Ridgeback Biotherapeutics and Merck are collaborating to develop it as a treatment for Covid-19. Molnupiravir produced promising results against coronavirus in studies this spring in cells and on animals. In October, the companies started two Phase 2/3 trials. Molnupiravir can be swallowed as a pill — a potential advantage for stopping the disease early in its progression.

Monoclonal antibodies are man-made proteins that act like human antibodies in the immune system the F.D.A. has approved them for 79 diseases ranging from cancer to AIDS. They are showing significant promise against COVID-19 but clinical trials are still ongoing. They are intended to be used as soon as possible after infection. If quantities are sufficient, they may also prove useful after an exposure but before illness to prevent infection.

Eli Lilly and Regeneron are most advanced in clinical trials. The trials for severely ill patients have not been promising but that is not surprising as they are designed to be used very early in illness. Lilly said it anticipates it could have as many as 1 million doses of its one-antibody treatment, LY-CoV555, available in the fourth quarter of 2020, with 100,000 available this month. But for the combination therapy, just 50,000 doses will be available in the fourth quarter of 2020. The initial trials are likely to extend to early 2021.

Interferons are molecules our cells naturally produce in response to viruses. They have profound effects on the immune system, rousing it to attack the invaders, while also reining it in to avoid damaging the body's own tissues. Injecting synthetic interferons is now a standard treatment for a number of immune disorders such as multiple sclerosis. The coronavirus appears to depress interferon production allowing it gain a foothold, synthetic interferon may help the body to fight the virus.

The British pharmaceutical company Synairgen has an inhaled form of interferon called SNG001 that lowered the risk of severe Covid-19 in infected patients in a small clinical trial. On August 6, the National Institute of Allergy and Infectious Diseases began a Phase III trial on a combination of Rebif and the antiviral remdesivir, with results expected late 2020.

Conclusion

We will likely reach the new normal by the end of 2021. While the timeline is fluid, we expect that Q1 will mark significant increase in the availability of rapid testing and the first doses of vaccine will be distributed. These will be very welcome measures following an intense rise in cases and deaths in November, December and January.

In Q2 we expect monoclonal antibodies and possibly an oral or inhaled antiviral. Vaccine should reach the most vulnerable population. This should significantly decrease the risk of becoming ill and increase the likelihood of a full recovery for those who do acquire an infection. Wider adoption of apps demonstrating immunity or recent test status in order to facilitate summer travel. Cases will decrease as the vaccine is distributed and rapid testing results in earlier isolation and reduced viral spread.

Q3 should see the wide distribution of vaccine. There will be pressure to ensure distribution includes high school and university students. Further advancement in treatments will continue to reduce the frequency of severe illness. By Q4 2021, those who want to be vaccinated will have access. There will be substantial societal pressure to be vaccinate in order to access large events, churches will encourage vaccination and businesses will encourage employees to be vaccinated. We may see a greater percentage of the population being vaccinated than early estimates.

By Q4 2021, we expect that we will be approaching herd immunity through vaccination and natural infection. That doesn't mean that the virus will disappear but we should see small outbreaks that public health can respond to quickly. People will have a sense of agency and control and will be comfortable returning to their pre-pandemic activities.

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BX RE Return to Normal: COVID Testing Types

	Molecular Test	Antigen Test	Antibody Test
Also known as	Diagnostic test, viral test, RT-PCR test, LAMP	Rapid diagnostic test (some molecular tests are also rapid tests) Best used as a screening test	Blood test, immunity test
Sample type	Nasal or throat swab (most tests) Saliva (a few tests e.g. Vault)	Nasal or throat swab Saliva likely to be approved	Blood draw or finger prick
Accuracy	Highly accurate; usually does not need to be repeated	Positive results are highly accurate, but negative results may need confirmation by a molecular test where symptoms & test results are not aligned	Occasionally, a second antibody test is needed for accuracy
Key Diagnosis	Active infection	Active infection	Past infection or immunity
Speed of results	Specimen processing time 30 minutes to 6 hours but, to a user, results take longer due to lab backlogs	Specimen processing takes 10-30 minutes; usually done at point of care	Within three days of testing
Other		If a home test is approved (i.e. similar to pregnancy test), it will be an antigen test	

Source: FDA