NEUBERGER BERMAN

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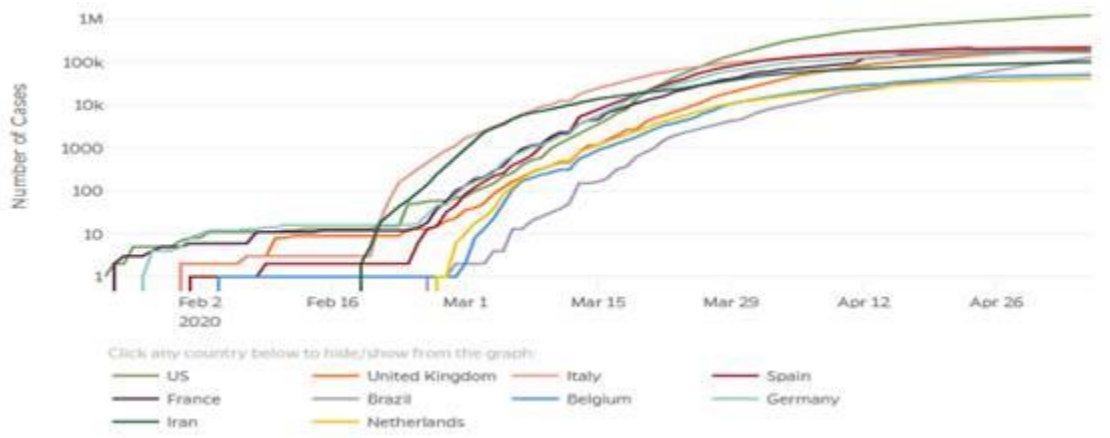
Better Prepared Should There Be a Second Wave; Improved Testing, Diagnosis and Treatment Advances Supports Our Cautious Optimism

It's safe to say we have flattened the curve; next steps to monitor on the path to returning "normalcy"; what might limit the severity of a second wave? We thought it would be helpful to discuss how we are tracking against the signposts for reopening the economy, both locally and across the country, and how prepared we are for potential COVID-19 clusters as well as a "second wave" that most experts expect to happen. Additionally, we highlight developments that may limit future outbreaks or at least reduce the clinical impact on the health of individuals as well as the economy ahead of vaccine availability, whose timeline is collapsing by the day.

We have flattened the curve; now what? The chart below shows that new cases have slowed in the U.S. as well as in Europe, reflecting an essential flattened curve. As various countries and, now, U.S. states begin the process of reopening, we are learning more about the virus; the country has increased molecular testing to roughly 265,000 tests per day and rising, is taking steps to ensure that only the best serology tests remain on the U.S. market, and saw the FDA issue an Emergency Use Authorization of the first treatment for COVID-19...all in two weeks.

COVID-19 Cases by Country



Source: JHU Covid tracking.

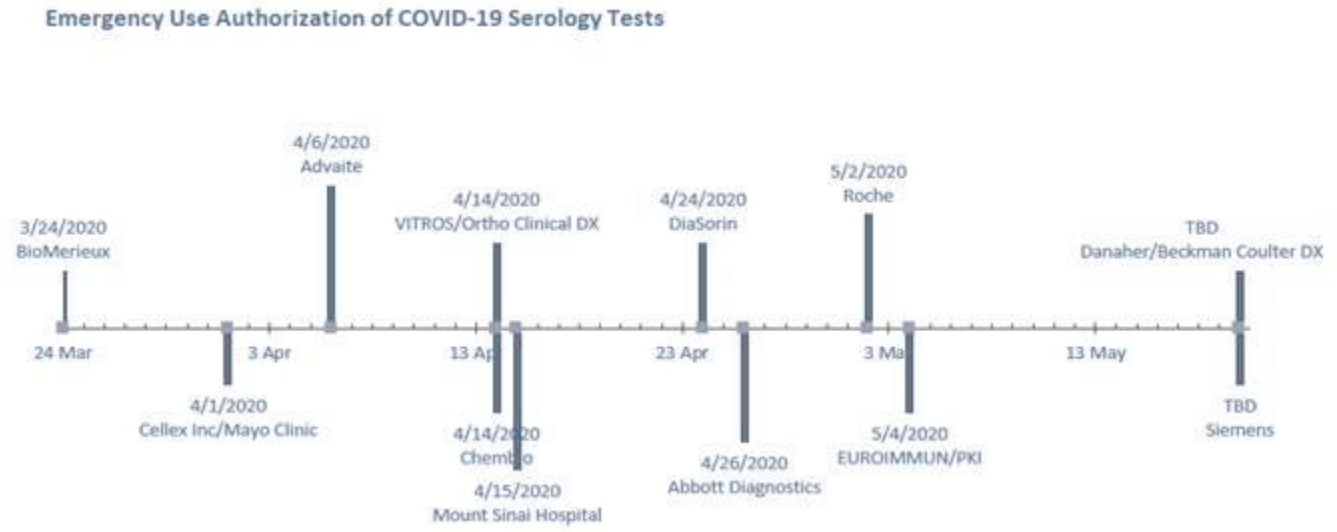
New facts about SARS-CoV2 and testing

The virus:

- There are over 4,300 sequenced SARS-CoV2 (the virus that causes the COVID-19 disease) genomes publicly available.
- 33 strains of the virus have been identified in Wuhan, China, and five in Iceland, with predominant strains derived from Austria, Italy and the U.K. Importantly, these variations are not sufficiently distinct to change how the virus behaves.
- Strains in the U.S. appear more like those in the EU than those from China.
- The mutation rate appears low and stands at about 22 – 25 mutations per year, suggesting limited antigenic shift.
- A dominant variant of SARS-CoV2 has been identified by the Los Alamos National Labs, with a mutation in the spike protein, although with limited consequence for how the virus enters cells. This is important given that the spike protein is the target of most vaccines in development, be it the full-length protein or subunits of it.

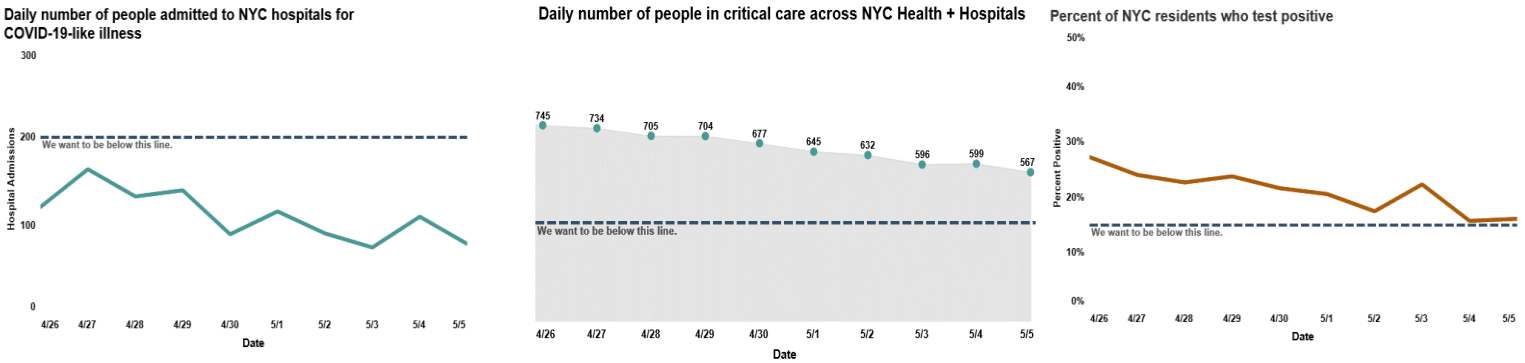
Testing: A blood test that could detect the virus 24 hours post infection and ahead of symptom development—a game changer?

- Beyond the potential to use saliva collection as the sample material to detect live virus vs. the deep nasal swabs we mentioned in a recent update (https://www.nb.com/en/gb/investing-in-volatile-markets), there is potential to use blood as the sample, with detection as soon as 24 hours post infection, before the individual displays symptoms. While at early stages, DARPA, in collaboration with Mt. Sinai and Fluidigm, has suggested using a RNA-based PCR technique with >95% accuracy and requiring only 1ml of blood.
- The implications of such a test for transmissibility and contact tracing are evident, and could limit the spread of SARS-Cov2 should a second wave hit later this year. Regarding capacity, Dr. Eric Van Geison said up to 1mm tests per day could be available should the data hold up and emergency use authorization be granted in late May.
- Regarding updated thoughts on serology testing, we will direct you to our previous notes, but suffice it to say that between the Roche, Abbott, Perkin Elmer, Diasorin and Biorad tests, as well as a few others now on the market, we think the FDA's pruning of lower-quality tests will result in higher confidence in results going forward.
- Additionally, the launch of direct-to-consumer COVID-19 serology tests could also help provide a better understanding of the true infection rate and, hence, fatality rate in the U.S., which is among the world's lowest at 6%.



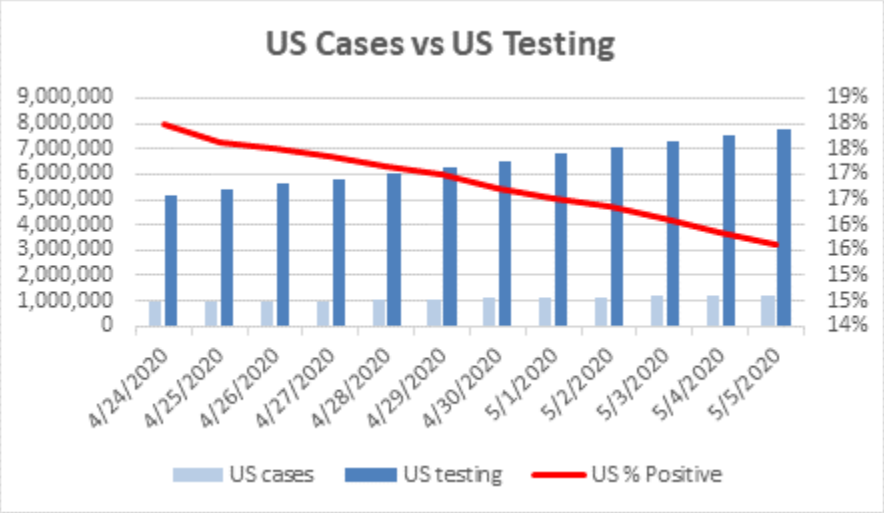
Source: FDA, Neuberger Berman, company websites.

So, if we have the testing in place, what else needs to happen to reopen? We have included the updated guidelines as well as most recent data that New York State and New York City has been monitoring in order to ensure that the health care system can handle a second wave upon reopening, as mentioned in our last update: new daily hospitalizations below 200, daily ICU occupancy below 375 and less than 15% of the population testing positive, all for 10 consecutive days. The good news is we have hit the hospitalization metric and held for 10 days, are bouncing off the 15% bogey for positive test rates for a few days; however, the critical care/ICU metric is a ways off, perhaps another week or so.



Source: nyc.gov.

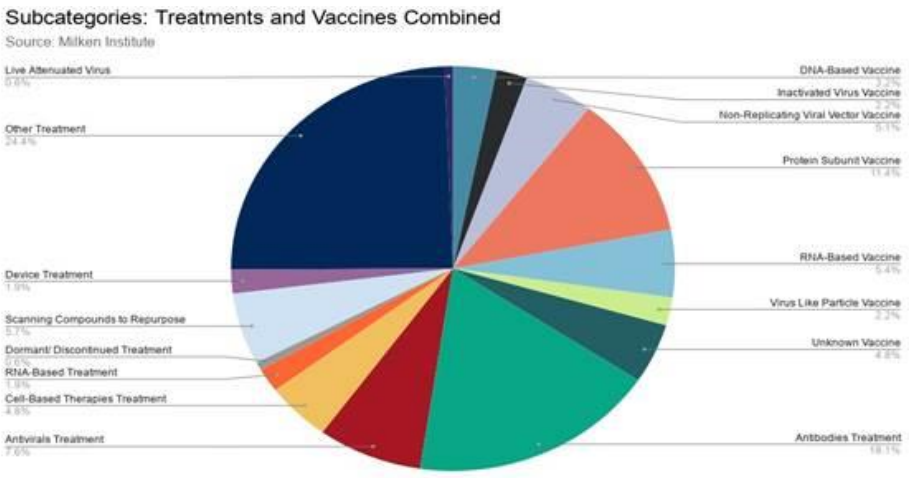
Importantly, the U.S. is approaching the New York City testing metric despite reopening across several states to date. While early, we will track this for the U.S. as a whole as well as in particular states with an eye on Florida, Georgia, Texas and South Carolina, as well as California as it approaches this decision. The U.S. has tested over 7mm people to date, one of the highest around the globe.



Source: Neuberger Berman, JHU COVID tracker, Coronavirus Taskforce press conferences.

First antiviral agent against SARS-CoV2 FDA approved; Remdesivir supply the only gating factor to broad use in hospitalized, severe COVID-19 patients. Recently, we joined a conference call with Gilead's CFO and head of R&D in which we discussed the supply of Remdesivir as well as allocation in the short term before supply inflects in early fall. Gilead confirmed that it has donated its entire finished product supply of Remdesivir to the U.S. government, which consists of enough vials to treat about 140,000 patients with a 10-day course, close to 1.5 times that number should only five-day courses be needed. Gilead has committed to a completed supply for 500,000 patients by October and >1mm treatment courses by the end of December. Additionally, the company is planning on forming partnerships for manufacturing as well as out-licensing to generic makers in India to supply the developing world. On the issue of allocation of limited supply, Gilead was clear that it is in consultation with the U.S. executive branch and regulators, and that the government has the ultimate say as to allocation, notwithstanding the obvious link to directing supply to the most impacted regions and taking into account the severity of disease. While Remdesivir is not a magic bullet, in our view, given the need for IV infusion, it represents hope/step one in treating COVID-19 and ultimately lowering the fatality rate. Gilead is working on an inhaled version of Remdesivir as well as administering the drug subcutaneously; both are at least a year away but would expand access substantially.

What other agents are in development for treatment of COVID-19 and prevention with vaccines? According to the Milken Institute database, there are over 200 treatment candidates and >90 vaccines either in preclinical or clinical studies with ~10 marketed drugs being repurposed outside of direct antivirals.



Source: Milken Institute as of May 7, 2020.

Near-term impact from repurposed drugs: We favor Roche's Actemra and Regeneron/Sanofi's Kevzara to treat lung inflammation resulting from SARSCoV2 infection and are carefully watching Alexion's Ultomiris as a means to address emerging events in COVID-19 patients. The chart below highlights currently marketed therapies as a means to address the clinical sequelae resulting from SARSCoV2 infection. While antiviral agents logically should have the best chance of changing the course of infection and consequent clinical manifestations, even Remdesivir has not shown an impact on viral load, at least in the blood. There is emerging evidence that this virus primarily replicates in the lungs, which triggers inflammation, leading to typical and atypical pneumonia. Whether direct or indirect, resulting damage to the lung vasculature could lead to clots or emboli and presents as thrombotic complications in many COVID-19 patients. For these reasons, we would argue that inhibiting the action of elevated levels of IL-6 with Actemra and inhibiting the complement cascade with Ultomiris are logical to address the lung inflammation and consequent damage, which may be permanent. Lastly, one drug in development called Ang-2 could address the thrombosis seen in these patients. It is a long shot in our view, but one worth investigating.

Company	Drug	Mechanism	Approved Indication
Abbvie	Ritonavir/Lopinavir	protease inhibitor	HIV
Alexion	Ultomiris/Soliris	C5 inhibitor	PNH, aHUS, gMG, NMOSD
Amgen	Otezla	PDE-4 inhibitor	Psoriasis
Astra Zeneca	Calaquence	BTK inhibitor	CLL
Eli Lilly	Olumiant	JAK inhibitor	Rheumatoid Arthritis
Gilead	TruVada	Non-nuc/nuc	HIV
Incyte/Novartis	Jakavi	JAK inhibitor	Myelofibrosis
Johnson & Johnson	Prezista	Protease inhibitor	HIV
Merck	Interferon beta	Type I INF	HCV
Novartis	Ilaris	IL-1 inhibitor	Systemic Juvenile Idiopathic Arthritis
Pfizer	Xeljanz	JAK inhibitor	Rheumatoid Arthritis
Roche	Xoflueza	Endonuclease inhibitor	Influenza
	Actemra	IL-6 inhibitor	Rheumatoid Arthritis
Regeneron/Sanofi	Kevzara	IL-6 inhibitor	Rheumatoid Arthritis

Source: Neuberger Berman & Biomedtracker as of May 7, 2020.

Other modalities in clinical development we are watching closely include passive immunity strategies involving recombinant antibodies as a bridge to a vaccine. Several biotech and pharmaceutical companies are actively advanced recombinant antibody cocktails directed primarily at the SARSCoV2's spike protein as a means to mimic convalescent plasma exchange (CPE). Recall that CPE is a collection of plasma and presumably neutralizing antibodies generated in recovered COVID-19 patients and has demonstrated benefits to hospitalized,

severe COVID-19 patients. Passive immunity strategies are a large-scale, recombinant way of producing cocktails of select antibodies that would be present in plasma, and allows for treatment as well as prophylaxis in healthcare workers and first responders on a broad scale. Regeneron's study is expected to initiate in June with data by fall 2020, followed by Eli Lilly/Abcellera's program and Vir Biotech/Glaxo SmithKline's studies. Additionally, Amgen partnered with Adaptive Biotech, utilizing the latter's vast antibody libraries from COVID-19 patients as well as investigating the role of immune cells called T cells in the body's immune response to COVID-19.

Finally, on vaccines, we will leave you with the chart below, which highlights either experienced manufacturers or novel modalities with manufacturing partners able to meet initial demand should a vaccine approach prove safe and efficacious. This is somewhat of a teaser to a future installment, where we will go into details regarding risks around vaccine development, timelines for broad access and plan B if these approaches fail.

Company	Vaccine Class	Partners Manufacturing	Timing/Data
Moderna	mRNA, mRNA1273	BARDA, Lonza	Phase I end of May
University of Oxford	Non-replicating viral vector (Chimp AAV)	AstraZeneca & Vaccitech	Phase I/II, data end of May/early June
Johnson & Johnson	Non-replicating viral vector (AAV26)	BARDA, Emergent Biosolutions	Phase I to begin in September
Vaxart	Non-replicating AAV5		Phase I imminent
Can Sino Pharma	AA5 viral vector	AMMSIB	Phase II imminent
Sanofi/Glaxo	Protein subunit-S protein baculovirus	BARDA	Phase I imminent
Novavax	Full length glycoP NVX-coV2373	Emergent Biosolutions	Phase I begins mid-May
BioNtech/Pfizer	mRNA, BNT-162	Fosun China	Phase I initiated May
Translate Bio	mRNA	AMRI	Clinic by end of 2020
Vir Biotech/Alnylam	Inhibitory RNAs		Clinic by end of 2020
Inovio	DNA, INO4800	Richter-Helm, CEPI	
Merck & others	Live attenuated BCG	SNY, Powderject	Marketed*

Source: Neuberger Berman & Biomedtracker as of May 7, 2020.

We believe we are over the hump with this virus and will be better prepared for round two should it materialize. In our view, advances in molecular testing, both in sample collection and in capacity, will better equip the U.S. in identifying any new infections going forward. Additionally, growing knowledge about the virus and its many strains, antibody testing and advances in how to treat the clinical manifestations of viral infection, as well as Remdesivir's Emergency Use Authorization by the FDA, could serve to decrease the severity of this disease and hopefully the fatality rate. While vaccine timelines are collapsing by the day and the all-hands-on-deck view from industry and foundations is astoundingly refreshing, we may have to rely on passive immunity strategies as a bridge should this second wave come. However, we have confidence we will be ready for it this time.

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For more information on COVID-19, please refer to the Center for Disease Control and Prevention at cdc.gov.

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