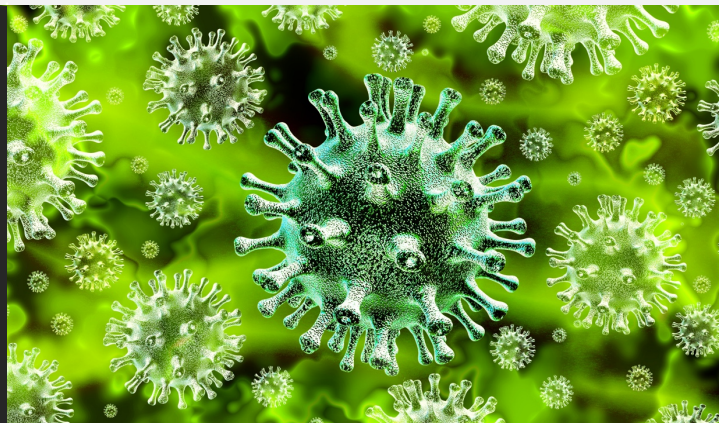
Coronavirus Review

Introduction

The 2019 Novel Coronavirus Disease (COVID-19) epidemic has roiled equity markets as recent headlines highlight disease spread outside of the initial epicenter in Wuhan, China. We reviewed the scientific / medical literature to provide an evidence-based summary of what is known about this outbreak, how it compares to others in recent memory and potential therapies in development.



Comparison of coronavirus epidemics

Perhaps unknown to the average citizen, SARS-CoV-2 is actually a member of the coronavirus family that leads to today's 2019 Novel Coronavirus Disease (COVID-19). It is genetically related to SARS-CoV, which is the coronavirus that caused the Severe Acute Respiratory Syndrome (SARS) global epidemic from 2002–2003, and also related to MERS-CoV, the coronavirus that caused the Middle East respiratory syndrome (MERS) from 2012-present (see table below for citations). Early data suggest that SARS-CoV-2 is much more easily transmitted compared to the aforementioned coronaviruses due to increased viral shedding from both symptomatic and asymptomatic patients. This means it's easier to spread and thus contract COVID-19. The enhanced infection rate helps explain why there is nearly a ten-fold larger number of these current coronavirus cases reported in less than three months compared to the total numbers observed for SARS and MERS combined throughout the entire outbreak. However, while there are a larger number of reported cases, the observed case fatality rate of 3.2% is well below that seen with SARS and MERS with the majority of deaths in elderly patients with co-morbidities. Epidemiologists estimate the mortality rate may prove to be much lower over time as more asymptomatic and mildly symptomatic cases are diagnosed. Todays coronavirus is associated with a 5-15% severe respiratory complication rate that requires acute medical care further contributing to the disease burden.

	2019 Novel Coronavirus Disease (COVID-19)[1,2,3]	Middle East Respiratory Syndrome (MERS)[4,5]	Severe Acute Respiratory Syndrome (SARS)[6]
First Reported	December 2019 Wuhan, China	2012 in Saudi Arabia	Mid-Nov. 2002 in Guangdong, China
Last case reported	Ongoing	January 13 2020 (suspected from camel transmission)	5 July 2003 (chain of human transmission broken)
Transmission	1. Close (droplet) or potentially more distant contact (aerosol) with both symptomatic AND asymptomatic patients 2. Possible transmission from surfaces that carry virus 3. Possible transmission from fecal matter	1.Close contact with infected camels or consuming their milk / meat 2. Limited human-to human transmission through close contact (droplet)	1. Close contact (droplet) with symptomatic patients 2. Possible transmission from surfaces that carry virus
Number infected	96,888 cases, 3,305 deaths (3.2%) as of March 5, 2020	2,506 cases, 862 deaths (34.4%) as of March 5, 2020	8,422 cases, 916 deaths (10.8%) as of March 5, 2020
Geography	48 countries	27 countries	29 countries

Future projections

Coordinated public health measures led to the rapid containment of SARS in 2002-2003, but the significantly higher case numbers and differentiated transmission characteristics of todays coronavirus make it difficult to predict the effectiveness of similar measures. Early data are conflicting, showing both reduction of cases due to containment measures in Wuhan, China, but sustained transmission in multiple new locations including South Korea, Italy and Iran. Expert projections for the ultimate course of the current epidemic range from "possible containment" to "40 to 70 percent of the adult global population will eventually become infected."[7] Fortunately, exciting developments from innovative biopharma companies have the potential to limit the impact of disease should it develop into a global pandemic.

Treatments in development

More than 80 clinical trials have been reported for potential COVID-19 treatments ranging from traditional Chinese herbal medicine to complex biologics highlighting the potential to rapidly mobilize scientific efforts to address emergent threats.[8] We believe molecularly targeted antiviral therapies, genetically defined vaccines and engineered monoclonal antibodies offer the strongest scientific rationale of all the approaches proposed. Below we summarize some of the most advanced efforts from US listed companies.

Clinical Programs

Gilead Sciences (GILD) - Remdesivir

Gilead's remdesivir is a molecularly targeted antiviral therapy designed to incorporate into nascent viral RNA chains and inhibit viral replication. Structurally, it is a nucleotide analog with broad-spectrum antiviral activity both in vitro and in vivo in animal models against multiple emerging viral pathogens including Ebola, Marburg, MERS and SARS. Remdesivir was previously studied in Phase 1 / 2 trials in healthy volunteers and in people with Ebola virus infection which enabled rapid advancement to Phase 3 clinical testing for COVID-19. There are multiple nucleoside analogs approved for other viral infections thereby validating the potential of this approach, but remdesivir was previously evaluated in a late stage Ebola trial with mixed results.[9] There are five ongoing clinical trials of remdesivir for COVID-19. The first two are being conducted independently by researchers at the China-Japan Friendship Hospital in Hubei, China where GILD is providing donated drug. Results are expected in April. In the US, the National Institute of Allergy and Infectious Diseases (NIAID) is conducting an investigational trial and Gilead is sponsoring two Phase 3 trials in COVID-19 patients expected to start in March. Data from these latter trials will likely take several months or longer. A positive result in these trials would enable remdesivir to be the first therapeutic agent approved for the treatment of COVID-19.

Moderna (MRNA) – mRNA-1273

Moderna's mRNA-1273 is an mRNA vaccine against SARS-CoV-2 encoding for the Spike (S) protein, which is necessary for membrane fusion and host cell infection. Moderna had previously used similar methodology to produce six other vaccines for separate infectious diseases that have completed phase 1 clinical testing showing safety and induction of an immune response to the target antigen. The most advanced candidate is now heading into a Phase 2 trial, but there are no mRNA vaccines yet approved. Moderna announced shipping the initial drug product to start the Phase 1 trial of mRNA-1273 on February 24, 2020. It is expected that it will take a couple of months to complete the Phase 1 trial of mRNA-1273 to evaluate initial safety and immunogenicity, which would then be followed by larger phase 2 / 3 trials evaluating actual protection from infection. The latter may take many months to a year realistically pushing out the earliest potential date for vaccine availability to late 2021 or 2022.

Preclinical Programs

Regeneron (REGN)

Regeneron's is using its proprietary VelociSuite® technologies – including the VelocImmune® platform which uses a unique genetically-engineered mouse with a humanized immune system that can be challenged with all or parts of a virus of interest – to facilitate swift identification, preclinical validation and development of promising antibody candidates against SARS-CoV-2. The company previously used a similar approach to identify its REGN-EB3 antibody candidate for the treatment of Ebola in ~6 months. REGN-EB3 was later advanced into clinical development where it showed a significant reduction in death related to Ebola infection vs a comparator group thus validating the approach.[9]

Vir Biotechnology (VIR)

Collaborating with WuXi Biologics on a preclinical program to identify rare antibodies from COVID-19 survivors that may offer treatment or prevention of SARS-CoV-2 infection via direct pathogen neutralization and immune system stimulation. The company announced they have identified a few preclinical candidates that bind to SARS-CoV-2, but may be many months to a year or longer away from completing the optimization and manufacturing work required to begin clinical testing.

Vir is also collaborating with Alnylam Pharmaceuticals on the development of RNAi therapeutics targeting highly conserved regions of SARS-CoV-2. The program will utilize Alnylam's recent advances in lung delivery of novel conjugates of siRNA, the molecules that mediate RNAi. It may be many months to a year or longer away from completing the optimization and manufacturing work required to begin clinical testing.

Novavax (NVAX)

Novavax's COVID-19 vaccine candidates use its proprietary recombinant protein nanoparticle technology platform to produce protein antigens derived from the coronavirus spike (S) protein, and combines them with their Matrix-M™ adjuvant to enhance immune responses. The Company is evaluating multiple nanoparticle vaccine candidates in preclinical animal models to identify an optimal candidate for human testing, which is expected to begin by the end of spring 2020. Novavax previously used a similar approach to produce two separate infectious disease vaccines that were shown to be safe and able to induce an immune response in Phase 1 trials and are now in Phase 3 testing. It is expected that it will take several months to complete the Phase 1 trial of the COVID-19 candidate to evaluate initial safety and immunogenicity, which would then be followed by larger phase 2 / 3 trials evaluating actual protection from infection. The latter may take many months to a year realistically pushing out the earliest potential date for vaccine availability to late 2021 or 2022.

Inovio Pharmaceuticals (INO)

Inovio is collaborating with Beijing Advaccine Biotechnology Co. to advance the development in China of INO-4800, Inovio's vaccine against the recently emerged SARS-CoV-2. The vaccine candidate will be designed to deliver DNA to induce an immune response. The program is in early preclinical development and manufacturing of a candidate has not yet begun. It may be months to a year or longer before this vaccine candidate enters clinical trials.

Preclinical Programs

Altimmune (ALT)

Altimmune is working on a COVID-19 vaccine using it's technology platform designed to provide systemic immunity following a single intranasal dose. The design and synthesis of the vaccine has been completed and the program is now advancing toward animal testing and manufacturing. It may be many months to a year or longer away from completing the optimization and manufacturing work required to begin clinical testing.

Dynavax (DVAX)

Collaborating with the University of Queensland as part of a Coalition for Epidemic Preparedness (CEPI) to develop a vaccine for COVID-19. Dynavax is providing technical expertise and the Company's proprietary toll-like receptor 9 (TLR9) agonist adjuvant, CpG 1018, to support this initiative. CpG 1018 was designed to increase vaccine immune response and is the adjuvant used in HEPLISAV-B®, an FDA approved adult hepatitis B vaccine. The program is at an early preclinical stage and it may be many months to a year or longer away from completing the optimization and manufacturing work required to begin clinical testing.

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