1. Background / basic virology and epidemiology

a. Characteristics of SARS-CoV-2

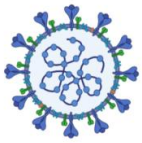
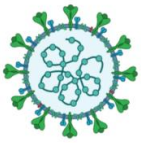
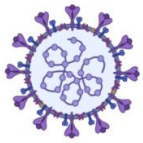
Covid-19 is caused by SARS-CoV-2, a member of the coronavirus family. Its closest relatives are the SARS-CoV virus, with which it shares roughly 79% genomic similarity, and MERS-CoV virus, with 50% similarity. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of coronaviruses ranges from approximately 27 to 34 kilobases (29.9 for SARS-CoV-2), the largest among known RNA viruses.

Compared to seasonal flu virus, SARS-CoV-2 is characterised by both higher infectivity (basic reproductive number 2.0-2.5 vs 1.3 for flu) and higher disease severity, both in hospitalization rate (~20% vs ~2%) and case fatality rate (~3% vs ~0.1%). SARS-CoV-2 also starkly contrasts with its closest relatives in these regards, causing much less severe symptoms than both SARS-CoV and MERS-CoV (with fatality rates around 10% and 35% respectively).

The clinical manifestation of different CoV infections varies greatly with the specific CoV type. Most are mild and asymptomatic infections, but can range from the common cold to 30% mortality (MERS-CoV). Most common symptoms include: “colds” with fever, sore throat, primary viral pneumonia and/or bronchitis, as well as secondary bacterial pneumonia and/or bronchitis.

SARS-CoV severe acute respiratory syndrome (SARS) led to both upper and lower respiratory tract infections. MERS-CoV, Middle East Respiratory Syndrome (MERS), led to fever, cough, shortness of breath, gastrointestinal symptoms (primarily diarrhoea), with or without pneumonia. Some positive patients were asymptomatic. MERS was highly lethal, and symptoms could progress to ARDS, MODS, and sepsis.

Epidemiological Comparison of Respiratory Viral Infections

Disease	Flu	COVID-19	SARS	MERS
Disease Causing Pathogen	 Influenza virus	 SARS-CoV-2	 SARS-CoV	 MERS-CoV
R_0 Basic Reproductive Number	1.3	2.0 - 2.5 *	3	0.3 - 0.8
CFR Case Fatality Rate	0.05 - 0.1%	~3.4% *	9.6 - 11%	34.4%
Incubation Time	1 - 4 days	4 - 14 days *	2 - 7 days	6 days
Hospitalization Rate	2%	~19% *	Most cases	Most cases
Community Attack Rate	10 - 20%	30 - 40% *	10 - 60%	4 - 13%
Annual Infected (global)	~ 1 billion	N/A (ongoing)	8098 (in 2003)	420
Annual Infected (US)	10 - 45 million	N/A (ongoing)	8 (in 2003)	2 (in 2014)
Annual Deaths (US)	10,000 - 61,000	N/A (ongoing)	None (since 2003)	None (since 2014)

* COVID-19 data as of March 2020.

Created in BioRender.com bio

Source: BioRender, Akiko Iwasaki (Yale University)

b. Immune response

For the moment, unlike the influenza virus, the members of the coronavirus family have shown little ability to reassort, responsible for major genetic shifts behind the known flu pandemics, bypassing existing immunities.

Nevertheless, the coronavirus family has its own adaptations that were observed in MERS-CoV and SARS-CoV, and are likely manifest in SARS-CoV-2. Coronaviruses interfere with multiple steps during initial innate immune response, including RNA sensing, signalling pathway of type I IFN production, and STAT1/2 activation downstream of IFN/IFNAR. This is not only responsible for the severity of the disease, but likely also for an uncharacteristically long incubation period (up to 14 days compared to 1-4 for influenza).

There is currently no reliable data on long-term immunity to SARS-CoV-2. A study (Bao et al., 2020) published on BioRxiv has shown no reinfection for macaques after initial infection. Yet, the study is very small (only 4 animals) and only examines short-term response. Several cases of potential human reinfection were reported, but at this time they are attributed to unreliable testing.

If SARS-CoV-2 behaves similarly to SARS-CoV and MERS-CoV, long lasting specific IgG and neutralizing antibodies are reported as long as 2 years after infection with SARS-CoV, indicating a possibility of long-term immunity.

c. Mortality

While SARS-CoV-2 is significantly less fatal than its closest relatives (see section a above), its lethality increases rapidly with patient age. The disease is largely asymptomatic in children and a large percentage of younger adults (current estimates point at 50-70% of cases being asymptomatic), but is 5-10% fatal (depending on the quality of hospital care) in the age group over 70.

d. Practical issues

- SARS-CoV-2 is spread through aerial route, and is able to persist for several hours on various surfaces (half-life in aerosol state and on copper is 1 hour, and almost 4 hours on cardboard, 6 - on stainless steel, and 7 - on plastic (van Doremalen et al., 2020)).
- SARS-CoV-2 is inactivated by 62-70% alcohol solutions, by 0.5% hydrogen peroxide or household bleach, which all can be effectively used to disinfect affected surfaces or items.
- Initial data shows that SARS-CoV-2 is stable at temperatures up to 37 degree Celsius, and as such little seasonal variability in infection rate can be expected. SARS-CoV has been shown to be inactivated at temperatures around 60 degree Celsius, and as such it can be assumed that SARS-CoV-2 should not survive boiling, but is not inactivated by water temperatures that are below scalding hot to human skin.
- Cats, dogs and other household pets are not susceptible to COVID-19, but can act as intermediaries for spread of the virus to healthy people on their fur/skin if in direct contact with the diseased, same as any other contaminated surfaces.
- Early reports from China show that there is no intrauterine transmission of COVID-19 in pregnant women, and SARS-CoV-2 does not pose a specific additional risk to pregnant women outside normal flu-like symptoms.

2. Progress: treatments and vaccines

Both the research and the industrial communities moved extraordinarily quickly in response to the epidemic. In particular, the research was spurred on by the very early publication of viral sequences, and the consequent publication of the crystal structure of the key surface proteins. This enabled drug development at a considerable pace.

In the current quickly escalating situation some old generation therapies are used off-label, despite the low level of evidence. One of these is alpha-interferon inhalation and the other is a lopinavir/ritonavir combination which was originally produced to treat HIV (Jin et al., 2020).

Also, Gilead recently started clinical tests of the antiviral drug remdesivir designed against EbolavirusThese remdesivir studies have attracted significant interest from many observers in the biopharma and scientific community due to observed in vitro activity against COVID-19 (Wang et al., 2020) and Gilead potentially having the infrastructure to manufacture and supply the drug in an accelerated fashion in the United States.Besides that, old anti-malaria generic drug chloroquine has shown some positive results in the first cohort of COVID-19 patients in China (Colson et al., 2020).

Alongside with the repurposed drugs, there are currently at least 22 COVID-19-specific therapeutics in development by various pharmaceutical companies and academic institutions. The majority of the work seems to be focused on searching for protease inhibitors, in line with other antiviral drugs.

At the time of writing, there are at least 69 separate efforts worldwide at producing a COVID-19 vaccine, with over 20 in China alone. These three COVID-19 specific vaccines currently in developmentwe find to be of particular interest we consider among the most promising:

a. On March 16 Phase 1 (safety) clinical trials of the investigational vaccine mRNA-1273 was started on 45 healthy volunteers. It was developed by National Institute of Allergy and Infectious Diseases (NIAID) in collaboration with Moderna, Inc. Previous development projects on other vaccines targeting spikes on the surface of other coronaviruses SARS and MERS gave a head start to this work. The active phase of the investigation will take at least 4 months, with a follow-up of more than a year.

b. On March 17 Pfizer Inc. in collaboration with BioNTech SE announced the development of another mRNA-based vaccine BNT162. It will enter clinical testing by the end of April 2020. Their partnership originated in 2018 under development of influenza vaccine, which promoted the fast progression of the BNT162 vaccine. Besides that, on March 13, 2020, Pfizer issued a five-point plan calling on the biopharmaceutical industry to join the company in committing to unprecedented collaboration to combat COVID-19.

c. On February 26 clinical stage vaccine company Novavax announced the progression in development of COVID-19 proprietary nanoparticle vaccine with adjuvant; they expect Phase I to start in May-June. They previously developed promising vaccine candidates against SARS and MERS, and currently have clinical trials of RSV and Flu vaccines successfully transitioning to Phase III.

Other biotech companies and academic institutions are also working towards a COVID-19 vaccine or treatment. The vaccination approaches include DNA vaccines (Inovio, Entos Pharma and others), protein-based vaccines (Sanofi, AJ Vaccines and others), viral vector-based vaccines (J&J, Altimmune and others), live attenuated vaccines (Institute Pasteur, Codagenix). Multiple routes are utilized for the search of the treatment: antibodies to neutralise viral particles (Takeda, NIH and others), small molecules (Insilico Medicine, Enanta Pharma and others), siRNA (Vir Biotech, Sirnaomics), and even cell therapy (Sorrento Therapeutics). There is no prediction as of yet for the efficacy and timeline of the new anti-COVID-19 drugs development.

Overall, we have strongly believe that both routes of vaccine development (novel mRNA/DNA vaccines and classical viral vector vaccines) can be applied to address the COVID-19 challenge, and it will be best if two or three effective vaccines can be developed. It's completely unclear right now if a commercial COVID-19 vaccine could ever be successful, so collaboration is vastly preferable to competition as it stands.

Moreover, we think that ensuring the lessons of SARS-CoV are learned well and we do obtain a fully working vaccine as well as an efficient therapeutic drug against COVID-19 should be a priority for charitable institutions and policy makers alike going forward. The successes of cross-reacting CoV-CoV2 antibodies indicate that if we had a vaccine and a therapeutic against SARS, the situation might have been significantly different. However, unfortunately, research funding for SARS dried up soon after the media attention looked elsewhere and the work has never been finalised. We must do better this time round.

3. Impact on our 4BIO Capital business and portfolio companies

Public universe: the small and mid-caps in the ATMP (Advanced Therapies Medical Products) universe suffered disproportionately compared to the rest of the market but in line with other biotech small and mid-caps. Several prominent companies in the universe are now well below their pre-IPO series B valuations, and the majority are under those for crossovers financing rounds (last private rounds prior to IPO). Impact on crossover and larger venture funds remains to be seen but we estimate it to be significant. We anticipate substantial disturbance to biotech companies' management, product development timelines slippages and supply chain issues to continue. This will result in additional cash-burn and larger than anticipated losses per share in Q1 - Q2 2020

Public strategy outlook: We are monitoring market volatility closely. Since we have control over when the I4BATLE Fund starts investing and building its portfolio **we are seeking an efficient buy-in**. We have not observed any systematic read-through of the supply line disruption into the public ATMP universe, but anticipate that this will lead to moderate slippage of timelines for several companies in our projected portfolio. Overall, our analysis right now revolves around this (i.e. how dependent the clinical trials and the approved drug shipping are on the global supply chain) as well as the cash reserves. The majority of our portfolio companies remain funded well into 2022 as we went more defensive on this in Q4 2019. With most investors looking for a minimum 2 year holding period in our Fund, we believe it is well positioned as a part of a recession playbook with its strong fundamentals and a good buy-in.

Private pipeline has not been affected significantly as of yet. We're currently negotiating the term sheet on our transaction #3 (formation deal in CAR-T, technology based at a Swiss university). The university counterparts transitioned to working from home so we expect mild delays, with the deal timeline slipping from end of March to end of April. We're in due diligence on four other transactions (2x series A, 2x series B) and no timelines were changed there as of yet. It's actually an extraordinarily busy time on the private side for us.

Private portfolio companies have not been significantly affected either. Our first portfolio company (still in stealth mode) had some initial drug development outsourced work being

done in Wuhan, China. This was mitigated quickly early in January through the diligent work of the company team and our Director. The resulting delay was not more than two weeks. Now that the new vendors are in place, we have no significant concerns with timelines there. Our second portfolio company is operating normally, with the only challenge being the closure of their lab on the premises of a US university (along with the rest of the campus). This is being mitigated through outsourcing more work to the CROs. Hires are proceeding as expected. We have concerns only for the worst-case scenario when the gene therapy manufacturing capability might be requisitioned for vaccines, which would indeed cause delays for the company's entry into the clinic.

Private strategy outlook: business as usual right now as we are yet to see any significant read through of the public market volatility into the private transactions. Once this filters through we expect more availability of reasonably priced late-stage rounds, and indicated to the relevant bank desks our willingness to look at such on rapid timelines. We plan our formation and seed-stage investments to be financed for two to three years at inception and hence the volatility doesn't concern us too much. We're still on track to make 4-5 investments total in the first year of the fund.

Policy: We have been in touch with the UK government as a part of their consultations with the venture capital industry, and raised the issues of supply chain disruption, timeline slippage and liquidity challenges for funds. We anticipate a significant relief package for the UK biotechs as the government clearly recognises the country's leadership in the sector and its long-term value.

Fundraising has been affected both ways. We have received significant new investor interest in the past two weeks to both funds as investors who were previously not willing to allocate to the sector are now seeking exposure and novel strategies. However, as you can expect, those investors currently in diligence have been affected in terms of their ability to come to our diligence days, and our own travel was cancelled. As a result of this, we made a decision to **extend our VCII fundraising timeframe and keep the fund open for another 3-6 months after YE 2020** as a courtesy to our potential investors. The hard cap and the investment period will remain unchanged as we have no desire to create potential for strategy drift. We are actively onboarding new investors into both Funds.

About 4BIO Capital

4BIO Capital is an international venture capital firm focused solely on the advanced therapies sector.

4BIO's objective is to invest in, support, and grow early-stage companies developing treatments in areas of high unmet medical need, with the ultimate goal of ensuring access to these potentially curative therapies for all patients. Specifically, it looks for viable, high-quality opportunities in cell and gene therapy, RNA-based therapy, targeted therapies, and the microbiome.

The 4BIO team comprises leading advanced therapy scientists and experienced life science investors who have collectively published over 250 scientific articles in prestigious academic journals including Nature, The Lancet, Cell, and the New England Journal of Medicine. 4BIO has both an unrivalled network within the advanced therapy sector and a unique understanding of the criteria that define a successful investment opportunity in this space.

For more information, please visit www.4biocapital.com