COVID-19 – Perspective from a Biotech Investor

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March 27, 2020

The purpose of this memo is not to try and repeat what so many people – both experts and non-experts - have been writing and saying for the past weeks and months. The avalanche of research reports and other documents produced addressing all aspects of the COVID-19 virus and its impact on every aspect of our lives, has been overwhelming (for clarity: SARS-CoV-2 is a coronavirus, a family of RNA based viruses, which causes the disease COVID-19). We – as so many others – are trying to keep up on a daily and hourly basis.

So rather than add to the onslaught of information you have undoubtedly been receiving about the spread of COVID-19 and the news of ever-increasing patient numbers – we wanted to summarize the efforts in motion to combat the pandemic. The world of healthcare professionals are truly the heroes of the story, putting themselves at risk at the cold face of the pandemic to help patients. But the healthcare sector is doing far more! Pharma, Biotech, regulatory agencies and other stakeholders of the industry have pooled their resources like never before to expedite the development of diagnostics, therapeutics and vaccines. We are receiving daily updates of scientific and medical progress on all fronts - what follows is our attempt to give a snapshot of where we are today and what has been achieved in such a short time.

Looking back only a couple of months, when we first heard of the coronavirus, we expected the impact to be like a flu season, admittedly a bad one. In some regards, it is.
In early January, the Director of the US National Institute of Allergies and Infectious Diseases Dr. Anthony Fauci told CNN that '*the current flu season is on track to be one of the worst in years*'. This was before he - and we - factored in the Coronavirus. The 2017/18 and 2009/10 flu seasons were also particularly harsh.

There are, however, a few critical differences. Obviously, we have vaccines for the flu, which means that the most vulnerable in our society are vaccinated and there is a certain herd immunity to dampen the effect. These flu vaccines are not perfect and work better some years than others, but overall, they do reduce the number of infections significantly. As a result, our healthcare infrastructure – doctors, hospitals etc. - are equipped to deal with the influx of these patients during the flu season. For SARS-CoV-2, however, not only do we not have a vaccine available, but also the infection has a *disproportionate* impact on the weak, the sick and the elderly. These patients – who quickly progress to becoming very sick after infection - come *on top of* the 'normal' or expected numbers during the more regular flu season. This is the biggest problem we are facing, and this is what threatens to overwhelm the healthcare systems across the world.

Fortunately – if one can use this word in times like this - and triggered by human drama seen in China, Iran, Italy and Spain, a massive R&D effort within the biopharmaceutical and biomedical industry has sprung to life, to come up with solutions to help address the problem in the fastest possible way.

So, what does this mean exactly? Why was such an effort not undertaken much earlier? Have people not been warning for this to happen? What are the hurdles? Why is it apparently so difficult to come up with a solution? And – most importantly - what is being done by whom right now?

Question 1: why only now?

Investment in diagnostics, vaccines and treatments targeting infectious diseases has lagged behind other areas of healthcare for quite some time. Too little has been invested for too long in this area of medicine. This should not be a surprise to anyone with an interest in drug development. In essence, the risk/reward in infectious diseases is skewed toward the wrong end. The simple underlying reason being that the regulatory hurdles are very high, making it relatively difficult – and thus costly – to develop a new vaccine for instance, *while the rewards for such endeavor are highly uncertain*. Why would shareholders of a public or private company allow "their" company to spend hundreds of millions on the development of a vaccine for a virus, *for which it may never generate any revenues to recoup its investment*? Demand for its product will be dependent on the occurrence – or not – of the infection. Effectively, developing new drugs for indications for which demand is certain, is – from a business point of view – less risky and therefore more interesting. Hence the lack of R&D investments in the area of infectious diseases.

Clearly, the Corona experience is likely to change all this. It has become shockingly clear to our society that a virus like this one, has the potential to stop the world's economy to a grinding halt. It has also become shockingly clear that a vaccine for the un-infected and a therapy for the infected, is lacking and people are dying as a result. So, without a doubt, initiatives will be taken by governments – hopefully together – to address this problem in the future. Setting up a giant - fifty or one-hundred billion - infectious diseases investment fund would be a good start, in our opinion.

Question 2: what are the hurdles?

The hurdles in developing a diagnostic test are not the same as those in developing new medicines. In fact, regulatory hurdles for developing diagnostic tests are lower, while unfortunately the commercial hurdles are higher. Main reason being that insurance providers are rather reluctant to pay for diagnostics – they are viewed as an additional cost burden on the healthcare system and the link to the ultimate cost benefits are not directly attributed to the diagnostic test. In addition, new tests must also compete against the standard microbiology tests, which in many cases have been used for decades. It is notoriously difficult to change clinical practice, making it very difficult to implement new testing protocols and use new devices. As only one example of many, look at Biocartis, the Belgian diagnostic company that has been facing huge difficulties in getting its molecular diagnostic products sold, despite hundreds of millions being invested in the company to date.

While the need and therefor demand for new drugs, e.g. new antibiotics, is very clear, the development and commercial hurdles have led to most of the key players dropping - or significantly reducing - their anti-infectives drug development programs. There are cheap generic antibiotics available to treat most patients. Therefore, any new antibiotic drug will be kept in reserve and only used for those patients who do not respond as a treatment of last resort. This makes medical sense, but it also means that drug companies cannot hope to recoup their development costs.

Vaccine development is also difficult because a new vaccine needs to be very carefully tested in many people over a long period of time, prior to being able to claim it is safe and effective. A vaccine is given to *healthy* individuals to prevent a *potential* infection. The tolerance for any safety issues or side effects is therefore very low. This means that the cost of developing a new and safe vaccine, is very high. The traveler vaccine market is perhaps the only out-of-pocket or elective vaccine business. Other vaccine programs are generally driven by healthcare systems or governments. It is therefore only worthwhile for a vaccine development company to develop a

vaccine if it has commitment from governments to deploy the vaccine or to stockpile it for emergencies.

Question 3: why is it so difficult?

Diagnostic, drug and vaccine development for infectious diseases is complicated by the need for government participation. The regulatory agencies are right to demand a high standard (that is what we demand!) but without being properly incentivized – fewer companies will use their scientific, medical and manufacturing resources to fight infectious diseases when they can choose to target other disease modalities where they have a higher chance of success.

Today, we are seeing governments around the world loosen the purse strings and release huge sum of money to alleviate the impact of COVID-19. If they had even put a very small fraction of that capital into innovation in infectious diseases – it could have been a very different situation today. Let us hope that this is a wake-up call for governments and significant capital is set aside to invest in the urgent need for better solutions to combat the threat of infectious diseases, including new viruses which will undoubtedly emerge in the coming years.

For example, grants or soft money to support innovative research, coupled with price guarantees for approved therapeutics and stockpiling initiatives for important vaccines would help tremendously.

Question 4: what is being done right now?

The massive R&D effort undertaken by the industry, targets three areas:

a. The development of better and faster diagnosis.
b. The development of new or repositioned medicines.
c. The development of new vaccines.

Step 1 – Better and faster diagnosis

The first SARS-CoV-2 tests were so called "PCR based tests". These work by amplifying the viral genetic material of a virus and thus specifically detecting the presence of such virus. Then "serological tests" were developed which measure antibodies or proteins, indicating that an individual has been exposed to a specific virus, in this case the one that are triggered by COVID-19. These serological tests or "antibody tests" as they are known, are valuable tools for tracking the spread and evolution of COVID-19 because they can identify individuals who have been exposed to the virus who didn't develop symptoms or who have recovered, and therefore wouldn't be identified by other diagnostic tests – i.e. the antibodies can be detected after the virus is gone. An added benefit to these tests is that they are less complex to perform.

All the major diagnostic companies, for example Roche (CH), Labcorp (US), Quest (US), Qiagen (GER) and Biomerieux (F) have been working hard to develop new tests and ramp up their production. The regulatory agencies (the FDA in the US for instance) have been far more lenient than usually in allowing the widespread distribution and use of these tests, *before* all the necessary performance data has been filed with them. With several new tests in mass production, it looks as though the bottle neck of diagnosis is starting to be addressed. As an example, one of the world's largest pharmaceutical and diagnostic companies - Roche from Switzerland - has stated that it alone can produce 8.5 mln tests per month, having shipped the first 400 thousand just this week. Another example is the German healthcare company, Qiagen, that just announced the first shipment

to the US of its new "*QIAstat-Dx Respiratory SARS-CoV-2 Panel test*" to aid in diagnosing patients infected with COVID-19. This test is different in that it can give an answer in about one hour and can distinguish between 20 different respiratory infections. French diagnostic company BioMerieux has received FDA approval for its "*BioFire COVID-19 test*". This test can detect the virus in approximately 45 minutes from a nose swab.

Smaller companies are playing a role too. For example, one of the company's that LSP co-founded – Curetis from Germany - announced in mid-March that it has started offering a certified PCR test for SARS-CoV2. The test was developed and manufactured by its Chinese partner BGI and is being made available to diagnostic laboratories throughout Europe via Curetis' distribution network. Another relevant company falling into this space – also an LSP company - is Lumeon. This company has developed a healthcare automation system to help hospitals quickly identify at risk patients and triage patients more effectively. Their electronic tools can be quickly deployed, reduce the burden on care teams and enable better communication to help limit the spread of the virus and to provide guidance and support. There are many other companies that try and develop tests and tools to help alleviate the problem of better and faster diagnosis.

Step 2 – New or repositioned medicines

The fastest and easiest way to come up with an effective and safe treatment for patients *that have already been infected with the virus*, is to repurpose existing drugs that are already on the market or those that are in the final stages of drug development. Why? Simply because these drugs have already shown to be safe and – importantly – also effective in other infections such as Malaria, or Ebola or HIV. Typically, as we have explained above, these drugs have gone through years of extensive testing already, precisely for the purpose of showing that they are safe and – hopefully – effective for the indications for which they have been developed. This means that one can test these drugs much faster on COVID-19 patients (for which the drug was not intended) than those drugs for which less safety data has been generated. Equally important, manufacturing is already in place such that the drug can be made available very quickly – if shown to be effective.

Based on the most recent numbers about thirty (!) of such clinical trials will read out before the end of April. Seven of these trials are testing anti-Malaria agents and are expected to be among the first studies to read out. Anti-viral drugs make up the largest group within the thirty, with eight trials due to complete by the end of April. Among these is a study using Remdesivir, an anti-viral nucleoside analogue drug from Gilead Sciences, which the WHO has prioritized. In total, some 1000 COVID-19 patients – both severe and mild – are being tested against standard of care in two dosing regimens (a 5-day and a 10-day dosing duration of Remdesivir). Other therapeutic categories that could yield data in the next few weeks and months include Vasodilators (drugs that widen the blood vessels allowing better flow), Corticosteroids (drugs that help reduce inflammation) and Immune Modulators (drugs that help stimulate immune responses to attack infections).

A lot of attention has shifted to the potential of using malaria drugs, Chloroquine and its derivative Hydroxychloroquine, for the treatment of COVID-19. This is largely based on a 2005 study in SARS-CoV-1, which caused the SARS outbreak, which suggested that these drugs reduce the spread of the virus.

Still, Dr Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases who appears regularly alongside President Trump, has maintained that the evidence for the drug's effectiveness remains "unconvincing". Studies are ongoing to gather the evidence and determine the potential of these drugs in combating COVID-19. President Trump has already declared it a

"game changer" which is rather unfortunate because it sets expectations too high, the last thing any president – let alone the one trying to lead the USA – should do. Whatever the controversy, at least three big drug companies, Mylan from the US, Novartis from Switzerland and Teva from Israel, have agreed to increase production of Chloroquine and Hydroxychloroquine (the less toxic version), with plans to donate literally tens of millions of doses of the drug, in case it is proven to be effective in the treatment of COVID-19 patients.

The very first new clinical results have already started to flow through. A small study in France treating COVID-19 patients with a combination of Chloroquine and the antibiotic Azithromycin, demonstrated a benefit in shortening the duration of infection in patients. The pace of development is such that we expect to have additional clinical data in the coming weeks. Still, and again, experts remain skeptical about the potential of this drug combination because data is limited and results from different small, largely uncontrolled studies are anecdotal at best or even conflicting. For now, the regulatory agencies remain cautious and rightfully so. They must balance the task of getting a drug with the potential to treat patients to people as soon as possible but to still gather sufficient information to determine if it is truly safe and effective.

Of note is other news out last week, when the US pharma company Abbvie announced the results of a study in which the combination of two anti-viral drugs, *failed* to demonstrate a benefit in COVID-19 patients. This was a small study and it is now thought that the drug combination could perhaps benefit patients at a less severe stage of disease. This hypothesis is currently being retested but it is an example to show that drug development is a difficult process and its outcome uncertain.

The next wave of R&D efforts are directed not at existing drugs, but rather at the development of totally new – and therefore totally unproven – drugs. Monoclonals have the biggest potential within that bucket.

Monoclonals – e.g. Monoclonal Antibodies or mAbs - have had tremendous success over the past two decades in treating a wide variety of diseases such as arthritis and various forms of cancer. One of the players in this field is the Dutch biotech company Genmab, but there are many more, both large and small. The key to these drugs their success is their specificity, e.g. their ability to target diseased cells and diseased cells only. In the clinical setting, this means that these treatment work well and the patients have less side effects.

Several companies are racing to develop new Monoclonals targeting the SARS-CoV-2 virus. One of the better-known companies doing this is the US biotech company Regeneron. They have announced plans to start a large-scale manufacturing of an antibody cocktail (several antibodies in one treatment) to treat COVID-19. They plan to start clinical trials by early summer. The company said it will choose two antibodies for the cocktail based on potency. The antibodies will be selected from a pool of over 1,000 human antibodies they have already identified which neutralize the virus. These were generated using the Regeneron platform technology and antibodies isolated from COVID-19 patients who have recovered. Regeneron has done this before. The company has successfully developed antibodies to treat Ebola and for the treatment of MERS in animals. This gives us confidence that they could be the one successfully targeting SARS-CoV-2. To put their effort into perspective: the Dutch research group within the Erasmus University headed by Frank Grosveld, recently announced the identification of one (!) such an antibody. In The Netherlands – and only in The Netherlands – this made the 8 o'clock news…

The new and unproven antiviral drug creating the most excitement right now is Remdesivir from Gilead. If ongoing trials demonstrate safety and efficacy, it will be the first available new treatment for COVID-19 patients. Daniel O'Day, chairman and CEO of Gilead, reported that two 400-patient

trials of Remdesivir that are being conducted in China currently, are "*getting close to halfway enrolled.*" Results should be available in April, he said. In anticipation of success, Gilead is gearing up for large-scale manufacturing of Remdesivir. If ongoing trials are successful, expedited regulatory approval for Remdesivir could come as soon as early summer. In the meantime, however, the company has temporarily halted compassionate use, as its system was overwhelmed by requests. The company is now developing a new system to deal with such requests as it rushes to complete the clinical studies.

We still have a lot to learn about this new virus and how it kills some patients but others have relatively mild symptoms. The current hypothesis is that serious illness will depend on how the immune system responds, and that can be influenced by age, gender, genetics and underlying medical conditions. The initial damage caused by the virus can trigger a powerful, sometimes dangerous, overreaction by the immune system. Addressing such "runaway host immunity" could be especially important for patients who have progressed to severe disease, where the symptoms are likely to be driven as much from damage caused by the patient's immune system as from viral load. We speculate that drugs targeting auto-immune disease, such as the JAK from Galapagos could be used alone or even combined with anti-viral drugs to address the immune storm caused by the infection. Roche just announced that it received the go-ahead from FDA to start testing its arthritis drug, Actemra, in hospitalized patients with COVID-19 pneumonia. In addition, Roche said it plans to donate 10,000 vials of Actemra for potential future use. We expect more studies to follow.

Step 3 – A vaccine

For SARS (2003) it took 20 months from the release of the viral genome to identifying a vaccine for clinical trials. For the Zika outbreak (2015) the timeline was 6 months. US company Moderna shipped the first batch of its RNA based vaccine within an amazing 42 days of the SARS-CoV-2 sequence being released. The company aims to test the vaccine in 45 healthy volunteers in a phase 1 study which is due to start in April with results potentially available in July or August. This does not mean there is any certainty that the trial or indeed the vaccine will be successful, but it does highlight the speed at which we are progressing. It is still expected to be 12 to 18 months before any vaccine is available. As SARS-CoV-2 is likely to remain in circulation – the development of a vaccine will be critical in preventing people from getting sick in the future. There are now about 15 potential vaccine candidates in the pipeline. These employ various different technologies, including messenger RNA (mRNA) (Moderna), DNA-based (Inovio), nanoparticle, synthetic and modified virus-like particles. In a bullish move, Moderna is ramping up manufacture of its mRNA-1273 vaccine candidate in anticipation of a positive trial read out. While the vaccine will not be generally available for 12-18 months – the CEO has suggested it may be available under emergency use, possibly for healthcare professionals by the autumn. Fast development does not guarantee efficacy nor safety. We have to wait for the clinical trials to read out.

Belgian company and LSP portfolio company, eTheRNA, has announced its intention to work with North American and European partners to develop a novel mRNA vaccine. Preclinical work has already started. The proposed vaccine would be administered intranasally to protect high risk population such as healthcare workers and families of confirmed cases. Interestingly, the vaccine is also designed to be protective against future variations of the virus by targeting conserved parts of the virus. *The company is targeting clinical testing in early 2021.*

So what is next?

BIO, the industry organization is organizing a 2-day virtual summit next week, with companies that are developing COVID-19 medical countermeasures, government officials and other stakeholders. Close to 60 companies, academic groups and government organizations are developing vaccines, and at least 20 companies are creating new COVID-19 therapies. An international team of hundreds of researchers embarked on a study of the genes of the corona virus to identify drugs already in use or in development which could be effective in treating coronavirus. They have come up with a list of nearly 70 compounds. While again there is no guarantee of success – the tremendous level of cooperation and cohesiveness with which the scientists and the healthcare industry is pooling resources to fight this pandemic is staggering.

The world is facing a terrible crisis. However, we have faced epidemics and pandemics in the past. Our modern lifestyle of travel has contributed to the rapid spread of corona virus. Nevertheless, our modern scientific and medical tools are far superior now than ever before. Modern communication methods allow the world's best scientists, drug developers, clinicians, regulators and healthcare professionals to come together to overcome this pandemic by rapidly developing diagnostics, therapeutics and vaccines. We are extremely confident this will happen within the shortest time possible, acknowledging that it will take time no matter what.

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