UNDERSTANDING
CORONAVIRUS

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of the disease. These drugs target different aspects of the virus life cycle, its replication, its interactions with humans, or are designed to help the immune system fight the virus.

A good place to start looking are the therapies that were tried during the SARS outbreaks. Extensive work has been done in animal models, and a variety of different therapeutic strategies in the SARS context have been proposed. Given the genetic similarity between SARS-CoV and SARS-CoV-2, it is likely that we could leverage some of the knowledge and models developed for SARS to accelerate the research into COVID-19 therapies. There is, however, no solid clinical data on the efficacy of potential treatments during that outbreak.

Remdesivir is a broad-spectrum antiviral drug developed as a treatment for the Ebola virus infection, with potential use in other viruses, including coronaviruses. It acts by interfering with the viral replication machinery. It has been shown to be effective *in vitro* and in animals infected with SARS. There are several ongoing clinical trials evaluating its efficacy in humans.

Favilavir is another broad-spectrum antiviral drug approved for treating influenza, and has also now been approved in China for the treatment of COVID-19. It works by targeting the replication machinery of the virus. It has been tested in animal models for many RNA viruses, including influenza, West Nile virus, and Ebola virus, among others.

Drugs used in HIV treatment (lopinavir and ritonavir) are also being studied. *In vitro* experiments and small-scale studies during the SARS outbreak in 2003 indicated a potential reduction in severe outcome (acute respiratory syndrome or death). Although case reports and small studies have indicated a potential benefit for COVID-19 patients, a randomized trial in 199 hospitalized patients in Wuhan did not reveal benefits beyond the standard of care.

Chloroquine and the related hydroxychloroquine, widely used to treat malaria, have been seen to inhibit SARS-CoV and SARS-CoV-2 in cells grown in lab conditions. Besides interfering with viral infection, these compounds can modulate immune responses, that are often dysregulated in severe COVID-19 cases. The effect and mechanism of action in COVID-19 cases is still unclear.

There are many other strategies that are being tested, such as the use of ACE2 decoys that will bind to the virus, competing with the cell ACE2, and strategies to modulate the immune response to the virus to prevent an

overacting immune system, including repurposing immune modulators that have been approved to treat immune disorders.

Are There Vaccines for Coronaviruses?

Vaccines work by activating an immune response and have been the most successful way to combat viruses. Vaccines prime the immune system by presenting parts of, or a weakened version of, a pathogen. This stimulates the adaptive immune system to recognize the pathogen. Extensive vaccination can lead to widespread immunity in the population (herd immunity), making it harder for the pathogen to infect individuals and cause a large number of diseases. Vaccines against viruses have been proven to be extremely effective, such as the vaccines for measles, mumps, rubella, smallpox, and hepatitis B, among many others. Systematic vaccination and active international efforts have ended smallpox, one of the most devastating infectious diseases in the history of humanity, which has killed nearly 300 million people in the twentieth century. The efficacy of some vaccines could be variable, like the influenza vaccines, due to the variations in the circulating viral strains.

Currently there are no vaccines for SARS-CoV-2 or SARS-CoV. In fact, there are no vaccines for any human coronaviruses, although there are now clinical trials underway. There are some vaccines for coronaviruses infecting domestic animals, including avian and dog coronaviruses. However, even these vaccines can present a challenge due to the continued emergence of novel serotypes.

There are many challenges ahead. It is important to understand whether any vaccine will help to develop immunity against the virus and how long it will last. Disease enhancement is a phenomenon in which the vaccine could lead to severe immune reactions that can worsen the disease. A study of a SARS vaccine in 2004, in ferrets, showed that the immunized animals developed a strong neutralizing antibody immune response when challenged with the virus, but they also presented inflammatory damage in the liver, leading to hepatitis. Finally, an important challenge is that, as in influenza, the high evolutionary rate of coronaviruses and their ability to recombine generates a continuous source of antigenic variability and a formidable challenge to vaccine development. A vaccine that effectively deals with the circulating diversity of the virus could be challenging, as it is for some of the coronavirus vaccines in animals.

Conclusions

Life can only be understood backwards; but it must be lived forwards.
Søren Kierkegaard

There are many, many important questions that remain to be answered regarding the SARS-CoV-2 viruses:

- Where is this virus coming from and how did it manage to infect humans? Understanding this route could help prevent further events like SARS or COVID-19 outbreaks in the future. Also, it will help to understand the specific mechanisms of adaptation of zoonotic viruses.
- What are the specific mechanisms by which SARS-CoV-2 causes disease? In an important fraction of infected individuals, SARS-CoV-2 causes severe disease, while in others only mild symptoms. Understanding the mechanisms of disease will help us develop and apply therapies to control the severity of the disease.
- How does this virus interact with the immune system? We need to understand the specific mechanisms of normal immune response to the virus, both the innate and adaptive responses. In many patients the virus triggers an abnormal immune response that becomes difficult to control and can kill them. We do not currently understand in detail how the virus interacts with the immune system in mild or severe cases.
- What is the true number of infected people? There have been varying estimates on how many people are really infected with the virus. Modeling suggests that there could be a significant number of infected individuals who do not develop any symptoms, or only develop very mild symptoms. Understanding these numbers could help us to better

understand the severity of the disease, the host factors that can control the progression to disease, and the transmission routes through unreported cases, among many other factors.

- What is the role of mild symptomatic and asymptomatic cases in the spread of the infection? Epidemiological models have suggested that there is a significant number of unreported cases that contribute to the spread of the disease.
- Very low numbers of cases have been reported in children and very low numbers of deaths. Why do most children exhibit only mild symptoms, while most fatalities occur in the elderly and mostly in males?
- Are there genetic or epidemiological markers of severity? Beyond age and other related diseases, there are other indicators to assess whether a person will suffer from serious disease. As in many other infectious diseases, there are genetic components that can contribute to the risk, predisposing some people to be protected or to develop serious disease. We do not yet know if there are genetic markers associated with COVID-19.
- How long will the immune response last after a person has recovered? Is it possible to be re-infected? It seems that after the infection, the generated antibodies are able to neutralize the virus. But in several coronaviruses, the memory of the response lasts only a few months and re-infections with the same virus have been observed. We do not know if that will be the case for COVID-19 or if recovered patients will be able to develop long-lasting immunity. Lack of long-lasting immunity could lead to future waves of COVID-19 unless the virus is eradicated.
- Will any therapy – antiviral drug or vaccine – be able to treat the disease effectively? In the next months and years, we will see the approval of antiviral drugs to treat COVID-19. It is to be hoped that a vaccine will become available too.
- Will society be able to generate herd immunity? If enough individuals develop a lasting immune response, we could make it difficult for the virus to spread again. With current numbers it seems that we need at least half of the population to be infected, or a vaccine, to tamp down the spread of the virus.
- Will there be subsequent waves of the disease? If so, will they be milder or affect different sections of the population? In other pandemics, such as

the 1918 influenza, several waves came through the population until the virus settled in as a seasonal influenza.

- Will the virus evolve to escape the therapies or the built immunity? RNA viruses evolve very rapidly. That constitutes a significant challenge to the development of therapy or vaccine. As the virus propagates it will diversify and we will have to make sure that whatever therapies we develop are able to challenge the majority of the circulating viruses.

All the questions above will keep the scientific community very busy, and the next few years will witness many developments. Each gene, each protein, each piece of knowledge about the virus is an opportunity to fight the disease. The scientific community is frenetically searching for ways to block the entrance, the replication, and the release of the virus; to understand the disease; to modulate the immune response; and to evaluate optimal public health measures for this and other many infectious diseases.

We are now in a very different time than when the influenza virus struck in 1918. In 1918 there was neither the technology nor the knowledge that we have today to study the infectious agent rapidly. Many national and international efforts are now in place to answer the questions above. It is likely that some treatments and vaccines now in clinical trials will have some effect on COVID-19 cases. They will not help in the first wave of the disease, but are likely to be available in the near future.

There are many viruses circulating in humans, all of which came at some point from different species. We have to remember that there were four coronaviruses circulating in humans before the SARS-CoV-2 outbreak. Other examples include the influenza viruses starting with the pandemics of 1918, 1957, 1968, and 2009. So, it is probable that as a larger fraction of the population is infected, humans will develop immunity, mitigating the surge in the number of cases and the overloading of healthcare systems. Immunity will also be achieved if efficient vaccination is deployed. It is likely that SARS-CoV-2 is here to stay, like some of its coronavirus cousins.

The emergence of this virus has been only one of many events, although a most disrupting one. The WHO has reported more than 1500 new pathogens since 1970, most of them of animal origin. Emerging viruses in the last 50 years include HIV, the H1N1 influenza pandemic, several Ebola virus outbreaks, the MERS coronavirus, and Zika, among many others.

proteins. They use the same entry point to the cell, the ACE2 receptor. The diseases also present some similarities, with common lower tract infections and severe respiratory complications. The case fatality rate of COVID-19 is lower, but the infectivity is higher than for SARS. The similarity between the two viruses helps us to use the previous clinical experience, scientific knowledge, and techniques from the SARS 2003 outbreak to accelerate the search for therapeutics.

Children and young adults do not get infected. Children and young adults get infected but, in most cases, they get a milder disease. Occasionally they get severe complications, including death. In addition, infected people, independent of age, contribute to the spread of the disease. There is a moral responsibility to care for all and particularly for the most vulnerable in our society.

Containment measures are ineffective. The highly proactive response taken by Asian countries (China, Hong Kong, Taiwan, Singapore, South Korea) in the first two months of the pandemic have proven that containment measures are effective. Rapid identification and testing of cases, contact tracing, early isolation, and treatment of infected cases together with social distancing measures reduced the number of infected cases.

When the number of cases is too high, strong public health mitigation measures can reduce the spread and the sudden surge of cases requiring medical attention. The surge of medical cases leads to an overwhelmed healthcare system and large numbers of unprotected healthcare workers unable to provide clinical care for patients of any disease. This increases the complications and deaths associated with COVID-19 and any other disease.

Historical evidence from previous pandemics has shown that social distancing and early public health measures can reduce the surge of cases. Examples from during the 1918 influenza have shown that cities that do not effectively implement mitigation strategies can suffer a dramatic increase in the number of cases and deaths.

The coronavirus is of extraterrestrial origin, and other interesting ideas. There are many questionable theories that have populated the Internet with increasing degrees of sophistication and creativeness. For instance, it has been suggested that the virus came to Earth in a meteorite or a comet that fell over northeast China in the fall of 2019. This theory follows the unorthodox line of thought


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