Race to COVID-19 cure
the Core Model for solving the pandemic crisis

Mitigation of COVID-19 pandemic requires a combination of effective epidemiological policies and the discovery/development of powerful drugs against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that causes this disease. This article examines the major initiatives being explored at the public policy level to contain the spread of COVID-19 as well as some of the most important innovative collaborative efforts at the research and development front to combat SARS-CoV-2. For a successful outcome, these efforts need a proven and effective organisational model. The 'Core Model', a collaborative paradigm and economic theory based on the structured collaboration between specific public and private sectors in society, is one such model to help alleviate the crisis. The Core Model could be strategically instrumental in bringing partners with a common goal from the public and private sectors with complementary technologies, learnings, expertise and infrastructure together under one single and focused enterprise, the International COVID-19 Initiative – an unprecedented centralised stewardship fostering global collaboration to combat the global pandemic!

By Ibis Sánchez-Serrano and Rathnam Chaguturu

SARS-CoV-2 could very well be nicknamed 'the virus of truth', for it has exposed the best and the worst sides of humanity. On one side, it has brought many people together through love, solidarity, altruism, compassion, co-operation, responsibility and other commendable virtues; on the other, it has brought division through open demonstrations of hatred, selfishness, greed, avarice, corruption, irresponsibility and other condemnable human traits.

SARS-CoV-2 is responsible for the greatest pandemic the world has experienced since the 1918 Flu Pandemic caused by the influenza A virus subtype H1N1 (A/H1N1). First reported in the city of Wuhan, Hubei Province, China in December, 2019[1], the origin of SARS-CoV-2 is still being debated. Though not nearly as mortiferous as the 1918 Flu Pandemic, COVID-19 has created enough devastating damage across the world to make us reconsider the way we are living as a human society and question the actual values, and even worthiness, of our political and socio-economic systems and leaders. COVID-19 has humiliated wealth, power and science. It has humbled the most powerful nations in the world and exposed to the world their unsuspected weaknesses.

To many people it may seem incredible that in a period of history with the greatest wealth, means

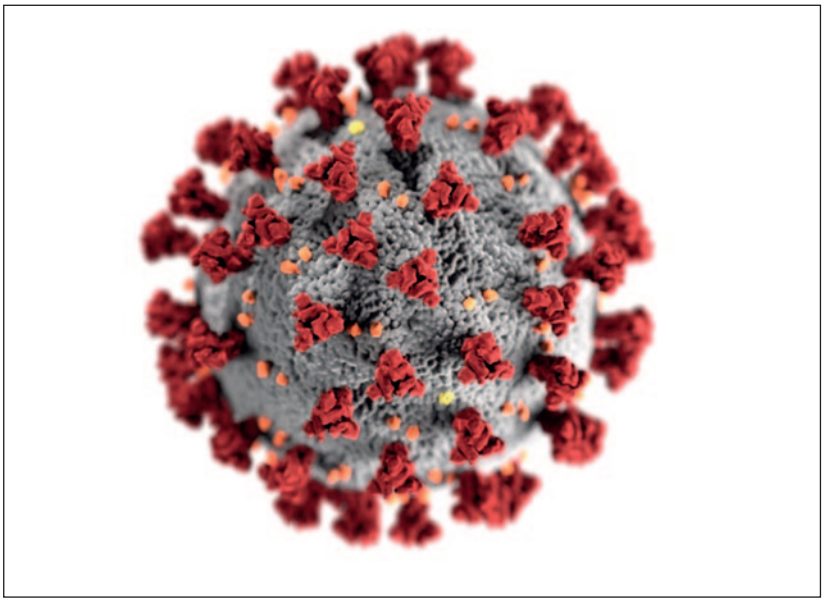

Figure 1
Cell entry mechanisms of SARS-CoV-2 virion
SARS-CoV-2 spike binds to its receptor human Angiotensin Converting Enzyme-2 (hACE2) through its receptor-binding domain (RBD). Rather than depending on target cell proteases for entry, SARS-CoV-2 is pre-activated by proprotein convertase furin. The high hACE2 binding affinity of the RBD, furin pre-activation of the spike and hidden RBD in the spike potentially allow SARS-CoV-2 to maintain efficient cell entry while evading immune surveillance. These features, among others, contribute to the wide spread of the virus. SARS-CoV-2 attacks lung cells primarily because there are many conserved receptor entries, namely hACE2. The presence of this virus in host cells then will initiate various protective responses leading to pneumonia and Severe Acute Respiratory Syndrome (SARS). *Source: J. Shang et al. PNAS first published May 6, 2020 https://doi.org/10.1073/pnas.2003138117*

of communication, access to information and most importantly, scientific and technological advances, driven by countries that are powerhouses of biomedical research such as the United States and some European nations, we are unable to find a quick cure for COVID-19. Interestingly enough, in four decades of investing billions of dollars in research and 23.6 to 43.8 million deaths[2], we still have not been able to find a vaccine for HIV/AIDS either. In fact, we become surprised every day by a new characteristic of the SARS-CoV-2 virus (see **Figure 1** for a description of the virus) or by a new manifestation of COVID-19. Not even the most promising and well-funded projects could guarantee the discovery and development of an effective vaccine in 18 to 24 months to combat the deadly SARS-CoV-2 virus.

Impact of COVID-19

From an economic perspective, COVID-19 has launched the world into the greatest recession ever since the 1929 Great Depression. It is estimated that by next year this pandemic would have cost the world at least US$ 8.8 trillion or 10% of the world's gross domestic product[3]. At present, there are more than 9 million people infected by SARS-CoV-2 and at least 470,000 mortalities in the 213 countries and territories that have been affected by it[4]. These numbers, last accessed on 22 June 2020, are changing as tracking modalities get better, and the reader is advised to visit https://coronavirus.jhu.edu/map.html for the most up-to-date information. Such devastating death and destruction will continue to increase dramatically until a vaccine and/or effective treatments are developed, approved and distributed worldwide. In the meantime, human society is living in total uncertainty, fear, anxiety and anguish, which will be reflected in massive current and post-traumatic depression, especially in the case of healthcare workers, public order officers, decision-makers and the at-risk population. Incalculable economic hardship – due to loss of employment, income, savings and investments – that millions of people in the planet are facing will continue to grow in to the near future and beyond.

Countries such as the United States, Italy, Spain, France, the United Kingdom, Iran, Brazil, Mexico, Ecuador and Russia are among the hardest hit by this pandemic. Some models, in fact, are trying to predict what could happen in the worst-case scenario, the one in which no vaccine is ever developed and the virus is left to run freely until it infects 60-90% of the world population and no longer represents a threat to human health – a phenomenon called 'herd immunity'. Because of SARS-CoV-2's high contagiousness and the fact that we still neither have enough knowledge about its behaviour nor have we any adequate treatment available, not even the worst thinkable nightmare could provide a glimpse of what would happen in the world if such a scenario becomes our nightmare. It is projected that a single symptomatic SARS-CoV-2 infection would cost, in the US alone, a median of US$3,045 in direct medical costs incurred only during the course of the infection. If 20% of the US population were to become infected, there would be a median of 11.2 million hospitalisations, 2.7 million Intensive Care Unit (ICU) admissions, 62.3 million hospital bed days and 1.6 million ventilators used, costing US$163.4 billion. In a similar fashion, if 80% of the US population became infected this could result in a median of 44.6 million hospitalisations, 10.7 million ICU admissions, 6.5 million ventilators used and 249.5 million hospital bed days, costing US$654 billion in direct costs over the course of the pandemic[5]. These numbers alone, not even considering the death tally and all the ramifications and domino effects of such a disaster on other sectors, clearly tell us that the potential cost of simply reopening the economy too early or of letting the virus run its course without any major intervention – the herd immunity approach – could be devastating for the US, a country that has not been able to cope adequately with this pandemic. Can we imagine extrapolating this to the rest of the world?

COVID-19 containment and mitigation

On December 31, 2019, Chinese authorities reported to the World Health Organization

(WHO)-China Country Office that they were treating 44 patients with a pneumonia of unknown cause in Wuhan City, Hubei province. On January 2, 2020, the WHO activated the incident management system across the three levels of WHO (country office, regional office and headquarters). Soon after, in mid-January, Wuhan-exported cases were identified in Thailand, Japan, South Korea and the US. On January 30, 2020, the WHO declared the COVID-19 outbreak a "Public Health Emergency of International Concern"[6]. On February 23, a surge of cases was reported in Italy, and immediately after in Iran, South Korea and Japan[7]. Cases began to be reported in other parts of Europe, Canada, the Sub-Sahara region, Latin America and the rest of the world. On March 11, 2020, the WHO announced that COVID-19 had become a pandemic[8] (see **Table 1** for a timeline of the spread of the infections across the globe during the first two months after the Chinese authorities informed the WHO of the 'pneumonia' outbreak that was taking place in Wuhan).

From the very beginning, the WHO made recommendations to China, then to other countries, to take preventive, basic hygiene measures to contain the epidemic, such as hand washing, mouth covering when coughing, maintaining physical distance, wearing a face mask in public settings and monitoring and quarantine (self-isolation) for suspicious cases of infection[6]. Authorities from all over the world responded to the WHO recommendations, even though there were many points of confusion and contention (for instance, whether to wear masks in public or not). As the virus began to spread within borders, most countries implemented travel restrictions, lockdowns, controls of potential workplace hazard and closures of facilities. Some countries were stricter than others with their lockdowns. A few, such as the UK and Sweden, decided not to act in the hope that herd-immunity would develop among the population. The UK backtracked from this approach in mid-March/early-April, 2020[9], but too late: today (June 2020), it has the third highest overall number of deaths in the world and the fifth highest amount of infected people. Sweden experienced a surge of unexpected deaths in the months leading up to May, 2020[10], confirming that such an approach would be very deadly. Panama, being Latin America's maritime, air traffic and banking hub, implemented one of the strictest lockdowns in the continent and one of the most creative ones on the planet, thus making headlines around the world[11].

As a result of this unorthodox, gender-based plan, according to the Panamanian Ministry of Health, the basic reproduction number (R_0) – that is, the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection – fell below one by the end of April, and the lockdown restrictions began to be lifted gradually[12]. Unfortunately, the original

Table 1: COVID-19: timeline of main events and disease spread across the globe*

- **December 31, 2019:** WHO China Country Office was informed of cases of pneumonia of unknown etiology (unknown cause) detected in Wuhan City, Hubei Province of China.
- **January 7, 2020:** The Chinese authorities identified a new type of coronavirus.
- **January 11-12, 2020:** WHO received further detailed information from the Chinese National Health Commission that the outbreak is associated with exposures in one seafood market in Wuhan.
- **January 12, 2020:** China shared the genetic sequence of the novel coronavirus for countries to use in developing specific diagnostic kits.
- **January 13, 2020:** The Ministry of Public Health, Thailand reported the first imported case of lab-confirmed novel coronavirus (2019-nCoV) from Wuhan.
- **January 15, 2020:** the Ministry of Health, Labor and Welfare, Japan (MHLW) reported an imported case of laboratory-confirmed 2019-novel coronavirus (2019-nCoV) from Wuhan.
- **January 20, 2020:** National IHR Focal Point (NFP) for Republic of Korea reported the first case of novel coronavirus in the Republic of Korea.
- **January, 21 2020:** The first confirmed case in the United States came the next day in Washington State, where a man in his 30s developed symptoms after returning from a trip to Wuhan.
- **January 30, 2020:** Amid thousands of new cases in China, the WHO declared the 2019-novel coronavirus a "public health emergency of international concern".
- **February 2, 2020:** The first coronavirus death was reported outside China, in the Philippines.
- **February 7, 2020:** A Chinese doctor Li Wenliang, who tried to raise the alarm about coronavirus, died.
- **February 11, 2020:** The WHO proposed an official name for the disease caused by the coronavirus causes: COVID-19, an acronym that stands for coronavirus disease 2019.
- **February 14, 2020:** France announced the first coronavirus death in Europe, an 80-year-old Chinese tourist.
- **February 19, 2020:** Iran announced its first two coronavirus cases. Less than a week later, the country said it had 61 cases and 12 deaths. Cases in Iraq, Afghanistan, Bahrain, Kuwait, Oman, Lebanon, the United Arab Emirates and one in Canada, have been traced back to Iran.
- **February 21, 2020:** A secretive church was linked to the outbreak in South Korea.
- **February 23, 2020:** Italy saw a major surge in cases.
- **February 26, 2020:** Latin America reported its first case in Brazil.
- **February 28, 2020:** Sub-Saharan Africa recorded its first infection. Nigeria, Africa's most populous nation, confirmed its first case of coronavirus.
- **February 29, 2020:** The United States reported a death.
- **March 3, 2020:** US officials approved widespread testing.
- **March 11, 2020:** the WHO announced that COVID-19 had become a pandemic.

** At some point this information provided by the WHO will need to be updated given recent discoveries. For instance, the National Institute of Health (ISS) of Italy has recently discovered that waste water from Milan and Turin showed genetic virus traces on 18 December. On the other hand, French scientists expressed in May 2020 that a patient treated for suspected pneumonia near Paris on December 27, 2019 actually had the coronavirus, according to sample tests. Meanwhile, Spain found virus traces in waste water collected in mid-January in Barcelona, some 40 days before the first local case was discovered (https://www.bbc.com/news/world-europe-53106444). Sources: World Health Organization; The New York Times*

Lockdown: a successful Panamanian perspective

- Citizens allowed two hours to buy groceries or medicines based on the last number of their ID and according to sex.
- Women allowed to exit their homes for two hours at a specified time during the day based on the last digit of their ID number on Monday, Wednesday and Friday.
- Men allowed to leave their homes, again at a specified time, for two hours during the day based on the last digit of their ID on Tuesday, Thursday and Saturday.
- No one could exit their homes on Sunday, unless with a special permit due to the indispensable nature or their job.
- Minors to remain at home at all times.

people over 60 were encouraged to do so as well.

- No alcohol was to be sold at all in the entire country during the lockdown.
- During some weekends, neither men nor women could exit their homes.

New Zealand: mitigation versus elimination

New Zealand pursued a strict elimination approach, a vastly different approach to usual pandemic planning.

- Implemented a full lockdown, involving the closure of schools and non-essential workplaces, a ban on social gatherings,and severe travel restrictions, enabling the country to consider elimination.
- The rules were communicated effectively.
- The lockdown was swift and tough.
- Followed the WHO advice around mass testing and robust contact-tracing, key to limiting the death toll.
- Allowed the country to get key systems up and running to effectively manage borders and carry out contact tracing, testing and surveillance.
- Centralised leadership in pandemic planning and execution.

The response has been one that placed science, leadership and careful language at the forefront.

The biggest benefits of pursuing an elimination strategy: few cases of infection and few deaths and businesses back up and running. New Zealand's economy would now operate at just 3.8% below normal.

Source: www.thelancet.com Vol 395 May 9, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31097-7

success of this approach has become compromised recently by corruption scandals and the lack of discipline, among other important factors, by some parts of the population once the restrictions began to be lifted. As a result the R0 and the COVID-19 cases and deaths began to increase rapidly in June, 2020. This is a clear demonstration (and warning) that even the most creative and effective measures to control COVID-19 during a lockdown could become threatened if the most vulnerable sectors of society are not sufficiently attended, if testing falls short, if all the elements of society are not well aligned and organised, etc. Other Latin American countries such as Costa Rica, El Salvador, Uruguay, Paraguay, Cuba and Colombia also took very strict measures to contain the virus, with much success.

In Europe, Germany became a leader on how to deal with the situation; while Australia and New Zealand, thanks to apt leadership, succeeded quickly in flattening the curve, in other words, spreading the number of infections along time as to avoid overwhelming the healthcare system.

Some countries have been able to provide their citizens and corporations some types of financial aid and loans and, in the case of individuals or population at risk, food, shelter and medicines. Others have failed terribly at this, exacerbating the burden of the pandemic. In the US, despite its provision of relief aid, the situation has been quite chaotic, the rate of unemployment has soared and the number of deaths is higher than any country in the world. Unfortunately, many countries did not have sufficient personal protective equipment, ventilators or adequate infrastructure to protect their healthcare workers and general population, nor were they able to carry out sufficient SARS-CoV-2 diagnostic tests. In an ideal situation a country such as the US should carry out approximately 900,000 COVID-19 tests on a daily basis, but at present it is only able to perform about 300,000 tests at the national level at best[13]. This has enormous implications in the process of reopening the economy and to contain the spread of the disease.

COVID-19: prevention versus treatment

In the midst of a societal upheaval resulting from the SARS-CoV-2, there have been many efforts in progress to find solutions to slow the spread of the disease and treat those who already have it. These efforts include those from governments, non-profit organisations and corporations both privately held and publicly traded. The race for COVID-19 cure is two-pronged: prevention, treatment or both. Under 'normal' circumstances, vaccine development, licensure and manufacturing are

processes that can take several years to complete. Most coronavirus vaccines are intended to force the body's immune system to make antibodies that latch on to the spike protein on the surface and kill the virus. At present, there is not a single vaccine or drug approved by the FDA against COVID-19.

COVID-19 prevention: vaccine development

According to FasterCures at the Milken Institute, at present, there are about 169 vaccines in development in nine different platforms and approximately 254 COVID-19 treatments under consideration (**Table 2**). (For a comprehensive and updated list of these treatments and vaccine efforts, the nature of each one of the them, their sponsors, clinical trials, please refer to the Milken Institute's Treatments and Vaccines Tracker, available at: https://milkeninstitute.org/centers/fastercures/covid-19 (last accessed on June 22, 2020); see also The Association of the British Pharmaceutical Industry website: https://www.abpi.org.uk/medicine-discovery/covid-19/what-are-pharmaceutical-companies-doing-to-tackle-the-disease/; and Pharmaceutical Research and Manufacturers of America (PhRMA website: https://phrma.org/Fact-Sheet/The-Biopharmaceutical-Industry-is-Leading-the-Way-in-Developing-New-Vaccines-and-Treatments-for-COVID-19.) To expedite development and distribution of a SARS-CoV-2 vaccine, unprecedented international alliances have been formed and billions of dollars have been allocated. At present, there are approximately 10 of the most promising candidates in one of the four phases of clinical trials (**Table 3**).

Attempts to address the tsunami of COVID-19 in either direction of treatment or prevention requires a strategic approach in tandem, sequential or parallel. Both have merits, but a parallel approach is the need of the hour: vaccine for prevention and treatment to contain SARS-CoV-2's infection progress. Since vaccine development is in itself a lengthy process of many steps (testing, producing and licensing) that are traditionally sequential, the Coalition for Epidemic Preparedness Innovation (www.cepi.net) proposes a truncated parallel process for COVID-19 vaccine development even before knowing the vaccine will work. Regarding the development of a vaccine, the fundamental question toggles between when or if. In spite of herculean efforts, no vaccine has ever come to fruition against viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Among others in development or consideration, pioneering DNA- and RNA-based platforms offer enormous hope (**Tables 2** and **3**). Moderna Therapeutics (Cambridge, MA, US) uses RNA technology, while Inovio Pharmaceuticals (Plymouth Meeting, PA, US) has developed DNA technology to package the genetic code of coronavirus spike proteins, which make up the crown around the virus and help it latch on to cells. This approach has the advantage of being able to move to trials faster than vaccines that require the production of viral proteins or a weakened version of the actual virus to induce an immune response. The DNA technology is still unproven and there are no approved RNA vaccines to date. The US government's Operation Warp

Table 2: COVID-19 therapies (vaccines and treatments) in development

TYPE OF TREATMENT	NUMBER
Antibodies	70
Protein subunit	56
Antivirals	25
RNA-based vaccine	23
Non-replicating viral vector	19
Unknown	20
Scanning compounds to repurpose	21
Cell-based therapies	17
Replicating viral vector	15
DNA-based	13
Virus-like particle	10
Inactivated virus	9
Device	8
RNA-based treatments	6
Dormant/discontinued	5
Live attenuated virus	3
Replicating bacterial vector	1
Other	107
TOTAL	**428**

Source: The Milken Institute; available at https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viweyymxOAtNvo7yH?blocks=bipZFzhJ7wHPv7x9z&bip=full; accessed June 22, 2020

Table 3: Most advanced candidates to prevent or treat COVID-19 in clinical trials

INSTITUTION	TYPE OF THERAPY	DEVELOPMENT TIMELINE
Moderna Therapeutics	Vaccine: mRNA	Phase I trial near complete, Phase II trial set to start. The company began the first Phase I human trial on 45 volunteers testing a vaccine to prevent the disease in March and has been approved to soon start its Phase II, which would expand the testing to 600 people, by late May or June. If all goes well, its vaccine could be in production as early as July.
Johnson & Johnson	Modified adenovirus	Johnson & Johnson began COVID-19 vaccine development in January. Its lead vaccine candidate will enter a Phase I human clinical study by September, the company announced in March, and clinical data on the trial is expected before the end of the year. If the vaccine works well, the company said it could produce 600 million to 900 million doses by April 2021.
Inovio Pharmaceutical	Vaccine: INO-4800	Inovio began its early stage Phase I clinical trials for a potential vaccine on April 6, making it the second potential COVID-19 vaccine to undergo human testing after Moderna. It says it will enroll up to 40 healthy adult volunteers in Pennsylvania and Missouri and expects initial immune responses and safety data by late summer.
Oxford University	Vaccine: ChAdOx1 nCoV-19	A coronavirus vaccine developed by researchers at Oxford University began Phase I human trials on April 23. UK Health Minister Matt Hancock said he would provide £20 million ($24.5 million) to help fund the Oxford project. The team said it aims to produce one million doses by September.
Pfizer	Vaccine: BNT162	Clinical trials. Pharmaceutical giant Pfizer, which is working alongside German drug maker BioNTech, began testing an experimental vaccine to combat the coronavirus in the US on May 5. The US-based drug maker hopes to produce "millions" of vaccines by the end of this year and expects to increase to "hundreds of millions" of doses next year.
Sanofi and GSK	Vaccine: Unnamed	Preclinical. Sanofi and GSK announced on April 14 that they had entered an agreement to jointly create a COVID-19 vaccine by the end of next year. The companies plan to start clinical trials in the second half of 2020 and, if successful, produce up to 600 million doses next year.
Novavax	Vaccine:NVX-CoV2373	Preclinical. Novavax announced on April 8 that it had found a coronavirus vaccine candidate and would start human trials in May with preliminary results expected in July. The potential vaccine, which is being called NVX-CoV2373, is using adjuvant technology and will attempt to neutralise the so-called spike protein found on the surface of the coronavirus which is used to enter the host cell.
Gilead Sciences	Drug: Remdesivir	Late-stage trials. The FDA granted EUA for Gilead's remdesivir drug to treat COVID-19 on May 1. The National Institute of Allergy and Infectious Diseases released results from its study showing patients who took remdesivir usually recovered faster than those who did not take the drug. Even though remdesivir was granted for emergency use, there are still several ongoing clinical trials testing whether it is effective in stopping the coronavirus from replicating.
Zhejiang Hisun Pharmaceutical	Favipiravir	Mid-stage trial. Favipiravir is an anti-flu drug sold by Fujifilm Holding under the name Avigan. Researchers in China are testing the drug to see if it is effective in fighting the coronavirus. Most of favipiravir's preclinical data is derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses, according to researchers in Japan.
Eli Lilly	Baricitinib	Clinical trials. Eli Lilly, in partnership with the National Institute of Allergy and Infectious Diseases, is seeing if its rheumatoid arthritis drug baricitinib is effective against the coronavirus. The company theorises that baricitinib's anti-inflammatory effects could curb the body's reaction to the virus.
Eli Lilly, AstraZeneca and Regeneron	Antibody treatments	Various stages. While some drug makers are looking for vaccines to stop the virus, Eli Lilly, AstraZeneca and Regeneron, among other companies, are working on so-called antibody treatments, which are made to act like immune cells and may provide protection after exposure to the virus. Earlier this month, Regeneron said its treatment could be available for use by the end of this Summer or Autumn/Fall.

Source: CNBC and other sources; https://www.cnbc.com/2020/05/13/coronavirus-scientists-race-to-find-a-cure-or-vaccine-here-are-the-top-drugs-in-development.html

Speed programme has selected five vaccine projects (Moderna, Oxford University and AstraZeneca, Johnson & Johnson, Merck and Pfizer) to receive billions of dollars in federal funding and support, again before there is proof that the vaccines work (Operation Warp Speed, www.hhs.gov.

Vaccine development is time consuming and financially exhaustive. Attrition is high and it is often an exercise in futility. Effective innovative paradigms are needed, but never forgetting safety over speed. Even if a vaccine is developed, several questions remain to be addressed: Do people develop immunity? If yes, what kind of response and how long does it take or last? Although the Society of Critical Care Medicine cautions against treatment using drugs, and the Infectious Diseases Society of America recommends patients should get the drugs only as part of a clinical trial, treatment options offer a viable promise, as has been the case against HIV.

COVID-19 treatment: post infection

Drug repurposing or drug repositioning – the identification of new indications from existing drugs – has in recent years successfully identified promising candidate drugs that can open new therapeutic avenues and offers great promise to counteract COVID-19. Several companies (AbbVie, Amgen, Bayer, Gilead Sciences, Incyte, Eli Lilly, Mesoblast, Novartis, Regeneron, Roche, Sanofi, Takeda, etc) have approved products on the market that could hold potential in treating patients with COVID-19. Others have experimental drugs included in testing for other viruses that could be effective in targeting novel coronavirus infection. For news concerning COVID-19 therapeutics development, refer to Coronavirus Today: https://www.coronavirustoday.com/covid-19-treatments.

Drug therapy, either singly or in combination, for example remdesivir, chloroquine/hydroxychloroquine, baricitinib, acterma, convalescent plasma, ivermectin, kaletra, etc for COVID-19 has a dual purpose of both preventing the virus from spreading inside the human body as well as protecting body's immune system from the havoc caused by the viral attack (**Tables 2** and **3**). The FDA recently created a new emergency programme, the Coronavirus Treatment Acceleration Program, aimed at speeding up research for the development of COVID-19 treatments. The investigational antiviral drug remdesivir (Gilead Sciences) received Emergency Use Authorization (EUA) by the FDA on May 1, as it appears to help some hospitalised SARS-CoV-2 patients to recover faster. In Japan, at the discretion of the Health, Labor, and Welfare Ministry, early-stage patients may receive the antiviral drug Avigan (favipiravir; Fujifilm Toyama Chemical).

SARS-CoV-19 testing

The most pressing immediate need in the battle against COVID-19 is for diagnostic tests to determine if individuals are infected by the novel coronavirus and post-treatment follow-up. On January 7, 2020, Chinese authorities isolated and identified the new coronavirus, whose genetic sequence was shared internationally on January 12, so that countries could use it to develop specific diagnostic kits.

In our fight against COVID-19, as with any epidemic, testing, and more explicitly the capacity to perform tests for a large sector of the population, is fundamental. Massive testing not only allows the healthcare system to identify, monitor and treat people who have been infected by the virus, but also to trace their contacts, who may be potentially infected, detect foci of infections and assess the healthcare, logistic and economic resources available and the ones that are needed. The better our knowledge of the actual number of infected people is, the better our decisions to mitigate the disease. A given number of tests at the national level daily could provide valuable insight on the basic reproduction number (R0) and guide key decisions such as the adequate timing to lift lockdown restrictions and the way in which this should be accomplished, the reopening of the economy, active surveillance to avoid potential second waves and when to end lockdowns completely. At the individual level, testing can guide the treatment of a given patient, as well as determine when that patient can be cleared and/or whether he or she has developed immunity – something which in the case of SARS-CoV-2 is at this point very uncertain.

Immediately after the Chinese researchers published the genomic sequence of SARS-CoV-2, a number of companies became engaged in activities related to testing for SARS-CoV-2. These include, among others, Abbott Labs, Becton Dickinson, Co-Diagnostics, Danaher, LabCorp, Quest Diagnostics and Thermo Fisher Scientific (see **Table 4** for a list of the key SARS-CoV-2 test developers). Since then a number of tests have been developed. The testing strategies include methods that detect the presence of the virus itself (RT-PCR, isothermal nucleic acid amplification, antigen) and those that detect antibodies produced in response to infection:

- Detect the presence of SARS-CoV-19 virus (for instance, Reverse Transcriptase Polymerase Chain

Table 4: Key developers of SARS-CoV-2 diagnostic tests

DATE	INSTITUTION	TEST
January 10, 2020	Public Health England, UK	Real-time RT-PCR (RdRp gene) assay based on oral swabs. The test detected the presence of any type of coronavirus including specifically identifying SARS-CoV-2. It was rolled out to 12 laboratories across the UK.
January 11, 2020	Institute for Medical Research (MIMR), Malaysia	Primers and probes specific to SARS-CoV-2; RT-PCR method.
January 23, 2020	Charité, Berlin, Germany	Through European and Hong-Kong collaborators, used rtRT-PCR and formed the basis of 250,000 kits for distribution by the WHO.
January 24, 2020	World Health Organization	Same as MIMR
January 24/ February 11, 2020	State Research Center of Virology and Biotechnology VECTOR, Russia	In Russia, the first COVID-19 test was developed by the State Research Center of Virology and Biotechnology VECTOR, production began on January 24. On February 11 the test was approved by the Federal Service for Surveillance in Healthcare.
January 29, 2020	BGI Group, China	This company was one of the first to receive EUA from China's National Medical Products Administration for a PCR-based SARS-CoV-2 detection kit.
February, 4 2020	Kogenebiotech, South Korea	This company developed a clinical grade, PCR-based SARS-CoV-2 detection kit (PowerChek Coronavirus) approved by Korea Centers for Disease Control and Prevention (KCDC). It looks for the 'E' gene shared by all beta coronaviruses and the RdRp gene specific to SARS-CoV-2.
February 28, 2020	Center for Disease Control and Prevention (CDC), US	In the US, the CDC distributed its SARS-CoV-2 Real Time PCR Diagnostic Panel to public health laboratories through the International Reagent Resource. One of three genetic tests in older versions of the test kits caused inconclusive results due to faulty reagents and a bottleneck of testing at the CDC in Atlanta; this resulted in an average of fewer than 100 samples a day being successfully processed throughout the whole of February 2020. Tests using two components were not determined to be reliable until February 28 and it was not until then that state and local laboratories were permitted to begin testing. The test was approved by the FDA under EUA.
March 5/9, 2020	LabCorp, Quest Diagnostics, US	As of March 5, LabCorp announced nationwide availability of COVID-19 testing based on RT-PCR. Quest Diagnostics similarly made nationwide COVID 19 testing available as of March 9.
March 12, 2020	Mayo Clinic, US	Developed a test to detect COVID-19 infection.
March, 18 2020	Abbott Laboratory, US	The FDA issued EUA to Abbott Laboratories for a test on Abbott's m2000 system; the FDA had previously issued similar authorisation to Hologic, LabCorp and Thermo Fisher Scientific.
March 21, 2020	Cepheid, US	On March 21 Cepheid similarly received EUA from the FDA for a test that takes about 45 minutes on its GeneXpert system; the same system that runs the GeneXpert MTB/RIF.
April, 13 2020	Spartan Bioscience, Canada	Health Canada approved a test from Spartan Bioscience. Institutions may "test patients" with a handheld DNA analyser "and receive results without having to send samples away to a [central] lab".

Sources: Wikipedia (verified) and other Internet sources

Reaction (RT-PCR) and its variants; isothermal gene amplification; and antigen test).

- Detect the antibodies produced in response to a previous infection (for instance, serological tests, for the detection of immunoglobulin M (IgM) and immunoglobulin G (IgG) specific to SARS-CoV-2 (detection of antibodies serological tests can be used both for diagnosis and for population surveillance).
- Assess the damage that SARS-CoV-2 is creating in the organism, especially in the lungs and in the brain (for instance, computerised tomography scan (CT Scan) and oxygen take-up test).

One of the major challenges for early detection of SARS-CoV-2 has been what type of test is more reliable. For instance, RT-PCR could produce false negatives depending upon at what stage the sample is taken. In addition, it is relatively time consuming and requires well-trained personnel, and it is not appropriate for fast mass-testing. Isothermal nucleic acid amplification-based tests are fast (they can provide results in 13 minutes) but not sufficiently reliable. Antigen tests are cheaper and simpler than the RT-PCR test and can provide readings faster (15 minutes), but are less accurate as a positive case may come up as negative because the level of antigen in a sample is below the detection limit of the test. So, an RT-PCR test may need to be used to confirm or discard a suspicion. Thus, there is at present a race by many companies to come up with test kits that are cheap, fast and reliable just like a pregnancy test. So far the US FDA has granted clearance for emergency use to three test kits in which the patient, under prescription, can take a nasopharyngeal swab or saliva sample at home and then send it to a diagnostic lab14 (see the following FDA link for a list of the Emergency Use Authorization Tests: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd). And many other countries, in all the continents, are doing the same.

With COVID-19 infection varying in severity from asymptomatic to lethal, the search is now under way for specific biomarkers as clinical predictors of mortality and morbidity due to COVID-19, and help speed up clinical trials and reduce the cost of drug development. According to GlobalData's Biomarkers database, the top two biomarkers being utilised for COVID-19 trials are diagnostic markers – the first is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) *per se*, which is currently being used in approximately 30% of COVID-19 trials; and the second is Coronavirus Nucleic Acid, which is being included in just over 5% of trials. In COVID-19, the severe acute respiratory syndrome appears to result from a disregulated hyperinflammatory response manifested by the release of excessive pro inflammatory cytokines and chemokines, coined a 'cytokine storm'. The main cytokines appear to be IL-6 and LIGHT (homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocyte). Other biomarkers used in COVID-19 trials include C-reactive protein, lymphocytes and SARS-CoV-2 RNA, procalcitonin and suPAR.

Additional initiatives

In addition to the work being carried out by biopharmaceutical companies, research institutes and academic centres, several important initiatives are being performed at multiple levels: for example, the WHO has been leading the international efforts to control the pandemic, it has activated its R&D Blueprint initiative to accelerate diagnostics, vaccines and therapeutics for this novel coronavirus, and sent more than two million personal protection equipment (PPE) and testing kits to more than 120 countries. It has also launched the SOLIDARITY trial aimed at assessing the most promising treatments, among many other initiatives. The FDA has created a special emergency programme for possible therapies, the Coronavirus Treatment Acceleration Program (CTAP), as well as many other strategies. The UK has launched its Recovery trial, which is the world's largest COVID-19 one with more than 5,000 patients already taking part. The National Institute of Health (NIH), among many different initiatives, has recently launched the public-private partnership for Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). Big pharma companies are trying to develop treatments and vaccines through alliances and collaboration with academic research centres (as discussed above), while multiple research centres around the world are exploring the use of blood (plasma with antibodies) from patients who have survived COVID-19 as a treatment.

Also, philanthropic organisations such as the Bill and Melinda Gates Foundation and the Wellcome Trust, among many others around the planet, have poured in funding to fight COVID-19. In addition to this and to what every country is investing in their own national fight against COVID-19, recently world leaders from France, Germany, UK, Japan, European Union, Italy and Spain and other countries pledged 7.4 billion Euros that will be

channelled through global health organisations such as CEPI, Gavi, the Vaccines Alliance, the Global Fund and Unitaid for research to find a vaccine against the new coronavirus[15].

The severity of the COVID-19 pandemic has prompted bioethicist Nir Eyal and epidemiologists Marc Lipsitch and Peter Smith to propose carrying 'challenge trials' that might ordinarily be dismissed as too risky (https://academic.oup.com/jid/article/221/11/1752/5814216). The proposed Challenge trials deliberately expose low-risk, healthy volunteers to SARS-CoV-2 to quickly learn more about the disease it causes or to gain early insight into whether a new vaccine or treatment works, thus speeding up the development of a vaccine for SARS-CoV-2, reducing the global burden of COVID-19 related deaths and potentially saving millions of lives. Geneva-based SGS and London-based hVIVO are gearing up to carry out the challenge trials in coming months. More than 28,000 volunteers in 102 countries have already signed up to participate in these challenge trials (www.1daysooner.org). Beyond ethical and legal issues, there are significant logistical challenges to conducting such trials and the high stakes of exposing volunteers to potentially fatal risks. It would be a mistake to rush the implementation of challenge trials without adequately considering what it will take for them to make a difference.

All of this (vaccine development, COVID-19 treatment, diagnostic testing) requires a strategy to integrate prevention and treatment options as one continuum, parallel over traditional sequential, paradigm. With the diversity in the ever-expanding operational models, a proven strategy is needed that is flexible to accommodate and address changing demands of the partners and should be the ultimate choice for vaccine/drug discovery and development. Until proven prevention and/or treatment options emerge, keeping the SARS-CoV-2 contained is crucial, requiring aggressive testing, tracking and isolating contacts of people who have the virus and continued physical distancing. The pandemic has exposed cascading weaknesses of varying proportions in global disaster response among countries and healthcare agencies within a country. What once worked, it is no longer applicable as evidenced by the longstanding procedures for sheltering victims in stadiums, churches or other crowded-spaces suddenly became dangerous because they risk worsening the pandemic. According to Chris Currie, US Government Accountability Office, the COVID-19 pandemic has complicated every aspect of disaster planning and response in a way that we have never experienced before. In combating the COVID-19

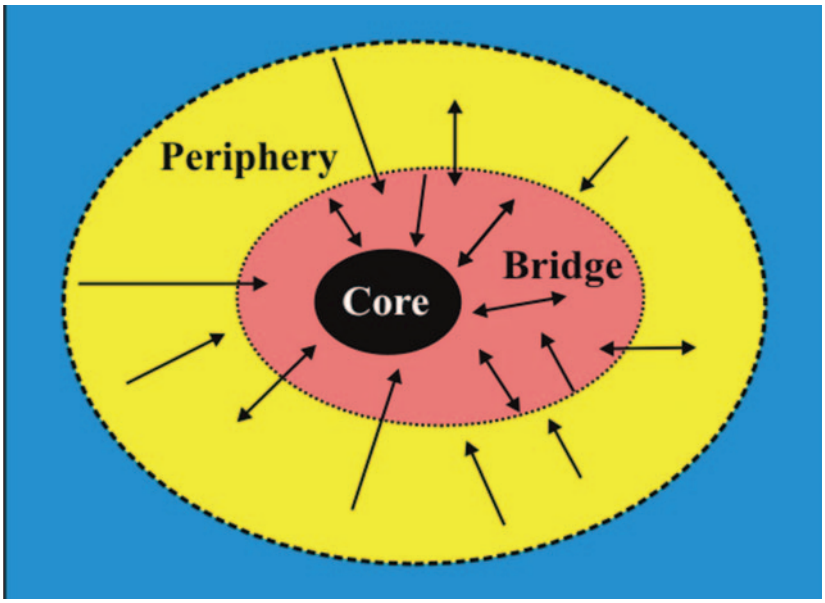

Figure 2: The Core Model. The Core is any autonomous entity in society interested in achieving a goal: it could be a single individual, an association of individuals, a small firm, a government agency or a large corporation. **The Bridge** is constituted by any external collaborators of the Core interested in the Core's goals (self-interested or otherwise). In the process of effective collaboration, the Bridge reduces the Core's needed amount of labour, time, personnel, economic resources and overall effort to achieve its goals; it benefits itself in an equal manner, while greatly augmenting the amount of knowledge in particular areas. The Bridge also can, and does, act as an intermediary between the Core and the Periphery. **The Periphery** encompasses all the institutions, resources, and regulations created by society for its own benefit and the common good. All of this is achieved via an exchange or trade of 'assets' (exchange of materials, animal models, knowledge, personal connections, resources, etc) which forms the basis of collaboration through which knowledge is transferred, integrated and finally translated into commercial products. *Source: Ibis Sánchez-Serrano: The Core Model: A Collaborative Paradigm for the Pharmaceutical Industry and Global Healthcare, Elsevier, 2019*

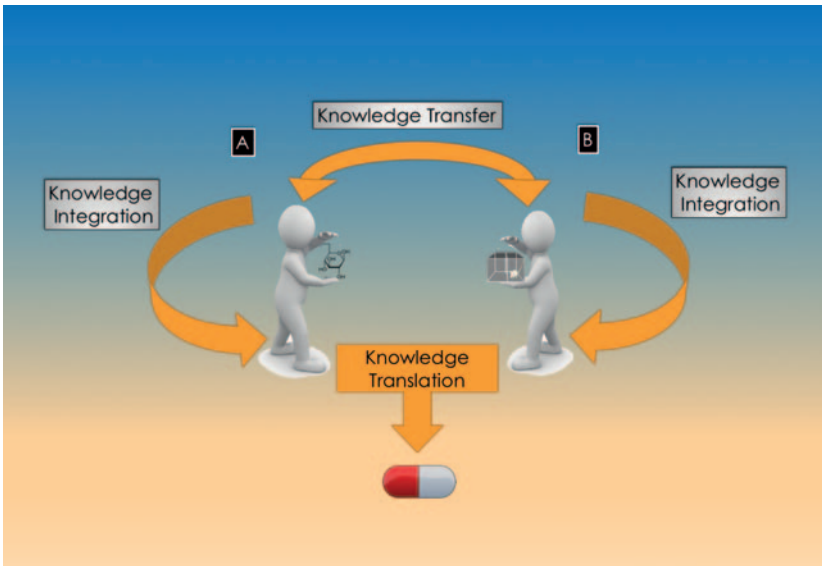

Figure 3: An exchange of 'assets', such as materials, animal models, knowledge, personal connections and resources, forms the basis of collaboration through which knowledge is transferred, integrated and finally translated into commercial products. *Source: Ibis Sánchez-Serrano: The Core Model, Elsevier, 2019*

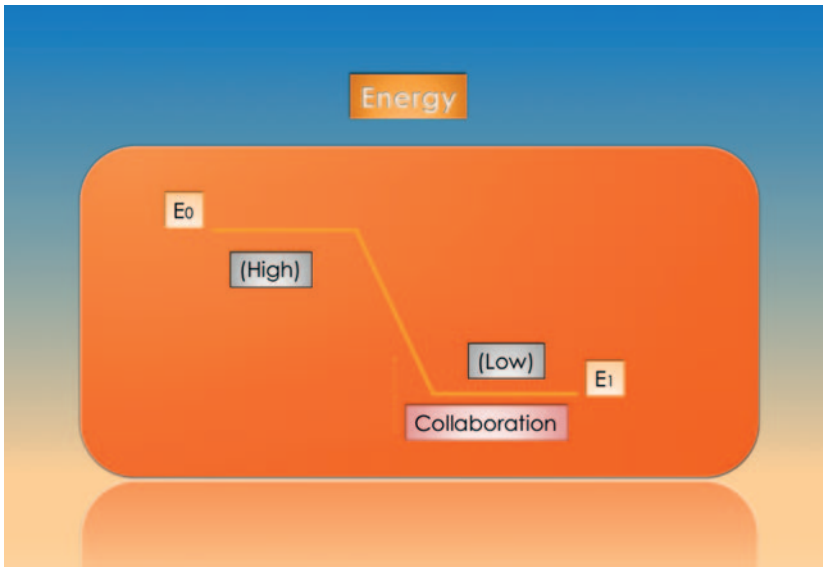

Figure 4
The Bridge lowers the activation energy from a 'High-State' to a 'Low-State'. The role of the Bridge (collaboration) within the Core Model is very similar to the one of an enzyme or catalyst: collaboration increases the speed of a reaction (the outcome) by lowering the activation energy (total amount of effort, time and investment) without getting consumed in the process. *Source: Ibis Sánchez-Serrano, The Core Model, Elsevier, 2019*

pandemic, we need to be reminded that we win or lose together. Now is precisely the time for a pragmatic operational model that integrates and swiftly addresses every aspect of the pandemic response from diagnostics to vaccine development to treatment options.

It is clear that many sectors in society are willing to co-operate and join forces. But there is a fundamental issue acting against this: all these alliances and efforts are scattered and unsynchronised – there is not a coherent and focused operational organisation in them. If these forces were joined cohesively through an organisational collaborative model, a cure for COVID-19 is possible sooner than expected. This is why the implementation of the Core Model, discussed below, can become crucial to combatting COVID-19.

The Core Model

The Core Model is an organisational model for R&D and an economic theory[16]. It lays out an adaptable novel organisational and design paradigm for drug discovery and development based on collaboration. It is also an economic theory for innovation and economic growth. The Core Model consists of three main structures named 'Core', 'Bridge' and 'Periphery' (for definitions, see **Figure 2**) through which knowledge is transferred, integrated and finally translated into commercial products (**Figure 3**) via an orchestrated exchange or trade of 'assets' (exchange of materials, animal models, knowledge, data, clinical trials results, personal connections, resources, funding, etc) among players and structures, which forms the basis of collaboration. This strategy allows for bi/multi-directional interactions that significantly save time, effort and resources and lowers the amount of 'energy' necessary to reach the agreed-upon common goal, from a high state to low state (**Figure 4**). An important finding in the Core Model is that it can be implemented in both for-profit and non-profit settings; for open-source innovation, as well for close-source innovation; for collaborative purposes as well as for competitive purposes. Furthermore, it reveals that intellectual property rights are not really needed for successful drug discovery and development for the benefit of society. The operating principles of the Core Model are exquisitely detailed in two recent books *The World's Health Care Crisis: From the Laboratory Bench to the Patient's Bedside*[17] and *The Core Model: A Collaborative Paradigm for the Pharmaceutical Industry and Global Health Care*[18].

Current efforts and alliances to develop a COVID-19 vaccine and/or therapy including the key players, resources, experiments and strategies at an international level are largely disorganised, unco-ordinated, misaligned and scattered without coherence. The research and development activities/platforms, despite establishing important partnerships, are not in synchrony with one another nor with individual national public health policies and socio-economic strategies – such as welfare, national security, economic stimulus packages, etc – all aimed at containing the pandemic and provide relief to their citizens.

It is an urgent and critical need to have a centralised, open and co-operative 'International COVID-19 Initiative' (ICOVIDI, **Figure 5**) based on the Core Model in a strategic place, for instance Europe or the United States, with multiple partners and key centres located in different parts of the world (eg Europe, North America, Latin America, Africa, Middle East, Asia and Australia) from academia; the pharmaceutical industry; government agencies; such as the NIH and like institutions (eg Center for Disease Control and Prevention (CDCP), Environmental Protection Agency (EPA)); consortia; pharmaceutical regulators (FDA/EMA/China's National Medical Products Administration (NMPA)); the WHO (SOLIDARITY is a good example); the United Nations; the European Union; governmental health care ministries; philanthropic organisations; and advocacy groups from all over the world working together in real time, exchanging information and models, addressing problems, analysing and synthesising data, making decisions in a very organised and focused manner. This is how it was done by the Event Horizon Telescope Project (EHTP) in order to

Figure 5
Proposed International COVID-19 Initiative (ICOVIDI) based on the Core Model
Key: Black oval = ICOVIDI (Core); Orange oval = pharmaceutical industry, federally-funded agencies, academia, consortia, policy-makers, regulators, investors, philanthropy (Bridge); Red = patient-society, advocacy groups, hospitals and healthcare centres (Periphery). Double-headed arrows (white) show bi-directional interactions. *Source: Based on Ibis Sánchez-Serrano. The Core Model, Elsevier, 2019*

obtain the first photograph of a black hole[19] or the Human Genome Project, among many other collaborative initiatives. It is obligatory for the creation of a global strategy, an inventory of resources and assets, of potential partners, a list of haves and have-nots, using the most sophisticated platforms, including artificial intelligence, which is ideally suited for this endeavour. The operational leadership should be centralised for the Core Model to be effective.

How could the Core Model help in the discovery of a vaccine and/or a treatment for COVID-19?

First it needs to be decided whether the ICOVIDI initiative will be an 'open' or 'closed' co-operative system[18]. In the discovery phase the Core Model could be extremely instrumental because it could bring together a number of different partners from the public and private sectors with complementary technologies, learnings, expertise and infrastructure together under one single and focused enterprise – the International COVID-19 Initiative. These partners could contribute with, and exchange information on, their basic knowledge of the structure and behaviour of the virus and how it affects human cells and the human body. Based on this, a series of strategies, depending on the assets and strengths of each partner, can be formulated for the development of COVID-19 vaccines or of drugs to treat the symptoms of the disease. The partners would freely exchange information, molecules, biological materials, animal models and platforms in real-time and perform all the necessary pre-clinical testing until having a clinical candidate. Once the clinical candidates for vaccines or drugs are ready – and after reaching a consensus in the clinical development strategies, locations, recruitment, and protocols, and involving the regulators – different Phase I safety studies would be run in parallel. Using translational research principles, the same is applied for efficacy testing in Phase II. At this point the most successful investigational vaccines or drugs could receive accelerated review approval or Emergency Use Authorization (EUA) from regulators and continue on to the large-scale Phase III trials. For manufacturing and world-wide distribution, the parallel (not waiting for Phase II and III results) operational model set-up by AstraZeneca in partnership with Coalition for Epidemic Preparedness Innovations (CEPI), Gavi and the Serum Institute of India, the world's largest manufacturer of vaccines by volume, to mass produce up to two billion doses of AZD1222 vaccine could provide a roadmap – an unprecedented, bold and gutsy 'ready to go' commitment if the vaccine 'checks out for safety'.

There are, at present, several high-profile collaborative efforts in motion and operational; they would be even more effective if they fully understood the Core Model, which is actually what they are trying to implement. For instance, ACTIV – the initiative in which the NIH is partnering with other agencies in the Department of Health and Human Services (DHHS) including the FDA, CDCP and Biomedical Advanced Research and Development Authority (BARDA); other US government departments including the Departments of Defense and Veterans Affairs; the European Medicines Agency; and representatives from academia, philanthropic organisations, more than 15 biopharmaceutical companies and the Foundation for NIH[20] follow the Core Model very closely[16-18,21]. Another example is one taken by Sanofi and GlaxoSmithKline, in which these otherwise rival companies are collaborating against COVID-19. Both companies will share their technology for this aim: Sanofi will contribute with its S-protein COVID-19 antigen based on recombinant DNA science, while GSK is contributing its adjuvant technology[22]. Both firms are powerhouses of manufacturing, so their combined capacity will allow them to mass produce hundreds of millions of doses yearly. A third major effort is the alliance between Gilead, Novartis, Schrödinger, Takeda Pharmaceutical and WuXi AppTec to share ideas, resources and data with the goal of developing 'custom pan-coronavirus antivirals'. It has been reported that the nature of this alliance is not commercial but philanthropic, and that the tools that are discovered during these efforts will enter the public domain[23].

The authors have clearly expressed and demonstrated that academia-industry/public-private partnerships and collaboration are not just nice things to have: they are essential for the creation of effective therapies[24-26]. They are even more critical now in our fight against COVID-19.

The implementation of the Core Model through the International COVID-19 Initiative, which incorporates a proven paradigm for efficient drug discovery and development, is our solution to the COVID-19 pandemic crisis. It is an unprecedented centralised stewardship fostering global collaboration to combat the global pandemic! It is a new way of thinking and we must embrace it and execute it, NOW. The International COVID-19 Initiative should also be a permanent organisation, since we should expect similar or worse pandemics (related to SARS-CoV-2 or not) in the future. The lessons learned will guide us in how we deal with future pandemics.

Conclusion: moral, ethical and social responsibility

Our global readiness for a pandemic such as COVID-19 has been surprisingly poor, judging by the best estimates of at least 9 million people infected and 470,000 deaths in 213 countries, as mentioned earlier. The astronomical emotional and economic impact that we are experiencing today is only the tip of the iceberg: there are many unknown and unavoidable challenges ahead of us.

A fundamental question we must ask, and for which we ought to have a convincing answer, is: What is the origin of SARS-CoV-2? At present there are three main hypotheses about it: first, that it was genetically engineered at the Center for Emerging Infectious Diseases at the Wuhan Institute of Virology. Second, that it is a natural virus that was either intentionally or unintentionally released from the Wuhan Institute of Virology. Third, that SARS-CoV-2 is a virus of natural origin with a subsequent zoonotic transmission (that is, from animals to humans), as was the case with Ebola, HIV and SARS. To this day the answer to this question remains uncertain. However, what is certain is the Chinese government's confession that the seafood market of Wuhan is the source of COVID-19. And inarguably certain is the fact that China allowed the spread of SARS-CoV-2 across the world by permitting international flights to and from Hubei province, the epicentre of the new coronavirus outbreak, while taking stronger measures to ensure that the virus did not spread within China by cutting off travel from Wuhan on January 23, 2020. Why did China allow international travel from Hubei to the rest of the world long past January 23? That question has to be answered so another epidemic from China does not spread like fire throughout the world... ever again! DDW

Disclaimer: COVID-19 pandemic is a dynamic and rapidly-evolving event. The numbers used in this article correspond to data available as of June 22, 2020, when the final draft of this work was submitted to the publisher.

Ibis Sánchez-Serrano *is a world-leading expert on healthcare. He is the President of the Core Model Corporation (Panama City, Panama) focused on global healthcare and biopharmaceutical innovation, and translational science policy. He is the author of two landmark books on the world's healthcare crisis and the solutions to it, including the Core Model. He is a regular speaker at major healthcare-related conferences, international TV guest commentator and an editorial board member of the scientific journal* Gender & The Genome. *He divides his time between Boston and his native Panama, where he is very much involved in community development and educational activities. Email: ibis.sanchezserrano@gmail.com*

Rathnam Chaguturu *is the innovation czar, founder & CEO of iDDPartners (Princeton Junction, NJ, US), a non-profit think-tank focused on pharmaceutical innovation, and was most recently, Deputy Site Head, Center for Advanced Drug Research, SRI International. He is the founding President of the International Chemical Biology Society, a founding member of the Society for Biomolecular Sciences and Editor-in-Chief-Emeritus of the journal* Combinatorial Chemistry and High Throughput Screening. *Rathnam passionately advocates the need for innovation and the virtues of collaborative partnerships in addressing pharmaceutical innovation crisis and aggressively warns of the threat of scientific misconduct in biomedical sciences. Email: mchaguturu@gmail.com*

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