PharmaVOICE

THERAPEUTIC DIGEST

COVID-19

AND ITS PIPELINE POTENTIAL

IN COLLABORATION WITH thinkgen

JUNE 2020

EDUCATION HAS AN IMPACT

Digital CME in the COVID-19 Era

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Medscape EDUCATION

With the unprecedented COVID-19 pandemic, the world of education has changed. From children in school to physicians keeping up with their practice, learners around the world have needed to adapt to a new reality. With the inability to meet in person at conferences and congresses, clinicians are looking to digital continuing medical education (CME), and seeking out new and innovative ways to learn. Medscape Education has been a leader in providing digital CME for more than 25 years and is committed to providing the timely and practice-relevant education and resources clinicians need.

The Spotlight on Digital CME

Digital CME is powerful because it is flexible and accessible in a way that allows clinicians to learn on their own terms and incorporate education into their busy practice schedules. Digital CME enables "just in time" education[1]—reaching clinicians right at the moment that they need the information. Physicians spend more than half of their time online expanding their medical knowledge, searching for materials to support their clinical practice, or answering questions that arise during visits with patients,[2] thus accessibility and availability of digital CME provides a timely solution for those who aim to learn.

Clinicians are increasingly relying on digital education due to the COVID-19 pandemic and the limited availability of live education, and research shows that will likely continue into the future. Clinicians expect to lean into digital more than ever—93% of physicians expect to use digital tools for clinical-decision support the same amount, greater, or significantly greater after the COVID-19 crisis.[3]

Digital CME Can Change Practice Behavior

A 2020 peer-reviewed study published in collaboration with the FDA demonstrates the power of Medscape digital education to positively impact public health. The study examines the efficacy of targeted short-form messaging and CME aimed at reducing overprescribing of fluoroquinolone antibiotics. The study examined nearly 24,000 high prescribers of fluoroquinolones and divided 11,774 into 3 treatment groups to evaluate and measure the effectiveness of communication and education methodology:

- Group 1 - Received short-form targeted messaging only (n = 8895)
- Group 2 - Received CME activity only (n = 1756)
- Group 3 - Received both short-form targeted messaging and CME (n = 1123)

The trial featured a case-matched control group (n = 11,774) and results were stated against that comparator population. The study demonstrated the statistically significant impact of digital CME (with or without messaging) to reduce inappropriate clinical behavior.[4]

Medscape Education and a Commitment to Digital CME

Medscape is the leading provider of digital education (CME) worldwide.[2] Throughout the COVID-19 pandemic, Medscape has launched a number of initiatives to help clinicians continue to get the education and resources they need. The Medscape Education COVID-19 Learning Center features 35 digital education activities focused on the identification and treatment of COVID-19 in variety of formats: audio, video, gaming, and case studies. The education has reached more than 800,000 clinicians. As an alternative to in-person events, Medscape Education has launched Virtual Symposia: livestreamed virtual events where expert faculty present on multispecialty topics. Virtual Symposia events have the potential to reach a large, engaged, global audience by being accessible and interactive.

As a trusted learning partner for the medical community with proven ability to deliver education that makes an impact, Medscape Education is committed to providing digital CME to learners where, when, and how they want to learn.

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[3] Kelleher K, Kumar K, Patel P, Schrader U. Pharma operations: The path to recovery and the next normal. McKinsey. 2020 May. Available at: https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharma-operations-the-path-to-recovery-and-the-next-normal#.

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COVID-19

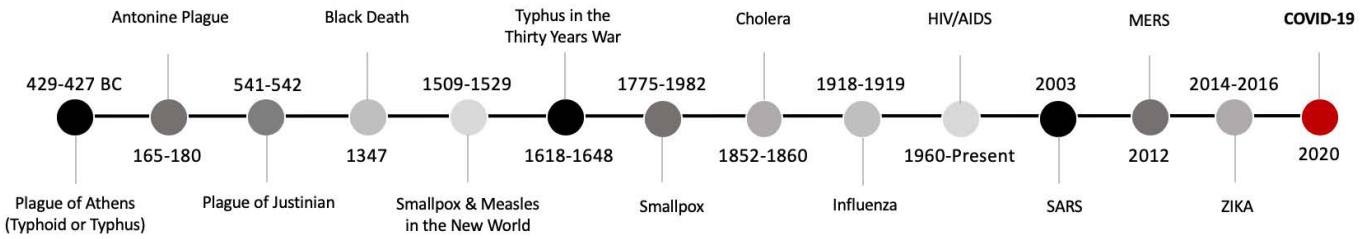
And Its Pipeline Potential

Throughout history, nothing has killed more human beings than the viruses, bacteria, and parasites that cause disease. Emerging and re-emerging infectious diseases are occurring at an unprecedented speed. According the World Health Organization (WHO), the world has witnessed the emergence of several disease outbreaks and epidemics caused by more than 20 infectious agents in the past decade[1]. Some of these epidemics were caused by novel infectious agents such as H1N1[2] and Middle East Respiratory Syndrome (MERS)[3].

In December 2019, several patients in Wuhan, Hubei, China, were diagnosed with pneumonia caused by an unknown virus. In response, an epidemiological alert was placed with the World Health Organization (WHO) on Dec. 31, 2019. By Jan, 7, 2020, Chinese scientists had isolated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[4] cases. In the months that followed, SARS-CoV 2, the cause of the coronavirus disease 2019 (COVID-19), spread across the globe resulting in the current pandemic. According to the Centers for Disease Control and Prevention (CDC), on May 27, 2020, there were more than 100,000 COVID-related deaths in the United States alone.

Pharmaceutical companies are doing their best to accelerate experimental drugs and vaccines for COVID-19 through the pipeline. Most existing preclinical and clinical data in antiviral therapy have been derived from other viruses, including SARS-CoV-1 (first reported in 2003), Middle East respiratory syndrome coronavirus (MERS COV, first reported in 2012), and non-coronaviruses such as the Ebola virus disease.

A Timeline of Infectious Diseases *Figure 1*

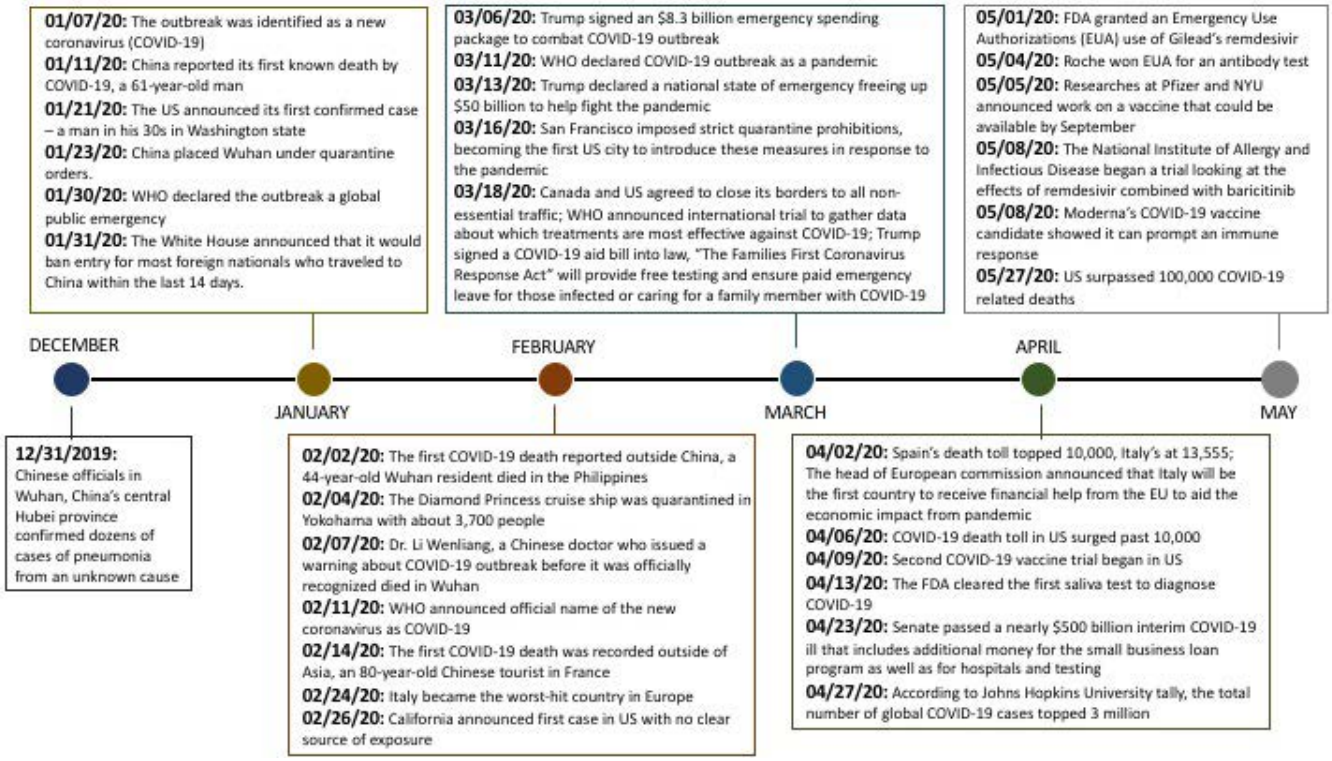


Source: National Science Foundation – Education Development Center

SO, WHAT IS COVID-19?

The size and reach of today's global travel network are unparalleled. In 2018 alone, more than 4 billion people (approximately 60% of the world population) traveled globally using commercial flights[5]. In today's global convergence, locally emerging pathogens have the capacity to spread rapidly and cross borders and become an imminent public health threat to the world. This is exemplified by the current COVID-19 pandemic where the appearance of a seemingly limited cluster of cases of pneumonia linked to a sea food market in Wuhan, China[6], has become one of the worst pandemics in human history with a staggering number of more than 6 .1 million infections in 177 countries and more than 372,000 deaths globally as of June 1, 2020[7].

A Brief Timeline of COVID-19 *Figure 2*



Source: World Health Organization and NBC News

The Difference Between SARS, MERS, and COVID-19

Coronaviruses are a large family of enveloped RNA viruses that mostly infect birds and mammals. In humans, they can cause a mild infection in the upper respiratory tract, like the common cold, but also result in more serious respiratory tract infections. These infections can manifest as bronchitis, pneumonia, or a severe respiratory illness, such as severe acute SARS, MERS, or COVID-19[8].

SARS

The coronavirus that causes SARS is called SARS-CoV. According to the WHO[9], the first cluster of SARS cases occurred in China's Guangdong province in November 2002. Research has identified horseshoe bats as the natural reservoir of SARS-CoV. Nocturnal mammals like civets and other animals in wet markets also likely contributed to the virus crossing from animals into humans[10].

The organization was first notified of more than 100 deaths due to a new infectious disease on Feb. 10, 2003. The next day, the Chinese health ministry made an official report of 300 cases and five deaths due to an acute respiratory syndrome. A paper published on May 15, 2003, in the New England Journal of Medicine identified a new coronavirus as the underlying pathogen. The WHO officially declared the SARS epidemic to be contained on July 5 of that year.

MERS

On Sept. 20, 2012, the Program for Monitoring Emerging Diseases reported a novel coronavirus isolated from sputum samples of a 60-year-old man from Saudi Arabia, who had died three months earlier[11]. Within the next month, the number of confirmed MERS cases rose to nine, with five fatalities. Across the globe, 27 countries have reported cases of MERS since 2012, but around 80% of cases occurred in Saudi Arabia[12].

MERS-CoV is a zoonotic virus, meaning that most cases of infection pass from animals to humans. According to the WHO, direct or indirect contact with dromedary camels is the most common route of infection[13]. While transmission among people is rare, it could occur among family members or in healthcare settings.

COVID-19

The coronavirus SARS-CoV-2 is the pathogen that causes COVID-19. The virus has a close resemblance to SARS-CoV. The first cases of COVID-19 were reported in Wuhan, China, in December 2019. On Jan. 5, 2020, the WHO published the first news of an outbreak of unknown cause. By the end of January, the organization had declared COVID-19 to be a public health emergency of international concern.

The name COVID-19 was officially coined by the WHO on Feb. 11, 2020. A month later, the organization declared a pandemic. To date, cases of COVID-19 have been reported on every continent except Antarctica. Governments across the world have responded with varying degrees of social distancing measures in a bid to curb the spread of the virus.

Summary of Differences for Coronavirus *Table 1*

	SARS	MERS	COVID-19
Pathogen	SARS-CoV	MERS-CoV	SARS-CoV-2
Total number of cases	8,439 (21% of which was developed in healthcare workers)	2,519	6,163,168*
Number of cases in the US	73	2	1,790,172*
Total number of deaths	823	866	372,014*
Case fatality rate	9.6%	34.3%	0.60-24.80%*
Mode of transmission	Droplets produced by coughing, sneezing, talking, or breathing	Droplets from person to person, unclear from camels to humans	Droplets produced by coughing, sneezing, or talking, limited evidence of other routes
Mean incubation period	5 days	Unknown	5 days
Key symptoms	A cough (dry at first), a fever, and diarrhea in the first or second week of illness, or both	A fever, a cough, shortness of breath	A fever, dry cough, shortness of breath
At risk groups	People with underlying medical conditions	Men above the age of 60, particularly those with underlying medical conditions such as diabetes, high blood pressure, and kidney failure	Adults aged 65 and over, and people of all ages with underlying medical conditions
Treatment	No specific treatment	No specific treatment	No specific treatment, although several candidate drugs are undergoing testing
Vaccine	No vaccine	No vaccine	No vaccines available yet, but several candidate vaccines are in development

** as of June 1, 2020*
Sources: Johns Hopkins University and Medicine. "Mortality Analyses." http://coronavirus.jhu.edu/data/mortality. Hewings-Martin Y. "How do SARS and MERS compare with COVID-19?" Medical News Today. April 10, 2020.

PIPELINE POTENTIAL

As the COVID-19 pandemic continues to move at record speed, the speed and volume of the scientific knowledge on SARS-CoV-2 and COVID-19 are correspondingly fast and unprecedented. Moderna Therapeutics' modified mRNA vaccine for COVID began Phase 2 testing at the end of May. From the first description of the novel coronavirus (SARS-CoV-20) genome on January 10, it took the company just 42 days to produce the first batches of its vaccine (mRNA-1273). If it can successfully negotiate safety and efficacy testing on a larger scale, batches of the mRNA vaccine could reach clinics as early as 2021. The question remains, will this timeline be too late for the current pandemic? Given that no mRNA vaccine has ever been approved, mRNA-1273 faces numerous challenges in clinical development and manufacture before it has the possibility of being made available for global immunization.

In the meantime, a host of other therapeutic modalities are being accelerated through discovery and development. Approved small molecules are already in use off label as adjunct therapies for critically ill patients, such as Fujifilm Toyama Chemical's favipiravir, and Gilead's remdesivir, which are currently in clinical trials. Repurposed monoclonal antibodies (mAbs) developed against previous coronaviruses, such as SARS and MERS, promise passive immunity before vaccines come online. And in the wings, newer experimental modalities, such as small interfering RNAs (siRNAs), virus-like particle or nanoparticle vaccines and DNA vaccines, are also waiting for their chance to contribute.

How long before treatment is available?

It could be months before treatments are available that are known to work against COVID-19. It could take longer for a vaccine. Commercial biopharmaceutical discovery is a less than ideal vehicle for responding to an outbreak of a new viral pathogen spreading like wildfire through an immunologically naïve population. Drug manufacturers are accustomed to navigating a regulatory and clinical development process that typically takes years, sometimes a decade or more[14]. Similarly, regulators have little experience for drug development in the context of a pandemic. There is no accelerated pathway for COVID-19 or any other emerging infectious disease, which is why many of the medications that are being eyed as potential treatments for COVID-19 are drugs that already exist[15].

In a recent review in the British Journal of Pharmacology, scientists from the United Kingdom called for a wider screening of existing drugs to see if they might work against the coronavirus[16]. They identified three stages of infection at which the coronavirus could be targeted: keeping the virus from entering our cells, preventing it from replicating inside the cells, and minimizing the damage that the virus does to the organs.

As of May 8, three medications had received emergency use authorization (EUA) from the FDA — the anti-malaria drugs chloroquine and hydroxychloroquine, the anti-viral remdesivir, and a drug used to sedate people on a ventilator[17]. An EUA allows doctors to use these drugs to treat people with COVID-19 even before the medications have gone through the formal FDA approval process.

Antivirals

Remdesivir

Developed by Gilead Sciences a decade ago, remdesivir failed in clinical trials against Ebola in 2014. But it was found to be generally safe in people[18]. Research with MERS showed that the drug blocked the virus from replicating[19]. The drug is being tested in many COVID-19 clinical trials around the world[20]. This includes studies in which remdesivir is being administered alongside other drugs, such as the anti-inflammatory drug baricitinib[21].

In late April, Gilead Sciences announced that one of its trials had been "terminated" due to low enrollment. Gilead officials said the results of that trial had been "inconclusive" when it was ended. A few days later, the company announced that preliminary data from another trial of remdesivir overseen by the National Institute of Allergy and Infectious Diseases (NIAID) had "met its primary endpoint."

Dr. Anthony Fauci, NIAID's director, told reporters that the trial produced a "clear cut positive effect in diminishing time to recover.[22]" He said people taking the drug recovered from COVID-19 in 11 days compared with 15 days for people who didn't take remdesivir.

However, another study published in The Lancet reported that participants in a clinical trial who took remdesivir showed no benefits compared with people who took a placebo[23]. Despite conflicting results, the FDA issued an order on May 1 for the emergency use of remdesivir[24].

Kaletra

Kaletra is a combination of two drugs — lopinavir and ritonavir — that work against HIV. Clinical trials are being done to see whether it also works against SARS-CoV-2[25]. One small study published May 4 in the journal Med by Cell Press found that lopinavir/ritonavir did not improve outcomes in people with mild or moderate COVID-19 compared with those receiving standard care[26]. Another study, published May 7 in the new England Journal of Medicine, found that the drug combination was not effective for people with severe COVID-19[27].

However, another study published in the Lancet on May 8 found that people who were given lopinavir/ritonavir along with two other drugs — ribavirin and interferon beta-1b — took less time to clear the virus from their body[28].

Favipiravir

Favipiravir is a Japanese-made drug approved in some countries outside the United States to treat influenza. Some reports from China suggest it may work as a treatment for COVID-19[29]. These results, though, haven't been published yet. Japan is sending the drug to 43 countries for clinical trial testing in people with mild or moderate COVID-19[30].

Arbidol

Arbidol is an antiviral that was tested along with the drug lopinavir/ritonavir as a treatment for COVID-19. Researchers reported in mid-April that the two drugs didn't improve the clinical outcomes for people hospitalized with mild to moderate cases of COVID-19[31].

Other Treatments

Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine have received emergency use authorization from the FDA at the end of March. At that time, manufacturer Novartis donated[32] about 30 million doses of hydroxychloroquine and 1 million doses of chloroquine to the nation's Strategic National Stockpile. Clinical results, though, have been mixed[33].

In late May, the WHO announced it was halting its clinical trials of hydroxychloroquine due to safety concerns[34]. The decision came a few days after researchers reported in The Lancet that patients receiving hydroxychloroquine and chloroquine were dying at higher rates than patients with COVID-19 who weren't given those drugs[35]. Around the same time, officials in France, Belgium, and Italy stopped the use of hydroxychloroquine for COVID-19 treatment due to safety concerns[36].

In early May, the authors of an observational study in the New England Journal of Medicine reported that patients who had been given hydroxychloroquine didn't benefit[37]. The medication didn't harm the participants who took it, but the drug also didn't lessen their need for ventilators or reduce their risk of death. Another study in JAMA published in May also found that hydroxychloroquine, with or without the antibiotic azithromycin, didn't help people with COVID-19.

Given the scarcity of good data, the authors of an opinion piece in the journal Annals of Internal Medicine questioned the use of these medications[38]. In late April, the FDA issued a warning against the use of both hydroxychloroquine and chloroquine outside of medical facilities[39]. The agency stated there were "serious and potentially life threating heart rhythm problems" connected with the drugs.

Monoclonal antibodies

Monoclonal antibodies trigger the immune system to attack the virus. Vir Biotechnology has isolated antibodies from people who survived SARS. The company is working with the Chinese firm WuXi Biologics to test them as a treatment for COVID-19[40].

AbCellera has isolated 500 unique antibodies from a person who recovered from COVID-19 and is set to start testing them.[41]

Blood plasma transfers

Along the same lines, the FDA has announced a process for medical facilities to conduct trials on an experimental treatment that uses blood plasma from people who have recovered from COVID-19[42].

The theory is that the plasma contains antibodies that will attack this particular coronavirus. In late March, the New York Blood Center began collecting plasma from people who have recovered from COVID-19[43].

Stem cells

Athersys Inc began a phase 2/3 clinical trial that will examine whether the company's stem cell treatment could potentially benefit people with acute respiratory distress syndrome (ARDS)[44]. This condition occurs in some people with severe COVID-19. Mesoblast has also developed a potential stem cell treatment of ARDS. The company is enrolling people with moderate to severe ARDS into a phase 2/3 clinical trial in the United States[45].

Immune suppressants

In some people with COVID-19, the immune system goes into overdrive, releasing large amounts of small proteins called cytokines. Scientists think this "cytokine storm" may be the reason certain people develop ARDS and need to be put on a ventilator. Several immune suppressants are being tested in clinical trials to see whether the drugs can quell the cytokine storm and reduce the severity of ARDS. These include baricitinib[46], a drug for rheumatoid arthritis; CM4620-IE[47], a drug for pancreatic cancer, and IL-6 inhibitors[48]. The FDA has also approved a device that filters cytokines[49] out of the blood of patients.

Selected experimental therapies under development for COVID-19 *Table 2*

Company	Modality	Status	Partners
RNAi			
Alnylam Pharmaceuticals	Aerosolized delivery of siRNA chemistry optimized for lung uptake	Alnylam has synthesized 350 siRNAs to SARS-CoV-2; Vir will conduct in vitro and in vivo testing	Vir Biotechnology
Sirnaomics	Respiratory-specific siRNA formulation that is delivered by a customized handheld nebulizer device	Preclinical	

Company	Modality	Status	Partners
Recombinant proteins			
Apeiron Biologics (Vienna)	Recombinant ACE2 enzyme (APN01; binds virus in circulation and blocks entry)	24 patients in randomized, unblinded clinical trial in China	
Monoclonal antibodies			
AbCellera Biologics (Vancouver, British Columbia, Canada)	Fully human IgG1 mAbs targeting SARS-CoV-2 developed from polyclonal antibodies identified in sera of convalescent patients	Discovered 500 unique antibodies from one patient with COVID-19	Eli Lilly for manufacture and scale-up
Beijing Defengrei Biotechnology	Fully human IgG1 mAb targeting complement factor 5a	Approved for phase 1 clinical trials in China in February 2020	
EUSA Pharma (Hemel Hempstead, UK)	Sylvant (siltuximab), human IgG1κ mAb against IL-6	Observational case-control study in patents with respiratory symptoms	Papa Giovanni XXIII Hospital (Bergamo, Italy)
Harbour Biomed (Shanghai)	Fully human IgG1 mAb (47D11) targeting the full-length spike (S) proteins of SARS-CoV and SARS-CoV-2	Antibody reformatted from chimeric mAb identified via SARS2-S1 subunit screening in hybridomas derived from mice engineered with two human heavy and light chains and a rat constant region (H2L2)	Research partnership with Mount Sinai Health System
ImmunoPrecise Antibodies (Victoria, British Columbia, Canada)	Fully human IgG1 mAbs targeting multiple undisclosed epitopes (polytope) on SARS-CoV-2	Reactive B cells were profiled in animals immunized with designed SARS-CoV-2 target antigens (e.g. 5 protein or Nsp15) and phage display used to identify neutralizing mAbs that show broad cross-species reactivity, which are reformatted as fully human molecules	EVQLV to provide computational antibody design expertise to optimize novel mAbs. Ligand Pharmaceuticals to combine its OmniMab platform with B Cell Select and DeepDisplay antibody technologies
InflaRx (Jena, Germany)	Fully human IgG1 mAb against complement factor 5a	Approved for clinical trial in China	
Vir Biotechnology	Human IgG1 mAbs targeting SARS-CoV-2 developed from polyclonal antibodies identified in sera of convalescent patients	Vir has also identified two mAbs targeting the human angiotensin-converting enzyme ACE2 receptor	QuXi and Biogen to provide scale-up/manufacturing in China and US, respectively

Company	Modality	Status	Partners
Others			
NanoViricides	SARS-CoV-2 S protein chemically attached to virucidal nanomicelle flexible polymer and polyethylene glycol	Testing candidates in culture	
Pharmamar (Madrid)	Aplidin natural product from marine tunicate *Aplidium albicans*, targeting elongation factor 1A	Positive in vitro studies against SARS-CoV-2 related corona-virus, requesting IND from regulators in mid-March	

Does not include polyclonal or IgG products extracted from convalescent patient serum
Sources: BioWorld, company sites, PubMed

Vaccines

Many groups[50] are working on potential vaccines for SARS-CoV-2, with several backed by the nonprofit Coalition for Epidemic Preparedness Innovations (CEPI)[51]. There are more than 100 projects[52] around the world centered on the development of a vaccine for the coronavirus. As of May 11, eight candidate vaccines were being tested in clinical trials in people.

Advances in genetic sequencing and other technological developments have sped up some of the earlier laboratory work for vaccine development. An official at the National Institutes of Health said in mid-May that large-scale testing could begin in July with a vaccine potentially available by January 2021[53]. Other experts say the more likely timeline is summer of fall of 2021[54].

Here's a look at some of the projects:

Moderna

In March, the company began testing its messenger RNA (mRNA) vaccine in a phase 1 clinical trial in Seattle, Wash. In mid-May, the company announced the vaccine had produced antibodies in all 45 trial participants in this initial clinical phase[56]. The study included 45 healthy volunteers, ages 18-55, who are getting two shots 28 days apart. The company has developed other mRNA vaccines before. Those earlier studies showed that their platform is safe, which allowed the company to skip certain animal testing for their specific vaccine. In early May, the company received permission from the FDA to start a phase II study of its vaccine[57]. The company expects to begin a Phase III clinical

trial in July[58]. The FDA also agreed to fast-track regulatory review of this vaccine if it succeeds in a Phase III clinical trial[59].

Inovio

When COVID-19 appeared in December, the company had already been working on a DNA vaccine for MERS[60], which is caused by another coronavirus. This allowed the company to quickly develop a potential vaccine for SARS-CoV-2. Company officials announced at the end of April that it had enrolled 40 healthy volunteers in its phase I clinical trial[61]. It is preparing to start a Phase II/III clinical trial this summer.

University of Oxford in England

A clinical trial with more than 500 participants began in late April[62]. Oxford officials said the potential vaccine has an 80% chance for success and could be available as early as September. The vaccine uses modified virus to trigger the immune system. The university has partnered with pharmaceutical company AstraZeneca. The company reported in mid-May the vaccine was effective against COVID-19 after it was given to six rhesus macaque monkeys[63]. The company expects to begin a late-stage clinical trial by the middle of this year[64]. Officials said in mid-May that if the clinical trial is successful, they could deliver 30 million doses by September[65].

University of Queensland in Australia

Researchers are developing a vaccine by growing viral proteins in cell cultures. They began preclinical testing stages in early April[66].

Pharmaceutical companies

Janssen[67] and Sanofi[68] are both working on a vaccine of their own. Pfizer has also teamed up with a German company to develop a vaccine. Their initial clinical trial with 200 participants was given the green light in late April[69]. The two companies began human testing in the United States in early May[70].

Selected vaccines under development for COVID-19 *Table 3*

Company	Modality	Status	Partners
Altimmune	Single-dose intranasal replication-defective adenovirus vector vaccine incorporating the SARS-CoV-2 S protein	Design and synthesis completed; moving toward animal testing and manufacture. Phase 1 trial planned for mid-August	
Arcturus	Self-transcribing and replicating RNA (STARR) vaccine expressing undisclosed epitope(s) delivered by lipid nanoparticle comprising 50% ionizable amino lipid or MC3, 7% 1,2-distearoyl-sn-glyceo-3-phosphocholine, 40% cholesterol and 3% 1,2-dimyristoyl-sn-glycerol, methoxypolyethylene glycol	Manufacturing stage	DUKE-NUS Medical School (Singapore) will provide rapid screening technology; $10 million in funding from Singapore government
BioNTechn (Mainz, Germany)	mRNA vaccine (BNT162) expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/ phosphatidylcholine/ cholesterol/ polyethylene glycol-lipid nanoparticles	Clinical testing began late April	Pfizer extends 2018 influenza agreement to work on COVID-19 candidate; Fosun Pharma, which paid $50 million in equity with a further $85 million in milestones, will collaborate in running clinical trials in China
(Sichuan) Clover Biopharmaceuticals (Chengdu, China)	Recombinant SARS-CoV-2 S protein trimer subunit vaccine	In preclinical testing with GlaxoSmithKline's pandemic adjuvant technology	Partnered with GlaxoSmithKline, which provides pandemic adjuvants platform comprising squalene, dl-α-tocopherol and polysorbate 80
Codagenix	Computationally designed and recorded live attenuated SARS-CoV-2 vaccine	Multiple codon-deoptimized SARS-CoV-2 vaccine candidate genomes designed on the bases of multiple genome sequences	Serum Institute of India to scale-up manufacture

Company	Modality	Status	Partners
CureVac (Tubingen, Germany)	Protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s)	Phase 1 in June or July	$8.3 million in funding from CEPI
Generex Biotechnology	Undisclosed SARS-CoV-2 derived synthetic peptide conjugated at N terminus to the C terminus of the key moiety of the major histocompatibility complex class II-associated invariant chain (li protein) containing a four-amino-acid (LRMK) modification (li-Key)	Human trials in June	EpiVax provides epitope prediction; Institute of Shandong Academy of Sciences tests the reactivity of candidate peptides in blood samples collected from convalescent patients
GeoVax	Modified vaccinia Ankara virus-like particle vaccine based on Wuhan strain of SARS-CoV-2	Candidates in animal studies	BravoVax (Wuhan, China) to provide manufacturing and clinical testing
Heat Biologics	Heat-shock protein gp96 complexed with undisclosed SARD-CoV-2 peptide(s)	Preclinical phase in progress	
iBio	Platform based on Agrobacterium-transformed tobacco for producing virus-like particle with undisclosed SARS-CoV-2 peptide(s) combined with its lichenase carrier immunostimulatory adjuvant	Program announced in February	Partnering with Beijing CC-Pharming, which has previous MERS vaccine experience
Inovio Pharmaceuticals	Electroporated DNA vaccine INO-4800 encoding SARS-CoV-2 S protein	Trials began in April in United States followed by China and South Korea; 3,000 doses available	Beijing Advaccine Biotechnology partnering for trials in China and Gates Foundation for Celletra electroporation device; funding from CEPI ($9 million) and Gates Foundation ($5 million)

Company	Modality	Status	Partners
Janssen	Single-dose intranasal recombinant adenovirus vaccine incorporating undisclosed SARS-CoV-2 protein using human retinal cell line scale-up technology	Seven constructs being tested in mice; phase 1 testing anticipated in October 2020 to February 2021	BARDA
LineaRx	Electroporated linear DNA vaccine	Four candidates of linear DNA vaccine based on S protein and selected epitopes ready for testing by the beginning of May or June	Takis Biotech (Rome) to clinical test candidates in Italy
Medicago (Quebec City)	Undisclosed recombinant SARS-CoV-2 protein virus-like particles produced in tobacco	Virus-like particles produced within 20-days; preclinical testing ongoing with clinical trials to begin summer 2020	Laval University Infectious Disease Research Centre
Moderna	mRNA vaccine encoding SARS-CoV-2 S protein encapsulated in ionizable lipid, distearoyl phosphatidylcholine, cholesterol and polyethylene glycol lipid	Phase 1 testing under way	NIAID, CEPI
Novavax	Nanoparticle vaccine displaying SARS-CoV-2 S protein with saponin-based (Matrix-M) adjuvant	Animal testing of candidates underway	$4 million in funding from CEPI
Sanofi (Paris)	Recombinant vaccine of undisclosed SARS-CoV-2 protein(s) expressed in baculovirus system	Advancing preclinical candidate; clinical trial to begin between March and August 2021	BARDA
Tonix Pharmaceuticals	Live-attenuated modified horsepox vaccine expressing undisclosed SARS-CoV-2 protein(s) (TNX-1800)	Pre-IND in February 2020	Collaboration with non-profit Southern Research

Company	Modality	Status	Partners
University of Queensland (Brisbane, Australia)	Recombinant subunit vaccine of SARS-CoV-2 S protein locked in prefusion conformation by polypeptide moiety (molecular clamp)	Preclinical phase in progress	CEPI; Dynavax Technologies to provide Toll-like receptor 9 agonist adjuvant CpG 1018; GlaxoSmithKline to provide pandemic adjuvants platform (squalene, dl-α-tocopherol and polysorbate 80); CSL (Parkville, Australia) to provide MF59 adjuvant (containing squalene in citric acid buffer with stabilizing nonionic surfactants Tween 80 and Span 85)
Vaxart	Oral recombinant adenovirus 5 vector vaccine of undisclosed SARS-CoV-2 protein(s) aimed at mucosal immune response	Preclinical phase in progress	
Vaxil Biotherapeutics (Ness Ziona, Israel)	Human signal peptide domain complexed with undisclosed SARS-CoV-2 protein(s) as vaccine	Vaccine candidate identified by in silico analysis as of mid-March	
Zydus Cadila (Ahmedabad, India)	Electroporated DNA vaccine and live attenuated recombinant measle vaccine vector of undisclosed SARS-CoV-2 protein(s)		
EUSA Pharma (Hemel Hempstead, UK)	Sylvant (siltuximab), human $IgG1_K$ mAb against IL-6	Observational case-control study in patents with respiratory symptoms	Papa Giovanni XXIII Hospital (Bergamo, Italy)

Abbreviation: IND: Investigational New Drug
Sources: BioWorld, company sites, PubMed

CONCLUSION

Appropriate management strategies for patients with COVID-19 are a rapidly evolving therapeutic challenge, and the optimal agents (if any) to treat infection or prevent progression to critical illness remain ill-defined. Although certain agents are encouraging, and the potential benefit of therapy likely outweighs the relatively minor risk of adverse events from short-course therapy, the evidence remains inconclusive and changes almost daily.

Recently, a new non-market vehicle has been launched, the COVID-19 Therapeutics Accelerator. With a total of $125 million committed by the Bill & Melinda Gates Foundation, the Wellcome Trust and the Mastercard Impact Fund, the accelerator will test existing small molecules and mAbs against SARS-CoV-2 and work with regulators to bring effective molecules to patients within a year[71]. The silver lining of COVID-19 was the necessary swift exchange of information as a response to a global public health crisis. The speed and volume of the scientific knowledge on SARS-CoV-2 and COVID-19 are correspondingly fast and unprecedented. We are at a unique time when competition amongst companies have turned to collaboration and transparency. If the pharmaceutical industry continues to cooperate with each other and aggregate their knowledge to flatten the pandemic curve, then a future without COVID-19 is truly at hand.

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