Developing Vaccines for the Coronavirus Disease (COVID-19) Outbreak

Every year, vaccines are administered to millions of people to mitigate the spread of a wide variety of infectious diseases. One of the best known and widely used vaccines is the influenza ("flu") vaccine. Prior to the widespread adoption of the flu vaccine, the influenza virus was associated with relatively high mortality rates. During the 1918 flu season, for example, a particularly deadly strain of influenza virus (commonly known as the Spanish flu) caused a global pandemic infecting about 500 million people (one third of the worldwide population at the time). The case fatality rate was more than 2.5% and at least 50 million people died.

The development of the first influenza vaccine by Jonas Salk and Thomas Francis in 1938 marked a new era in the fight against global flu pandemics. By 1942, the flu vaccine was being studied in large-scale clinical studies. Thanks in large part to the widespread adoption of flu vaccines, no influenza outbreaks affecting such a large proportion of the global population or with such a devastating effect as the 1918 pandemic have occurred in the last century.

However, despite the success of the annual flu vaccine, serious flu pandemics still occur (e.g., H1N1 pandemic of 2009), and the potential for a worldwide outbreak has remained an ever-looming threat. Importantly, this threat exists not only for influenza but also for other viruses. The current COVID-19 outbreak provides one of the most sobering examples of this and reminds us that responding effectively and efficiently to emerging viral disease threats remains a significant healthcare and public policy challenge.

COVID-19 and Future Threats

COVID-19 is caused by a betacoronavirus called SARS-CoV-2. This virus is structurally similar to SARS-CoV-1, which caused the deadly SARS epidemic of 2003. SARS-CoV-2 shares 85% DNA sequence identity with a SARS-like coronavirus found in bats, indicating that the COVID-19 virus (like prior outbreak-causing coronaviruses, SARS and MERS) most likely originated in this species. It is believed that SARS-CoV-2 may have crossed into humans at a wildlife market in Wuhan, China, in late 2019.

Viruses that originate in animal species and then pass into humans can be particularly problematic. These viruses can mutate rapidly and, given their animal origin, there is essentially no preexisting immunity in the human population. Fortunately, while mutations within a virus's

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genome will occur during outbreaks, most mutations tend to be limited and do not meaningfully affect virus function. Such mutations are also unlikely to present any significant resistance to a future vaccine. Despite this, scientists will continue to monitor the genetic sequence of this virus to gather critical data that could help guide appropriate responses to this and future outbreaks.

Current Therapeutic Developments for COVID-19

Due to rapid action by regulatory authorities, academic institutions, and pharmaceutical companies, multiple COVID-19 vaccine and therapeutic candidates have already emerged. These efforts continue to involve countless researchers, support staff, and others tirelessly working to understand the virus and to develop ways to combat it. Current approaches include everything from traditional vaccines to cutting edge nucleic acid-based therapies and even repurposing certain existing drugs that might prove beneficial. While the development of COVID-19 vaccines and therapeutics is still in its infancy, here we highlight the efforts of 3 companies seeking innovative solutions to the current crisis. *Please note, this information is based on publicly available information and does not disclose any confidential information from Nuventra clients or other companies.*

MODERNA

Working closely with the U.S. National Institutes of Health, Moderna's platform-based therapy (mRNA-1273) has emerged as a promising option, and the company has begun recruiting for a Phase I clinical trial. Moderna's approach is unique in that, instead of using dead or weakened viruses like traditional vaccines, they are using messenger RNAs (mRNAs). Once administered, these mRNAs will direct a vaccine recipient's cells to produce proteins that mimic a "spike protein" that SARS-CoV-2 uses to gain entry into host cells. The hope is that these proteins will elicit an immune response that will protect the recipient from future infection with the COVID-19 virus.

Moderna has already produced clinical trial-ready batches of its product and is simultaneously conducting necessary pre-clinical studies in animals and recruiting human volunteers for safety trials.

INOVIO

Like Moderna's mRNA-1273, Inovio's investigational coronavirus vaccine (INO-4800) seeks to harness the body's ability to produce proteins mimicking the SARS-CoV-2 spike protein from a nucleic-acid-based template. However, unlike Moderna's use of mRNA, Inovio is using DNA as the basis of its vaccine. The company already has a DNA-based vaccine in Phase II development for the prevention of Middle East Respiratory Syndrome (MERS), which is caused by a different type of coronavirus, but one that shares some similarity with SARS-CoV-2.

Like the MERS vaccine, Inovio's COVID-19 vaccine relies on the introduction of plasmid DNA into human cells using an electroporation device. The device temporarily opens tiny holes in a patient's cells to allow the DNA to enter. Once inside the cell, the DNA is transcribed into mRNA and then translated into proteins. It is hoped that the immune response to these proteins will prevent subsequent infection with the COVID-19 virus. The company plans to begin a Phase I trial in the U.S. in April 2020.

GILEAD

Gilead is in Phase 3 clinical development of a potential broad-spectrum antiviral therapy called remdesivir. Remdesivir was first investigated several years ago as a treatment for the Ebola and Marburg viruses and has shown promising results in animal and in vitro studies. The drug works by preventing viruses from replicating once inside the body, allowing the immune system time to catch up and neutralize the infection. While not originally developed for COVID-19, a new study has begun enrolling hospitalized adults with COVID-19 in Nebraska to test the safety and effectiveness of this therapy in this indication.

Remdesivir has gained significant attention in the past for its isolated use in patients with Ebola and more recently for its "compassionate use"—a term that describes drugs that are allowed to circumvent full regulatory approval to be used in life-threatening situations—in a Washington man with COVID-19. The man's condition improved after administration, but more research is needed to determine whether the drug truly interrupted the natural progression of the disease.

Timeline of COVID-19 Vaccine Development

Even with the frantic pace at which developers are working to produce a COVID-19 vaccine, such a vaccine is unlikely to be available for widespread use for another year or more. So why can't we move faster? The reason is to ensure that any marketed vaccine or therapy is both safe and effective before it is administered to wide swathes of the population. The only way to do this is by going through the appropriate drug development and regulatory channels.

The CDC outlines the six stages of vaccine development as:

1. Exploratory stage
2. Preclinical stage
3. Clinical development
4. Regulatory review and approval
5. Manufacturing
6. Quality control

While vaccine development often takes many years, several vaccine candidates are already moving out of the initial exploratory stage and into the preclinical and clinical stages. Impressively, recruitment of healthy volunteers for first-in-human clinical trials has begun less than 2 months after the release of the SARS-CoV-2 full genome map.

The clinical stage is typically the longest. Because no drugs or biologics (including vaccines) are without risk, safety assessments in human clinical trials are critical. Following initial clinical studies, additional patients suffering from COVID-19 will need to be enrolled and treated until safety and effectiveness have been sufficiently demonstrated. It is likely that thousands of COVID-19 patients will need to participate in clinical studies before a vaccine or therapy is approved for use in the general population.

From the data generated during these clinical studies, the FDA (and other regulatory authorities around the world) will be able to evaluate the safety and efficacy profile of the vaccine. Promising therapies will almost certainly receive expedited review by the FDA in order to get these products onto the market as quickly as possible.

One final hurdle for any approved vaccine is that it must be produced in sufficient quantities to serve a large portion of the world's population. Manufacturing scale up can be challenging for any product, but especially in times like these when regulatory, political, and public scrutiny are intense, and the margin for error is minimal. Once a vaccine is made available to the public, continuous safety surveillance and testing will be necessary to ensure that the vaccine continues to be produced to specified quality standards and that the vaccine is acting as expected in the intended population.

Conclusions

While it can take many years to develop a new vaccine or therapy under normal circumstances, the current situation with COVID-19 is clearly not normal. Given the intensive backing of the healthcare industry, federal, state, and local governments, regulators, and the general public, the race to a safe and effective COVID-19 vaccine is on.

As mentioned in our recent news release, Nuventra is committed to do our part in fighting this global pandemic by helping sponsors bring their COVID-19 vaccines and therapies to the general population as soon as possible. Our team has years of experience in developing therapies for viral infections and we have former FDA staffers who are ready to help. Please contact us with any questions you may have related to developing your vaccine or anti-viral therapy.

In the meantime, let's all remember to practice preventative measures like handwashing, covering your cough, and social distancing to help mitigate the virus's spread. Together, we can help "flatten the curve" until an effective vaccine becomes available.

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