Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

In Pursuit of a SARS-CoV-2 Vaccine

Recently, some of our patients have inquired about the availability of a vaccine for the prevention of COVID-19 disease. Currently, everyone wants to know when a safe and effective vaccine for the SARS-CoV-2 coronavirus will be ready to administer to the world's citizenry. In an effort to provide foot and ankle surgeons with information that they can use to accurately respond to their anxious patients, we are providing a synopsis of the current status or coronavirus vaccine development.

In the United States, the Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health (1). Like new drugs, new vaccines are developed through a process that entails a number of distinct phases [https://www.cdc.gov/vaccines/basics/test-approve.html]. In the preclinical phase, investigators conduct laboratory work in order to understand the basic science that underlies a vaccine's physical and chemical properties. Thereafter, human testing begins with a Phase I safety assessment, during which a small group of volunteer participants is administered the vaccine and followed in order to screen for potential adverse effects related to the vaccine. If the vaccine is determined to be safe, then its efficacy is assessed in a Phase II trial, wherein the primary aim is to determine whether or not the vaccine actually results in the development of antibodies to the target virus. If the vaccine is determined to be efficacious, then a Phase III comparison trial is conducted in order to see if the vaccine is better than or at least comparable to standard preventive measures. Phase IV, the last and longest period of observation, monitors the safety and effectiveness of the vaccine over an extended period of time following widespread use of the vaccine.

On May 15, 2020, in the White House Rose Garden, United States President Donald Trump formally announced Operation Warp Speed (OWS). OWS is a combined effort of both public and private sectors with oversight by the US Department of Defense, Department of Health and Human Services, FDA, and the Centers for Disease Control and Prevention, for the safe development and distribution of SARS-CoV-2 vaccines. The mission objective of OWS is to deliver 300 million doses of safe and effective vaccine by January 1, 2021 (2). This operation is unusual, in that the traditional process for vaccine development typically takes >70 months to complete; however, this mission's accelerated process aims to reduce the timeline to a duration of just 14 months (2). The reasons for such an effort are outlined by 4 key goals of the mission: (1) ensure safe and effective SARS-CoV-2 vaccine/s, (2) reduce morbidity and mortality of COVID-19 infection via distribution of vaccines, (3) support rapid vaccine distribution, and (4) assist with the return to a prepandemic quality of life (2). Like all government-funded projects, at least in the United States, funding is covered by taxpayer dollars; and, at present, approximately 6 billion US dollars are funding development of 6 different vaccines that are being investigated by 8 different companies, namely AstraZeneca (Cambridge, UK), Johnson & Johnson (New Brunswick, New Jersey), Moderna (Cambridge, Massachusetts), Novavax (Gaithersburg, Maryland), Sanofi (Paris, France), GlaxoSmithKline (Brentford, UK), Pfizer (New York, New York), and BioNTech (Mainz, Germany) (3-8).

Around the world, operations similar in scope to OWS are also in progress. As of September 19, 2020, worldwide efforts are directed toward a total of 40 vaccines in human clinical trials, with another 92 preclinical efforts in animal studies. Including the United States, there are 27 vaccines in Phase I, 15 in Phase II, 9 in Phase III, and 5 vaccines that have received approval for early or limited use; however, not a single vaccine has been approved for general use worldwide (9). These numbers are everchanging and will certainly be outdated by the time this editorial gets to press. On August 11, 2020, Russia announced approval of a vaccine, nicknamed "Sputnik V," based on the results of 76 patients in 2 open, nonrandomized Phase I/II studies at 2 hospitals in Russia. The results of the combined phase trials were later published on September 4, and revealed good immunogenicity for both humoral and cell-mediated immune responses; however, further investigation is needed in order to determine how effective the vaccines will be in preventing COVID-19 disease (10). Two other vaccines developed by Chinese companies have received emergency approval for use in China, where a number of clinical trials are underway (9). It is also not surprising that there have been some pitfalls associated with the human trials, with one volunteer in the AstraZeneca/Oxford trial in the United Kingdom developing serious neurological symptoms after being administered a vaccine, causing the Data Safety Monitor to temporarily halt the trial. That particular trial resumed 6 days later (9). Adverse effects such as this "unexplained illness" could impact just how swiftly such an effort of this magnitude is able to effectively and safely enable mass production and distribution of a SARS-CoV-2 vaccine. In the United States, notwithstanding the political implications of a deployable vaccine, most experts agree that a vaccine is likely to be approved in late 2020 with initial deployment to healthcare workers and vulnerable populations after completion of Phase III trials (11). Manufacturing and organization of the vaccine deployment infrastructure has already begun in US-based facilities as a part of OWS, an approach to rapid distribution known as fill-finish manufacturing, wherein millions of doses are quickly packaged and shipped upon approval (3). Recently, both National Institute of Allergy and Infectious Diseases Director Anthony Fauci, MD, and Centers for Disease Control and Prevention Director Robert Redfield, MD, have stated publicly and in Congressional testimony that they expect general deployment of SARS-CoV-2 vaccines in the summer of 2021, with widespread immunizations and a "return to regular life" in late summer or fall 2021 (12).

Alton R. Johnson, DPM[1]
Adam R. McDonald, DPM, AACFAS[1]
D. Scot Malay, DPM, MSCE, FACFAS[2,3]
[1] Podiatric Medicine and Surgery Clinical Research Fellow, Penn Presbyterian Medical Center, Philadelphia, PA
[2] Director, Podiatric Research, Penn Presbyterian Medical Center, Philadelphia, PA
[3] Editor, *The Journal of Foot & Ankle Surgery*

E-mail address: editorjfas@gmail.com (D.S. Malay).

1067-2516/$ - see front matter Published by Elsevier Inc. on behalf of the American College of Foot and Ankle Surgeons.
https://doi.org/10.1053/j.jfas.2020.09.011

References

1. *Mission Possible: How FDA Can Move at the Speed of Science. Report of the Science Looking Forward Subcommittee*. Prepared for FDA Science Board, September 2015. Available at: http://www.fda.gov/downloads/scienceresearch/aboutscienceresearchatfda/ucm456328.pdf. Accessed September 20, 2020.
2. U.S. Department of Defense. *Coronavirus: Operation Warp Speed*. 2020 [online] Available at: https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/. Accessed September 19, 2020.
3. U.S. Department of Health and Human Services. *Trump Administration Collaborates With Moderna to Produce 100 Million Doses of COVID-19 Investigational Vaccine*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/08/11/trump-administration-collaborates-with-moderna-produce-100-million-doses-covid-19-investigational-vaccine.html. Accessed September 19, 2020.
4. U.S. Department of Health and Human Services. *Trump Administration's Operation Warp Speed Accelerates Astrazeneca COVID-19 Vaccine to Be Available Beginning in October*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/05/21/trump-administration-accelerates-astrazeneca-covid-19-vaccine-to-be-available-beginning-in-october.html. Accessed September 19, 2020.
5. U.S. Department of Health and Human Services. *HHS, DOD Collaborate With Johnson & Johnson to Produce Millions of COVID-19 Investigational Vaccine Doses*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/08/05/hhs-dod-collaborate-with-johnson-and-johnson-to-produce-millions-of-covid-19-investigational-vaccine-doses.html. Accessed September 19, 2020.
6. U.S. Department of Health and Human Services. *HHS, DOD Collaborate With Novavax to Produce Millions of COVID-19 Investigational Vaccine Doses in Commercial-Scale Manufacturing Demonstration Projects*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/07/07/hhs-dod-collaborate-novavax-produce-millions-covid-19-investigational-vaccine-doses-commercial-scale-manufacturing-demonstration-projects.html. Accessed September 19, 2020.
7. U.S. Department of Health and Human Services. *HHS, DOD Partner With Sanofi and GSK on Commercial-Scale Manufacturing Demonstration Project to Produce Millions of COVID-19 Investigational Vaccine Doses*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/07/31/hhs-dod-partner-sanofi-gsk-commercial-scale-manufacturing-demonstration-project-produce-millions-covid-19-investigational-vaccine-doses.html. Accessed September 19, 2020.
8. U.S. Department of Health and Human Services. *U.S. Government Engages Pfizer to Produce Millions of Doses of COVID-19 Vaccine*. 2020 [online] Available at: https://www.hhs.gov/about/news/2020/07/22/us-government-engages-pfizer-produce-millions-doses-covid-19-vaccine.html. Accessed September 20, 2020.
9. New York Times. *Coronavirus Vaccine Tracker*. 2020 [online] Available at: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html. Accessed September 19, 2020.
10. Logunov DY, Dolzhikkova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet 2020 Sep 4 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext. https://doi.org/10.1016/S0140-6736(20)31866-3.
11. NPR. *NPR Choice Page*. 2020 [online] Available at: https://www.npr.org/sections/coronavirus-live-updates/2020/09/08/910863680/covid-19-vaccine-trial-paused-due-to-illness-in-one-volunteer. Accessed September 19, 2020.
12. New York Times. *When Will You Be Able to Get a Coronavirus Vaccine?* 2020 [online] Available at: https://nyti.ms/2FlHaMy. Accessed September 19, 2020.