VIEWPOINT

Developing a SARS-CoV-2 Vaccine at Warp Speed

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Viewpoint

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The coronavirus disease 2019 (COVID-19) pandemic has unleashed major and substantial changes in the provision of health care, including public health policy and the practice of medicine, and in the ways most individuals live their lives.[1] Significant changes also have occurred in vaccine development, with shortening the usual 15- to 20-year timeline to one that might be as short as 1 to 1.5 years.[2] COVID-19, the acute illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, Hubei province, China, in December 2019, and rapidly progressed to a global pandemic. By June 27, 2020, a total of 9.76 million people had been infected with this virus and 492 000 had died. Although widespread quarantine, isolation, and social distancing measures have, to some extent, countered the spread of SARS-CoV-2 and "flattened the curve," countries now face a multitude of challenges to the "re-opening" of society. Yet, it is clear the only way to provide effective herd immunity is with a safe and effective vaccine.

With this background, the US Department of Health and Human Services (HHS) launched Operation Warp Speed—a partnership between government and industry—with the goal of delivering 300 million doses of a safe and effective vaccine by January 2021.[3] This ambitious plan initially focused on 125 potential vaccine candidates, but was rapidly narrowed to 14 candidates in May 2020, and, as reported in June 2020, the current administration plans to narrow this list to 5 core candidates (**Table**).[4] In this Viewpoint, we describe the proposed mechanisms and current status of each of these leading candidates, all of which are aimed at inducing antibodies directed against the receptor-binding domain of the surface spike (S) protein of SARS-CoV-2.

> As the COVID-19 pandemic continues to cause significant disruption to both the physical and economic health of the world's population, pathways of vaccine development are adapting in ways that could not have been predicted even a year ago.

Messenger RNA–Based Vaccine Candidates

Messenger RNA (mRNA) vaccines offer a novel methodology in the field of vaccinology. Although this strategy has displayed promise in early studies, mRNA vaccines have never been used commercially to prevent infections.[5] mRNA is the intermediate step between the translation of DNA and production of proteins in the cytoplasm. mRNA vaccines function on the premise that mRNA coded for pathogen antigen can be delivered to human cells and, once there, can be used for production of antigen within the cell. This is unique in that it would lead to a robust immunogenic response without the introduction of live, killed, or subunit portions of the pathogen of interest. However, because mRNA is highly susceptible to extracellular ribonucleases and is rapidly degraded, its use depends on the inclusion of a complex lipid delivery system, which is also untested.

Two of the 5 candidate vaccines are based on mRNA methodology. Moderna, a Massachusetts-based biotechnology company, has developed mRNA-1273, a lipid nanoparticle-encapsulated mRNA vaccine that encodes a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2.[6] This vaccine candidate is currently being tested in a phase 2a dose-ranging trial that has enrolled 600 adult participants. This program is supported by a $483 million grant from the Biomedical Advanced Research and Development Authority (BARDA), which is part of HHS.

Pfizer, in concert with BiBioNTech, a German company, is also developing an mRNA platform that is similarly focused on lipid nanoparticle-encapsulated mRNA that encodes for SARS-CoV-2 spike (S) protein.[7] Currently, the developers are conducting phase 1-2 trials that focus on dose-ranging studies among 4 candidates, using 1- or 2-dose regimens. Pfizer and BioNTech did not seek US governmental financial support in the development of their product.

Recombinant Vesicular Stomatitis Virus–Vectored Vaccine Candidate

Replicating viral vector vaccines are predicated on the concept that live attenuated vaccines, for which replication ability remains intact, tend to have more robust and sustained immunogenic responses than killed or subunit vaccines, which often require several doses or adjuvants. Viral vector vaccines, rather than using attenuated versions of the target pathogen, use replication-competent versions of other viruses (the vector) to shuttle antigen-producing genes from the target pathogen to human cells. The most recent example of a successful replicating viral vaccine product is Merck Sharp & Dohme's Ebola vaccine, Ervebo, a recombinant vesicular stomatitis virus (rVSV)–vectored Ebola Zaire live vaccine, which uses a surface protein of Zaire Ebolavirus (EBOV).

Encouraged by its recent success with the Ebola vaccine, Merck Sharp & Dohme is now partnering with the International AIDS Vaccine Initiative to develop an rVSV-vector platformed vaccine against SARS-CoV-2,

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Table. Operation Warp Speed Vaccine Candidates

Candidate	Technology	Single dose	Stage
Moderna (mRNA-1273)	Messenger RNA	No	Phase 2a clinical trial
BioNTech/Fosun Pharma/Pfizer (BNT162a1, BNT162b1, BNT162b2, BNT162c2)	Messenger RNA	Potentially	Phase 1-2 clinical trials
Merck, Sharpe & Dohme and the International AIDS Vaccine Initiative	Recombinant vesicular stomatitis virus vector	Unknown	Preclinical
Johnson & Johnson/Janssen Pharmaceuticals	Replication-defective human adenovirus 26 vector	Yes	Phase 1-2a clinical trials
AstraZeneca and the University of Oxford (ChAdOx1 nCoV-19)	Replication defective simian adenovirus vector	Yes	Phase 1-2 clinical trials

using spike (S) protein as an antigenic target. The Merck Sharp & Dohme vaccine is supported by a $38 million grant from BARDA.[8]

Adenovirus Replication-Defective Vectored Vaccine Candidates

Two additional strategies involve replication-defective recombinant adenoviral vectors. Unlike the rVSV-vectored vaccine, which uses a replication-competent but harmless virus as a vector, these candidates use either a replication-defective simian adenovirus or replication-defective human adenovirus type 26. Both vectors deliver recombinant SARS-CoV-2 spike (S) protein genes to human cells. Similar to the mRNA vaccines, no vaccines to prevent human disease are commercially available using this strategy. Rather, their clinical use has been limited to 1 licensed vaccine against animal rabies. Johnson & Johnson, the maker of the replication-defective adenovirus type 26 vector (Ad26.COV2-S), is now moving into phase 2-2a trials, supported by $456 million in grants from BARDA.[9] AstraZeneca, the manufacturer of the replication-defective simian adenovirus vector (ChAdOx1 nCoV-19), in combination with the Jenner Institute at the University of Oxford, is similarly pursuing a phase 1/2 single-blinded study.[10] AstraZeneca has received $1.2 billion in funding for development of its product from BARDA.

With all these vaccines, efficacy—as defined by robust and durable immunogenic response—will be the key metric of success. Without long-lasting immunity that persists season to season, the capacity of any candidate vaccine to effect community transmission will be limited. In addition, safety will be an equally important second metric. All 5 candidates are undergoing rigorous investigation of their safety profile, inclusive of unintended adverse events. In the setting of accelerated vaccine development timelines, robust safety monitoring will be crucial in setting a foundation of public trust in the ultimately successful candidate vaccine.

Conclusions

As the COVID-19 pandemic continues to cause significant disruption to both the physical and economic health of the world's population, pathways of vaccine development are adapting in ways that could not have been predicted even a year ago. The rapid identification of immunogenic targets of a novel coronavirus, the leveraging of experimental vaccine platforms, and the tragic nature of an ongoing pandemic have created a fertile breeding ground for innovation. Although the ultimate success of a vaccine candidate, or candidates, remains unknown, the changes in the field of vaccinology that these exigent circumstances have brought are likely here to stay.

ARTICLE INFORMATION

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