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Perspective

# Developing Safe and Effective Covid Vaccines — Operation Warp Speed's Strategy and Approach

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Announced on May 15, Operation Warp Speed (OWS) — a partnership of the Department of Health and Human Services (HHS), the Department of Defense (DOD), and the private sector — aims to accelerate control of the Covid-19 pandemic by advancing development, manufacturing, and distribution of vaccines, therapeutics, and diagnostics. OWS is providing support to promising candidates and enabling the expeditious, parallel execution of the necessary steps toward approval or authorization of safe products by the Food and Drug Administration (FDA).

The partnership grew out of an acknowledged need to fundamentally restructure the way the U.S. government typically supports product development and vaccine distribution. The initiative was premised on setting a "stretch goal" — one that initially seemed impossible but that is becoming increasingly achievable.

The concept of an integrated structure for Covid-19 countermeasure research and development across the U.S. government was based on experience with Zika and the Zika Leadership Group led by the National Institutes of Health (NIH) and the assistant secretary for preparedness and response (ASPR). One of us (M.S.) serves as OWS chief advisor. We are drawing on expertise from the NIH, ASPR, the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research and Development Authority (BARDA), and the DOD, including the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense and the Defense Advanced Research Projects Agency. OWS has engaged experts in all critical aspects of medical countermeasure research, development, manufacturing, and distribution to work in close coordination.

The initiative set ambitious objectives: to deliver tens of millions of doses of a SARS-CoV-2 vaccine — with demonstrated safety and efficacy, and approved or authorized by the FDA for use in the U.S. population — beginning at the end of 2020 and to have as many as 300 million doses of such vaccines available and deployed by mid-2021. The pace and scope of such a vaccine effort are unprecedented. The 2014 West African Ebola virus epidemic spurred rapid vaccine development, but though preclinical data existed before the outbreak, a period of 12 months was required to progress from phase 1 first-in-human trials to phase 3 efficacy trials. OWS aims to compress this time frame even further. SARS-CoV-2 vaccine devel-

opment began in January, phase 1 clinical studies in March, and the first phase 3 trials in July. Our objectives are based on advances in vaccine platform technology, improved understanding of safe and efficacious vaccine design, and similarities between the SARS-CoV-1 and SARS-CoV-2 disease mechanisms.

OWS's role is to enable, accelerate, harmonize, and advise the companies developing the selected vaccines. The companies will execute the clinical or process development and manufacturing plans, while OWS leverages the full capacity of the U.S. government to ensure that no technical, logistic, or financial hurdles hinder vaccine development or deployment.

OWS selected vaccine candidates on the basis of four criteria. We required candidates to have robust preclinical data or early-stage clinical trial data supporting their potential for clinical safety and efficacy. Candidates had to have the potential, with our acceleration support, to enter large phase 3 field efficacy trials this summer or fall (July to November 2020) and, assuming continued active transmission of the virus, to deliver efficacy outcomes by the end of 2020 or the first half of 2021. Candidates had to be based on vaccine-platform technologies permitting fast and effective manufacturing, and their developers had to demonstrate the industrial process scalability, yields, and consistency necessary to reliably produce more than 100 million doses by mid-2021. Finally, candidates had to use one of four vaccine-platform technologies that we believe are the most likely to yield a safe and effective vaccine against Covid-19: the mRNA platform, the replication-defective live-vector platform, the recombinant-subunit-adjuvanted protein platform, or the attenuated replicating live-vector platform.

OWS's strategy relies on a few key principles. First, we sought to build a diverse project portfolio that includes two vaccine candidates based on each of the four platform technologies. Such diversification mitigates the risk of failure due to safety, efficacy, industrial manufacturability, or scheduling factors and may permit selection of the best vaccine platform for each subpopulation at risk for contracting or transmitting Covid-19, including older adults, frontline and essential workers, young adults, and pediatric populations. In addition, advancing eight vaccines in parallel will increase the chances of delivering 300 million doses in the first half of 2021.

Second, we must accelerate vaccine program development without compromising safety, efficacy, or product quality. Clinical development, process development, and manufacturing scale-up can be substantially accelerated by running all streams, fully resourced, in parallel. Doing so requires taking on substantial financial risk, as compared with the conventional sequential development approach. OWS will maximize the size of phase 3 trials (30,000 to 50,000 participants each) and optimize trial-site location by consulting daily epidemiologic and disease-forecasting models to ensure the fastest path to an efficacy readout. Such large trials also increase the safety data set for each candidate vaccine.

With heavy up-front investment, companies can conduct clinical operations and site preparation for these phase 3 efficacy trials even as they file their Investigational New Drug application (IND) for their phase 1 studies, thereby ensuring immediate initiation of phase 3 when they get a green light from the FDA. To permit appropriate comparisons among the vaccine candidates and to optimize vaccine utilization after approval by the FDA, the phase 3 trial end points and assay readouts have been harmonized through a collaborative effort involving the National Institute of Allergy and Infectious Diseases (NIAID), the Coronavirus Prevention Network, OWS, and the sponsor companies.

Finally, OWS is supporting the companies financially and technically to commence process development and scale up manufacturing while their vaccines are in preclinical or very early clinical stages. To ensure that industrial processes are set, running, and validated for FDA inspection when phase 3 trials end, OWS is also supporting facility building or refurbishing, equipment fitting, staff hiring and training, raw-material sourcing, technology transfer and validation, bulk product processing into vials, and acquisition of ample vials, syringes, and needles for each vaccine candidate. We aim to have stockpiled, at OWS's expense, a few tens of millions of vaccine doses that could be swiftly deployed once FDA approval is obtained.

This strategy aims to accelerate vaccine development without curtailing the critical steps required by sound science and regulatory standards. The FDA recently reissued guidance and standards that will be used to assess each vaccine for a Biologics License

Application (BLA). Alternatively, the agency could decide to issue an Emergency Use Authorization to permit vaccine administration before all BLA procedures are completed.

Of the eight vaccines in OWS's portfolio, six have been announced and partnerships executed with the companies: Moderna and Pfizer/BioNTech (both mRNA), AstraZeneca and Janssen (both replication-defective live-vector), and Novavax and Sanofi/GSK (both recombinant-subunit-adjuvanted protein). These candidates cover three of the four platform technologies and are currently in clinical trials. The remaining two candidates will enter trials soon.

Moderna developed its RNA vaccine in collaboration with the NIAID, began its phase 1 trial in March, recently published encouraging safety and immunogenicity data,[1] and entered phase 3 on July 27. Pfizer and BioNTech's RNA vaccine also produced encouraging phase 1 results[2] and started its phase 3 trial on July 27. The ChAdOx replication-defective live-vector vaccine developed by AstraZeneca and Oxford University is in phase 3 trials in the United Kingdom, Brazil, and South Africa, and it should enter U.S. phase 3 trials in August.[3] The Janssen Ad26 Covid-19 replication-defective live-vector vaccine has demonstrated excellent protection in nonhuman primate models and began its U.S. phase 1 trial on July 27; it should be in phase 3 trials in mid-September. Novavax completed a phase 1 trial of its recombinant-subunit-adjuvanted protein vaccine in Australia and should enter phase 3 trials in the United States by the end of September.[4] Sanofi/GSK is completing preclinical development steps and plans to commence a phase 1 trial in early September and to be well into phase 3 by year's end.[5]

On the process-development front, the RNA vaccines are already being manufactured at scale. The other candidates are well advanced in their scale-up development, and manufacturing sites are being refurbished.

While development and manufacturing proceed, the HHS–DOD partnership is laying the groundwork for vaccine distribution, subpopulation prioritization, financing, and logistic support. We are working with bioethicists and experts from the NIH, the CDC, BARDA, and the Centers for Medicare and Medicaid Services to address these critical issues. We will receive recommendations from the CDC Advisory Committee on Immunization Practices, and we are working to ensure that the most vulnerable and at-risk persons will receive vaccine doses once they are ready. Prioritization will also depend on the relative performance of each vaccine and its suitability for particular populations. Because some technologies have limited previous data on safety in humans, the long-term safety of these vaccines will be carefully assessed using pharmacovigilance surveillance strategies.

No scientific enterprise could guarantee success by January 2021, but the strategic decisions and choices we've made, the support the government has provided, and the accomplishments to date make us optimistic that we will succeed in this unprecedented endeavor.

Disclosure forms provided by the authors are available at NEJM.org.

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