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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Evaluating and Deploying Covid-19 Vaccines — The Importance of Transparency, Scientific Integrity, and Public Trust

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An unprecedented effort is under way to rapidly develop Covid-19 vaccines, with pharmaceutical companies, academic researchers, and government agencies aiming to compress into several months a process that typically requires at least several years. This work is supported by extraordinary public and private investments and by newly created entities such as Operation Warp Speed. Concurrent with clinical testing of vaccine candidates, new mechanisms are being established to expedite manufacturing ahead of a future vaccination campaign. Critical decisions will

soon need to be made, including evaluations of data on vaccine safety and efficacy, which could lead to the approval of one or more products and the development of recommendations for deployment.

Although new entities and investments have aided the pursuit of Covid-19 vaccines thus far, regulatory and policymaking activities are well within the capabilities of the existing, well-established processes and personnel at the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC), each of which is supported by long-standing committees of independent scientific advisors. Relying on these highly regarded, time-tested mechanisms for evaluating and regulating vaccines and for developing recommendations for their use would promote transparency, independence, and scientific integrity.

With phase 3 clinical trials of Covid-19 vaccine candidates under way, safety and efficacy data will be presented to the FDA as early as this fall. Decisions regarding approvals and Emergency Use Authorizations (EUAs) will be made by the FDA's Center for Biologics Evaluation and Research (CBER), which in June 2020 released detailed guidance on Covid-19 vaccine development.[1] Since 1981, CBER's decision making has been supported by the Vaccines and Related Biological Products Advisory Committee (VRBPAC), a panel of nongovernment scientists, physicians, and other experts that reviews evidence for vaccine candidates — including their benefits and risks — and makes recommendations regarding approval.

As is the case with all FDA advisory committees, the work of the VRBPAC expands the expertise that informs decision making and is thought to enhance the transparency and legitimacy of the FDA's decisions.[2] The VRBPAC meets openly, as required by the Federal Advisory Committee Act (FACA), which allows the public to view trial data, observe deliberations, and comment on products under consideration. Meetings may be scheduled far in advance, but even the required 15-day minimum-notice period can be waived in exceptional circumstances. Although the FDA isn't obligated to follow recommendations from the VRBPAC and other advisory committees, it usually does.

Concerns have been raised over the possibility of interference in the FDA's decision-making process for Covid-19 vaccines for the purpose of meeting politically advantageous timetables for vaccine introduction. More generally, the pace of vaccine development — even the name "Operation Warp Speed" — could be interpreted as suggesting that corners are being cut with regard to safety and efficacy. FDA officials have sought to dispel both concerns, stating that decisions will be made independently based solely on science and that there will be no compromises with respect to evidence standards required for approval or an EUA.[3]

These assurances of independence and rigor would be enhanced by steps reflecting these principles, including the participation of the VRBPAC in the review of Covid-19 vaccines. The FDA isn't legally required to convene the committee, but not to do so in this case would be a marked departure from normal practices. FDA leaders recently commented that transparent discussion about Covid-19 vaccines by the VRBPAC will be needed to ensure public understanding of evidence regarding safety and efficacy.[3]

On August 6, 2020, Representative Raja Krishnamoorthi (D-IL) introduced legislation that would require the FDA, before licensing or authorizing any Covid-19 vaccine, to receive recommendations from the VRBPAC in public and to make all data provided to the committee publicly available. Separate, bipartisan legislation introduced on August 4 by Senators Maggie Hassan (D-NH), Mike Braun (R-IN), and Lisa Murkowski (R-AK) would require the VRBPAC to meet and provide recommendations before issuing an EUA for a Covid-19 vaccine. If either bill is passed, it would be a rare case of direct congressional intervention in the FDA review process for specific products. But such bills would merely affirm and codify the FDA's traditional process for including the VRBPAC in its work — a process that FDA leaders have indicated that they anticipate following for Covid-19 vaccines. Such procedural safeguards would strengthen the FDA's independence if it were to face external pressure to deviate from its customary evidence-review practices in the months ahead.

Meanwhile, several groups are developing recommendations for vaccine deployment, particularly for the initial stages of a vaccination campaign, when supplies will be limited. The CDC's Advisory Committee on Immunization Practices (ACIP), another panel of federal advisors, has been the primary U.S. body responsible for establishing guidelines for vaccine use since 1964. ACIP rec-

ommendations are widely considered the standard for expert advice regarding vaccination.[4]

The committee's work has long included the identification of priority groups for vaccine allocation when supplies are limited. Since April, a Covid-19 workgroup composed of ACIP committee members, liaisons from medical professional organizations, CDC staff, and outside consultants has been discussing the development of prioritization guidance, prelicensure and postlicensure safety and effectiveness monitoring needs, and related issues. The workgroup meets weekly in private and presents its ongoing work at meetings of the full ACIP — all of which are public, as dictated by FACA requirements — for the committee's consideration. The ACIP typically meets three times per year but is meeting monthly during the pandemic.

It is unclear, however, whether the ACIP will play its traditional role by establishing guidelines for Covid-19 vaccine prioritization and deployment. In July, the National Academies of Sciences, Engineering, and Medicine (NASEM) established a committee charged with creating a framework for the equitable allocation of Covid-19 vaccines that includes priority tiers. The stated directive for the group's work is to inform that of the ACIP, not replace it. How the two committees will interact, and the consequences if their prioritization schemes differ — particularly for public understanding and support for government-led vaccination efforts — remain unresolved. Unlike the ACIP, NASEM committees are largely exempt from FACA requirements.[5] Although information-gathering meetings are generally open to the public and committee conclusions are publicly released, NASEM committee deliberations occur in private.

An audio interview with Dr. Schwartz is available at NEJM.org

Moreover, the leaders of Operation Warp Speed, which will coordinate many of the logistic aspects of vaccine distribution, have yet to indicate publicly the degree to which they intend to defer to other groups regarding allocation decisions. Difficulties surrounding the distribution of other scarce medical resources during the pandemic — including personal protective equipment and the antiviral medication remdesivir — underscore the importance of establishing clear lines of organizational responsibility and evidence-based approaches to directing vaccines to the populations and locations where they can do the most good. The 2009 H1N1 influenza vaccination program, a CDC-led effort that relied on existing vaccine-distribution infrastructure and the ACIP's prioritization guidance, offers a contrast to the more diffuse approach to planning regarding Covid-19 vaccine allocation and distribution.

Progress on Covid-19 vaccine development has been remarkable, but translating promising clinical trial results into successful vaccination programs will require overcoming a new set of challenges. Although the government's willingness to rapidly innovate has facilitated advances thus far, aspects of the regulation and policy work ahead wouldn't be as well served by deviating from well-established practices. The evaluation of Covid-19 vaccine candidates and the development of recommendations are appropriate activities for the FDA's and CDC's traditional evidence-review processes.

Public confidence in vaccination is fragile. Covid-19 vaccination programs will succeed only if there is widespread belief that available vaccines are safe and effective and that policies for prioritizing their distribution are equitable and evidence-based. Trust in science and expertise are threatened, as the pandemic has shown with catastrophic results. Relying on nonpartisan government scientists, their expert advisors, and the transparent, science-based processes that have served U.S. vaccination-related activities exceedingly well for generations would provide the best chance for Covid-19 vaccines to realize the high hopes for their role in addressing the current public health crisis.

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