Evaluating SARS-CoV-2 Vaccines After Emergency Use Authorization or Licensing of Initial Candidate Vaccines

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The US Food and Drug Administration (FDA) will likely issue emergency use authorizations for 2 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one developed jointly by Pfizer and BioNTech and the other by Moderna. According to company press releases and data made available by the FDA, both vaccines have shown approximately 95% efficacy in preventing symptomatic COVID-19 infections in phase 3 trials, without significant safety concerns that might hinder authorization by the FDA. Additional phase 3 trials of vaccines manufactured by Janssen and AstraZeneca are underway; with rapidly rising case counts in the US, initial results from those trials may not be far behind. All of these trials compare the incidence of symptomatic infection among vaccine recipients with that among a placebo control group. However, once authorized vaccines become widely available, conducting placebo-controlled trials of subsequent vaccine candidates may become challenging. Alternative strategies to evaluate those vaccines, and to compare their safety and efficacy with those of authorized products, are needed.

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Potential Strategies to Study Future SARS-CoV-2 Vaccines

The most scientifically rigorous way to study vaccines that have not yet entered clinical trials is to conduct randomized, blinded clinical trials that compare the vaccines with placebo controls. Influential groups have called for the use of such trials to evaluate novel candidates as well as to continue to gather data on early vaccines, even after they receive authorization or licensing approval. This strategy may be tenable for a brief period, while access to emergency-authorized vaccines is limited and only selected subpopulations such as front-line health care workers and residents of nursing homes can be vaccinated. However, once authorized vaccines become available in sufficient quantities to begin immunizing broader groups at high risk of severe disease, such as community-dwelling older people and persons with comorbidities, it may no longer be feasible or ethical to include such individuals in placebo-controlled trials. Given the importance of evaluating vaccine efficacy and safety in high-risk subgroups, excluding them from placebo-controlled trials will substantially diminish the value of those trials.

A second strategy, which the FDA contemplates in its guidance once immunologic correlates of efficacy such as levels of antibodies to vaccine antigens are established, is to administer experimental vaccines to groups of participants and to then base decisions to authorize or approve those vaccines on surrogate measures. However, adequate evidence is not yet available to define what constitutes a validated surrogate marker of vaccine efficacy. In addition, evaluating efficacy alone will not suffice; determining safety, which requires comparative trials involving large numbers of participants, is equally critical. Thus, at least in the near term, trials based on surrogate measures of efficacy are not a viable approach.

A third strategy is to conduct head-to-head randomized trials comparing a novel vaccine candidate with a vaccine that has previously received emergency authorization or full licensure. Such trials could use noninferiority designs that could declare the novel vaccine effective if the incidence of symptomatic COVID-19 infection or other primary end point is not higher by some specified margin than incidence in the comparator group. These trials also could facilitate direct comparisons of safety between the novel vaccine and its established comparator; such comparisons are of particular importance given widespread public concerns about safety. Interpretation of such trials would require confidence that historical efficacy estimates of the comparator vaccine from prior trials also hold true in the current trial. The high reported efficacy of the vaccines from Pfizer/BioNTech and Moderna provide reassurance that, if the infection rate in the novel vaccine group was shown to be noninferior to the rate in the comparator group, it would be possible to conclude that the novel vaccine was effective even without a placebo control group to allow direct inferences (in other words, that the trial had assay sensitivity). Conducting such a trial would hinge on cooperation between the manufacturer of the novel vaccine and the manufacturer of the established vaccine, a requirement that poses both logistical and financial challenges.

The fourth strategy, and the one that would be most valuable from a scientific and public health point of view, would be to initiate a multigroup platform trial that tests authorized or approved vaccines alongside novel, as-yet-unauthorized vaccine candidates. Such a trial, which could be conducted under the auspices of Operation Warp Speed, would allow for direct comparisons of efficacy and safety among established as well as investigational vaccines. Investigational vaccine groups would be added to the platform as soon as the candidate vaccines met safety and immunogenicity benchmarks in smaller, earlier-phase trials. Based on interim safety and
efficacy analyses, candidate vaccines would be dropped from the platform and their development discontinued using an adaptive design if they proved to have inferior efficacy or significant safety concerns as measured against benchmark comparators. Conversely, once reassuring initial safety and efficacy data were available, enrollment in novel vaccine groups could be extended to children and other populations that have largely been excluded from current phase 3 trials. Adaptive designs have been used in other COVID-19-related settings, such as the evaluation of therapeutic agents for patients hospitalized with serious disease.10

Advantages of a Platform-Trial Approach
A platform trial that includes both established and investigational vaccine groups would have numerous benefits. First, it could provide an efficient mechanism for evaluating novel vaccines in the setting of available alternatives and ethical reservations about inclusion of placebo control groups. Second, it could allow for comparative safety and effectiveness evaluation not only of novel vaccines but also of those that have previously been compared only with placebo. Third, particularly while access to authorized vaccines is limited, offering priority access to individuals willing to enroll in the platform trial and thereby to contribute to the generation of critical public health data would promote rapid accrual. Fourth, the federal government could leverage the substantial taxpayer investment in vaccine development and the infrastructure that Operation Warp Speed has built—including the COVID-19 Prevention Trials Network and a single independent data and safety monitoring board—to encourage manufacturers to cooperate and to facilitate enrollment of large numbers of participants reflective of the diversity of the US.

Conclusions
The rapid and, to date, highly successful development of vaccines to prevent COVID-19 represents a scientific triumph. At the same time, there remains a need to develop additional vaccines, some of which may be preferable for reasons of safety, efficacy, subgroup advantages, or logistics, that may offer alternatives to those that are first authorized for use or licensed. Yet the existence of highly effective, safe vaccines that have received emergency use authorization or approval by the FDA will complicate the testing of subsequent vaccines. An adaptive platform trial that provides data on the safety and efficacy of investigational vaccines while simultaneously allowing comparative assessment of authorized or approved vaccines could represent the optimal way to move the COVID-19 vaccine testing enterprise into its next phase.

ARTICLE INFORMATION
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REFERENCES