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EDITORIAL

U.S. COVID-19 Vaccination Challenges Go Beyond Supply

A trio of current *Annals* articles each takes a different route to the same conclusion: Using initial supplies of coronavirus disease 2019 (COVID-19) vaccines to immunize as many persons as possible with a single-dose regimen may achieve more benefit than a more effective 2-dose regimen in a smaller population.

The model of Paltiel and colleagues (1) makes the case for a single-dose vaccine, even if it is somewhat less effective than a 2-dose regimen of another vaccine. Barnabas and Wald (2) argue for single-dose immunization campaigns involving the Pfizer/BioNTech and Moderna vaccines, despite the absence of long-term efficacy data from clinical trials. The model from Tuite and colleagues (3) questions the practice of reserving the second dose for every person immunized.

In large-scale trials with tens of thousands of participants, the 2-dose regimens of the Pfizer/BioNTech and Moderna vaccines both demonstrated about 95% efficacy in preventing COVID-19. These studies were designed to test a 2-dose regimen, but the data reported to the U.S. Food and Drug Administration (FDA) raised the possibility that even a single dose of these vaccines might offer a clinically significant, albeit lower, level of protection against the disease. The FDA has issued emergency use authorization for a 2-dose regimen of these vaccines, a prime and a booster, 21 days apart for the Pfizer/BioNTech vaccine and 28 days apart for the Moderna vaccine.

In a public health emergency, a powerful argument exists for doing something with less-than-perfect results if it can help more persons quickly. However, whether alternative approaches with current vaccines would accomplish this goal is far from clear.

Several constraints stand in the way of getting COVID-19 vaccine doses into the arms of the persons who stand to benefit most from them. *Supply constraints* in the production and procurement of vaccine doses, as well as vials, syringes, and other vaccine-related materials, limit or delay their availability to patients and providers. *Administration constraints* are obstacles that emerge in the distribution and administration of the vaccines to patients. *Demand constraints* reflect the hurdles that exist in vaccinating members of high-risk and high-priority populations who may be reluctant to be vaccinated.

A single-dose regimen of the current vaccines that offers a lower but still substantial level of protection against COVID-19 may alleviate vaccine supply constraints, but may do so at the expense of aggravating the demand and administration constraints that present the greater hurdle to vaccinating vulnerable groups in the United States. The United States has historically struggled to vaccinate adults. In the pastdecade, the rate of seasonal influenza vaccination among U.S. adults has never exceeded 50%. Coverage rates for seasonal influenza have been even lower for Black and Latinx Americans and high-risk adults between the ages of 18 and 49 years (4). During the last pandemic for which there was a vaccine—the 2009 H1N1 pandemic—only 22.7% of American adults were vaccinated (5). After months of wariness, recent polls show that interest in receiving COVID-19 vaccines is finally rising among Americans, including Black and Latinx populations, in part because of the news that clinical trials showed the Pfizer/BioNTech and Moderna vaccines to be highly effective (6). Offering reluctant populations a less effective regimen of a vaccine, or failing to offer its second dose on schedule, may cause confusion, create a multitiered system of vaccine access, and exacerbate historical concerns that certain groups are more likely to receive substandard care.

In the United States, COVID-19 vaccine administration will depend on the same overworked and underresourced U.S. state, local, and tribal public health systems that have delivered H1N1 and seasonal flu vaccines. Despite months of pleas for at least $6 billion to prepare state and local governments for what will be the largest vaccination campaign in U.S. history, Congress only recently appropriated the necessary funds, and it will be weeks more before those federal resources are distributed and put to good use. In the interim, administration will continue to be a greater challenge than limited doses in the early roll-out of COVID-19 vaccines. As of December 30, the Centers for Disease Control and Prevention reported that only 2.6 million of the 12.4 million vaccine doses distributed had been administered to U.S. patients (7).

The United States is unfortunately demonstrating the public health axiom that what saves lives is the practice of vaccination, not just the existence of vaccines. The immediate task facing the public health system is to deliver vaccines swiftly and surely to high-priority populations and, in the process, to build momentum and confidence. There are no short cuts to inspiring trust among those at greatest risk, developing and implementing an effective vaccination program, and monitoring for safety and effectiveness over time. Models of alternative strategies—particularly those that make large assumptions about vaccine efficacy in the absence of reliable data—should not drive policy without a full consideration of the challenges of implementation and potential unintended effects.

Ideas for stretching vaccine supplies may yet have utility, but they will have greater application when and where supply constraints are the rate-limiting steps. There is no shortage of those settings, because a few wealthy nations, including the United States, have already purchased most early supplies of the most promising COVID-19 vaccines (8). Yet, a moment may soon arrive when COVID-19 vaccine supplies are a greater limitation on U.S. vaccination than at present; therefore, considering various alternative approaches is worthwhile. For now, the priority should be to grow the evidence base by pursuing clinical testing and observational studies to

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determine whether a single dose or a delayed second dose of the current vaccines will generate immunity similar to that of the FDA-authorized 2-dose regimen. Supported by strong public health systems, rapid vaccine production, and equitable vaccine distribution within the United States and around the world, vaccination strategies driven by data can bring an end to COVID-19.

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