At the forefront of innovations during the coronavirus disease 2019 (COVID-19) pandemic is the design and testing of the Pfizer-BioNTech and Moderna mRNA vaccines, both of which have extremely high efficacy in the prevention of COVID-19 after 2 doses given 21 to 28 days apart. These vaccines were administered to thousands of people in placebo-controlled randomized trials; the rollout to high-risk persons has begun in the United Kingdom, the United States, and Canada.

The next critical step is population-wide delivery of COVID-19 vaccination to maximally reduce morbidity and mortality. Regardless of the extent to which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination decreases transmission in addition to disease, a public health COVID-19 vaccination strategy should aim to maximize the health gains for every vaccine dose.

Efficacy for prevention of COVID-19 after a single dose but before the second dose of the Pfizer-BioNTech mRNA vaccine was reported at 52% (95% CI, 30% to 68%) based on 39 cases in the vaccine group and 82 in the placebo group (1). Longer-term data on 1 dose are not yet available, and because most (98%) people in the clinical trial received the second dose, data on a single dose from this clinical trial will remain sparse. Similarly, the Moderna mRNA vaccine reported 51% (CI, −53.6% to 86.6%) vaccine efficacy in the first 14 days after the first dose, with 5 cases in the vaccine group and 11 in the placebo group (2). Further, a single dose of the Moderna vaccine decreased asymptomatic SARS-CoV-2 infections by two thirds. This substantial efficacy—above the 50th percentile threshold put forth by the U.S. Food and Drug Administration (FDA) as the minimum threshold for efficacy—was noted in the initial 2 to 3 weeks after the first injection. Because we do not expect a protective immune response in the initial 14 days after immunization, this suggests that once immune response is more mature, the efficacy of a single dose may be higher than 51%. In fact, the survival curves for the cumulative incidence of COVID-19 in the trial separate at about 10 days, consistent with high efficacy once immunity to the first dose is induced.

Currently, 3 million doses of vaccine are being shipped throughout the United States, with an equal number being held back to maintain sufficient supply for the second dose. We propose that priority should be given to providing a single dose to as many people as possible, rather than emphasizing the 2-dose vaccination. The Table lists pros and cons for each strategy.

Our rationale for single-dose COVID-19 vaccination is 4-fold. First, doubling the vaccine coverage with a single dose compared with a 2-dose regimen will accelerate pandemic control. At the start of the SARS-CoV-2 pandemic, the basic reproductive number $R_0$ (the number of secondary infections in an entirely susceptible population) was between 2.5 and 3.5 (3). Currently, the effective reproductive number $R_e$ (the number of secondary infections with infectious and susceptible individuals in the population) for SARS-CoV-2 hovers around 1 in most communities due to transmission mitigation strategies. Thus, even lack of complete protection on an individual level is likely to lower it sufficiently to achieve the $R_e$ less than 1 required to stop epidemic growth. With heterogeneities in mixing within the population such that similar people mix with each other rather than at random, and with physical distancing, mask use, and mobility restrictions, the proportion requiring vaccination to reach herd immunity is likely to be lower than originally estimated (4). Given the uneven spread of the infection and the high potential for super-spreading events, providing partial protection to many is likely to be more effective than providing complete protection of a smaller subset of the population. A single-dose SARS-CoV-2 vaccine approach deals directly with the shortage of vaccines by vaccinating twice the number of people while maximizing the probability of achieving herd immunity.

Second, providing effective protection for as many people as soon as possible is more ethical because it distributes the scarce commodity more justly. A single-dose COVID-19 vaccination approach would follow the Advisory Committee on Immunization Practices’ (ACIP) ethical principles for allocating initial supplies of the COVID-19 vaccine to 1) maximize benefits and minimize harms, 2) promote justice, 3) mitigate health inequities, and 4) promote transparency (5). With administering only a single dose of SARS-CoV-2 vaccine initially, twice the number of people could receive the vaccine and reduce harm from COVID-19. With limited vaccine supply, this could avoid potential exacerbation of health disparities and the creation of new ones.

Third, a single-dose vaccine approach could mitigate the higher incidence of many vaccine-associated adverse events seen with the second vaccine dose, increasing tolerability and thus likely acceptability in the general population. Reports from both vaccines have higher rates of systemic adverse events within 7 days after the second dose compared with the first dose (1, 2). Fever, fatigue, headaches, chills, myalgias, or arthralgias were reported, with some participants taking a day off from work to recover.

Lastly, concern about behavioral disinhibition after immunization, such as abandoning masks and distancing, has been voiced. In fact, our own medical colleagues

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have voiced the hope that they will no longer need to wear personal protective equipment after receipt of such an effective vaccine. Thus, a vaccine that is only partly protective may ensure continued adherence to other mitigation strategies that will continue to be critical for many months to come.

There is precedent for reduced-dose vaccine strategies to save lives during epidemics. In 2016, during a yellow fever outbreak in Kinshasa, Democratic Republic of the Congo, the global supply of yellow fever vaccines was insufficient to provide full-dose vaccination to millions of people. To mitigate the shortage, a fractional-dosing strategy was used to maximize the number of people receiving the yellow fever vaccination (6). Since then, the results of fractional-dosing trials for yellow fever have been encouraging and the fractional-dosing approach has demonstrated protective, durable vaccine responses.

We acknowledge that detailed data on the efficacy of a single-dose vaccine are not available, including the very important question on protection from severe disease; data on effect on transmission are not available for any dose. The FDA has issued an emergency use authorization with an indication for a 2-dose vaccine, reflecting the design of the pivotal clinical trials. We agree that the 2-dose regimen in the initial clinical trials was preferable as the possibility for protection after immunization had to be demonstrated. However, public health bodies have flexibility in their authority to recommend and implement a vaccination program that does not stringently reflect the product label. Further, evaluation of a delayed, second-dose approach in high-incidence settings would contribute data on the effectiveness of single-dose vaccination. Use of a single dose of the Pfizer-BioNTech and Moderna COVID-19 vaccines should be considered.

From University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington (R.V.B., A.W.).

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Corresponding Author: Ruanne V. Barnabas, MBChB, MSc, DPhil, University of Washington, Box 359927, 325 Ninth Avenue, Seattle, WA 98104-2499; e-mail, rbarnaba@uw.edu.

Current author addresses and author contributions are available at Annals.org.

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| Table. Pros and Cons of Two-Dose Versus Single-Dose Vaccination Strategy |
|-----------------------------|-----------------------------|
| **Vaccination Strategy**    | **Pros**                    | **Cons**                                                      |
| 2-dose vaccine              | Very high efficacy          | Requires delivery of 2 doses                                  |
|                             | Closely mirrors the clinical trial | May exacerbate inequities                                    |
|                             | Prevents severe disease     | May lead to behavioral disinhibition                          |
|                             |                             | Doubles time required for a critical proportion of the population to be vaccinated |
| Single-dose vaccine         | Higher proportion of population protected | Partial efficacy                                           |
|                             | Promotes equity             |                                                          |
|                             | Reduces sequelae of reactogenicity |                                                    |
|                             | Potential to accelerate pandemic control |                                                    |
Current Author Addresses: Dr. Barnabas: University of Washington, Box 359927, 325 Ninth Avenue, Seattle, WA 98104-2499. Dr. Wald: University of Washington, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98122.

Author Contributions: Conception and design: A. Wald. Analysis and interpretation of the data: R.V. Barnabas, A. Wald. Drafting of the article: R.V. Barnabas, A. Wald. Critical revision for important intellectual content: R.V. Barnabas, A. Wald. Final approval of the article: R.V. Barnabas, A. Wald.