CLINICAL DECISIONS
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Delayed Second Dose versus Standard Regimen for Covid-19 Vaccination

This interactive feature addresses the approach to a clinical policy issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Task Force on Administration of Covid-19 Vaccine

Siri R. Kadire, M.D.

You chair the Governor's task force on rollout of the Covid-19 vaccine. Given concerns about the limited availability of the two-dose mRNA vaccine, you have been asked to weigh in on the debate regarding the most effective use of the currently available doses. Should people who have already received a first dose of vaccine have their second dose delayed by a number of months until there is a greater supply, so that more people can receive a first dose? Or should those who have gotten the first dose receive the second dose according to the standard schedule, 3 to 4 weeks after the first dose, as recommended by the Food and Drug Administration (FDA)? You must consider the benefits and risks of the two approaches, on both individual and population levels, and decide what to recommend to the task force.

TREATMENT OPTIONS

Which one of the following approaches would you take? Base your choice on the literature, your own experience, published guidelines, and other information sources.

1. **Recommend delaying the second dose.**
2. **Recommend following the standard regimen.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

OPTION 1

Recommend Delaying the Second Dose

Robert M. Wachter, M.D.

The clinical trials of the Pfizer–BioNTech and Moderna vaccines involved two injections given 3 to 4 weeks apart. Both vaccines had approximately 95% efficacy after the second dose — an impressive finding.[1-2]

Under normal circumstances, the vaccines should be deployed in keeping with the trial protocols. However, the current circumstances — a slow vaccine rollout, a limited vaccine supply, and the recent emergence of more infectious SARS-CoV-2 variants that threaten to outpace our vaccination program — are anything but normal. This may be a case in which the risks of strict adherence to the plan outweigh the risks of modifying it.

Some argue that any deviation from the protocol used in the clinical trials is unscientific. But the argument is based on an overly narrow definition of science. In both trials, the cases in the placebo and active vaccine groups began to diverge about 10 days after the first dose, with growing vaccine efficacy over time. By the day of the injection of the second dose, the efficacy of the first dose was somewhere in the range of 80 to 90%.[1,2]

Why consider delaying the second vaccine dose? First, with Covid-19 currently killing approximately 3000 people in the United States per day, we face a crucial tradeoff: do we use our limited vaccination capacity to increase the protection of persons who have received a first dose

from approximately 85% (after dose one) to 95% (after dose two) by administering a second dose? Or do we use that same capacity to take a similar number of people from an unprotected state to one in which they are 80 to 90% protected? One model shows that the expected number of Covid-19 cases would be significantly lower if more people were given a first dose, even if it came at the cost of deferring the second doses.[3]

Second, we have recently seen the emergence of several viral variants, with one (B.1.1.7, often referred to as the U.K. variant) that is approximately 50% more infectious than the native coronavirus.[4] This variant rapidly became the dominant strain in much of England, and the Centers for Disease Control and Prevention (CDC) now predicts the same for the United States in the next 6 weeks.[5] This prospect further increases the imperative to vaccinate the population, particularly people at high risk, more quickly.

Are there potential risks from delaying the second dose? Sure. It is possible that the second dose will be less effective when given later, though few scientists believe this will be the case.[6] Immunity may begin to wane between the first dose and a delayed second dose, although the rarity of recurrent infections probably means that immunity, at least that created by native infection, lasts for much longer than 3 months.[7] Some people may forget to return for their second dose after a longer delay, though a reminder system that works for a return in 3 to 4 weeks should work a month or two later. It is possible that some people will be confused by a change in the vaccine schedule, and the confusion may lead them to eschew vaccination altogether or believe that they need only a single dose. The probability of this is hard to quantify, though it can most likely be addressed with a strong messaging campaign. Finally, some experts have warned that partial vaccination leading to a less robust immune response may increase the risk of mutations, which, as we've seen, can lead to variants with more problematic characteristics.[8] This too is hard to quantify.

Although there are risks to the strategy of a delayed second dose, the benefits of giving far more people a first dose sooner merit strong consideration of the strategy, particularly since the vaccine shortage is likely to ease by late spring. On December 30, 2020, the United Kingdom endorsed the delayed-second-dose approach.[6] And on January 21, 2021, the CDC liberalized its guidance regarding the timing of the second dose, saying for the first time that a delay of up to 6 weeks after dose one would be acceptable.[9] These moves toward a more flexible approach seem wise.

Although sticking with the plan is always comforting, our current Covid-19 crisis offers a classic case in which the plan — by protecting too few people too slowly, in the face of a growing threat — may represent the riskier option. Of course, any deviation in the protocol should be rigorously and rapidly studied, and second doses should be administered promptly as the vaccine supply becomes more abundant.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend Following the Standard Regimen

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Public health leaders must make the best decisions they can with the available science, balancing population health, social and economic concerns, and the need to maintain public trust. Data for decision making are rarely available when needed, but the "retrospect-o-scope" is always ready to judge decisions that have been made. U.S. science agencies (the National Institutes of Health, the FDA, and the CDC) and vaccine developers alike are committed to making Covid-19 vaccine recommendations that are guided by science.

My recommendation is that at this time in the United States, we should not delay the second dose of mRNA vaccine beyond the intervals evaluated for their emergency use authorization. Although the immune response to the first dose is unlikely to degrade quickly, it is incomplete, and there are no data to inform how long a second dose could be delayed without compromising effectiveness. We don't even know the duration of immunity produced by the two-dose regimen or how dose timing affects immunity in elderly and immunocompromised persons, who account for most hospitalizations and deaths. Substantially delaying a second dose might si-

multaneously leave these people inadequately protected and impede progress toward the goal of alleviating the surge in hospitalizations.

Populations essential to social and economic functioning, such as frontline health care personnel and other essential workers, need assurance that if they get vaccinated, they can expect a high level of protection and can work more safely. Delaying a second dose cannot provide that assurance and may have an untoward impact on their future willingness to work or to be vaccinated.

Some models have suggested that using a less effective vaccine or delaying a second dose to provide first doses to more people will end the pandemic sooner.[10,11] However, these models do not account for the potential degradation of the immune response or for spillover effects of such decisions on vaccine acceptance. Many people are skeptical of vaccines, fearing that the speed of development has necessitated cutting corners and that political pressure has influenced vaccine recommendations. Suddenly changing dosing recommendations puts public confidence at serious risk and will impede willingness to be vaccinated at all. Cases of Covid-19 have already occurred in vaccine recipients, as was seen in the phase 3 trials, which will raise questions about the delayed-second-dose strategy and erode trust in the vaccine rollout. If these breakthrough cases appear to occur more frequently before the second, delayed dose, confidence will be further compromised, ultimately delaying the end of the pandemic and social and economic recovery.

The appearance of SARS-CoV-2 variants implies that the virus is under evolutionary pressure. Some have postulated — although this is speculative — that subinhibitory levels of antibody response before a second dose, if widespread, could contribute to selection of antigenic variants that could escape current vaccines.[12] Even though we now know how to make Covid-19 vaccines, designing, testing, manufacturing, and administering a vaccine against a new variant will take time and will be challenging.

Currently, our nation is unable to rapidly administer the doses it has. It is likely that supply constraints will ease within a month or two, as manufacturing becomes more efficient, and other vaccines will probably become available. Meanwhile, vaccines are not the only tool for quashing this pandemic. In the short term, adherence to basic public health measures is projected to save 1.5 times as many lives as vaccines.[13] While we ramp up vaccination, I would strongly urge that we use science to rapidly evaluate alternative approaches to expanding the vaccine supply (e.g., delayed second dose, half-dose, and use of adjuvants that could increase dose-sparing) to answer critical questions for now and in anticipation of new, vaccine-resistant strains.

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From the Coalition for Epidemic Preparedness Innovations, Oslo.

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