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OPINION

Can We Do Twice as Many Vaccinations as We Thought?

Data suggests significant protection even without a second shot. If studies prove that's true, it could be a game changer.

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By Zeynep Tufekci and Michael Mina

Dr. Tufekci, a contributing opinion writer, has written extensively about the pandemic. Dr. Mina is an assistant professor of epidemiology at the Harvard T.H. Chan School of Public Health.

It's been a very good month for Covid-19 vaccines. Last week, the Food and Drug Administration provided an emergency authorization for a vaccine produced by Pfizer-BioNTech. On Thursday, an advisory committee recommended authorizing a vaccine by Moderna, and the F.D.A. is expected to authorize it soon.

These vaccines are a triumph. In large-scale trials with tens of thousands of participants, both demonstrated around 95 percent efficacy in preventing Covid-19 — a stunning number exceeding our best hopes.

Both vaccines are supposed to be administered in two doses, a prime and a booster, 21 days apart for Pfizer and 28 days for Moderna. However, in data provided to the F.D.A., there are clues for a tantalizing possibility: that even a single dose may provide significant levels of protection against the disease.

If that's shown to be the case, this would be a game changer, allowing us to vaccinate up to twice the number of people and greatly alleviating the suffering not just in the United States, but also in countries where vaccine shortages may take years to resolve.

But to get there — to test this possibility — we must act fast and must quickly acquire more data.

For both vaccines, the sharp drop in disease in the vaccinated group started about 10 to 14 days after the first dose, before receiving the second. Moderna reported the initial dose to be 92.1 percent efficacious in preventing Covid-19 starting two weeks after the initial shot, when the immune system effects from the vaccine kick in, before the second injection on the 28th day.

That raises the question of whether we should already be administrating only a single dose. But while the data is suggestive, it is also limited; important questions remain, and approval would require high standards and more trials.

First, the science. While the vaccine trials were designed to evaluate a two-dose regimen, some immunity might be acquired before a second dose is administered. We know, for instance, that a Covid-19 infection appears to yield protection for at least five to seven months. While infections are not vaccinations, and while we need more data on this, it's plausible that the immunity gained from a vaccination may turn out to be even stronger than what comes from an infection. The reason we do a second — booster — vaccination is that these later doses help to solidify immune memory, in part by giving extra training to the cells that produce antibodies, a process called affinity maturation. But this process begins with the single dose, and the evidence collected between the time of the first and second doses in tens of thousands of people in the Phase 3 trials suggests that the level of affinity maturation *may* provide enough protection to meet the standards we have set for vaccine approval during this pandemic even without the second dose.

While we know that the single dose can protect against disease, we don't yet know how long this immune protection will last, and at what level. However, there is no rule that says that vaccines must be boosted within weeks of each other. For measles, the booster dose is given years after the first dose. If the booster dose could be given six months or a year after the first dose, while maintaining high efficacy before the second dose, that would allow twice as many people to get vaccinated between now and later next year, accelerating herd immunity — greatly helping to end the crisis phase of the pandemic in the United States.

How would we go about being more sure and getting the proper authorizations? First, we should look at what data we do have. In both trials, a number of people dropped out before getting the second dose. While these are small but nonrandom samples, we could follow up to see what happened to these people. Lack of infection among this smaller group would not be sufficient to give us the green light we need, but a spike of infections would be a reason for caution.

Crucially, though, we should begin immediate single-dose trials, recruiting volunteers from low-risk populations who are first in line for the vaccinations. For example, among health care workers protective equipment works, rates of infection among this group have fallen sharply and severe disease is much more rare.Younger essential

workers without risk factors are less likely to be severely affected if they are exposed since this disease's impact rises steeply with age. Just as tens of thousands of people volunteered for the earlier vaccine trials, many may well volunteer to test a placebo against a second dose, allowing us to quickly ascertain questions of durability and effectiveness of the single dose.

Is it very risky for those volunteers? There are scientific reasons to believe that the risk is not that high. For one thing, the initial shot — the prime — is clearly providing some immunity, and even if low-risk people are exposed to the virus later on, the natural infection in them could act like the booster: bolstering their immune system even further without causing severe, or even mild, disease. The rarity of reinfections from natural infections supports that line of thinking. Second, what we know about the immune system and Phase 1 and 2 data suggests that older people's immune systems do not respond as strongly to the single dose, which means that we should keep both this trial and the possibility of a single dose reserved for lower-risk groups: healthy people under 65 without significant multiple comorbidities. The key question we're looking at is the durability of the immunity provided by that dose, whether it wanes over time and by how much. Immunity is not a switch that gets turned off overnight; we could monitor these volunteers monthly and stop the trial quickly if a significant uptick was detected.

The numbers need not be huge to provide us an answer. The benefit, however, is great. For one thing, we could double the number of lower-risk groups we could cover, especially essential workers who have suffered so much during this pandemic as they do not have the luxury of working from home. Second, we'd be able to roll out the vaccine much more quickly — now, the United States is planning to hold off half the doses in freezers, delaying vaccination. And a quicker rollout would help us get the pandemic under control much faster.

Even if we found the single dose to be somewhat less efficient than two doses, it's important to remember that not long ago we would have been thrilled to have a vaccine even less effective than the single-dose numbers we're seeing now.

If we start examining the effectiveness of a single dose now, and if we find that the data warrants it, we can go forward with it as quickly as possible. The prospect of adding hundreds of millions to those who can be vaccinated immediately in the coming year is not something to be dismissed.

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Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults

BACKGROUND

Testing of vaccine candidates to prevent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in an older population is important, since increased incidences of illness and death from coronavirus disease 2019 (Covid-19) have been associated with an older age.

METHODS

We conducted a phase 1, dose-escalation, open-label trial of a messenger RNA vaccine, mRNA-1273, which encodes the stabilized prefusion SARS-CoV-2 spike protein (S-2P) in healthy adults. The trial was expanded to include 40 older adults, who were stratified according to age (56 to 70 years or ≥71 years). All the participants were assigned sequentially to receive two doses of either 25 μg or 100 μg of vaccine administered 28 days apart.

RESULTS

Solicited adverse events were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Such adverse events were dose-dependent and were more common after the second immunization. Binding-antibody responses increased rapidly after the first immunization. By day 57, among the participants who received the 25-μg dose, the anti–S-2P geometric mean titer (GMT) was 323,945 among those between the ages of 56 and 70 years and 1,128,391 among those who were 71 years of age or

older; among the participants who received the 100-μg dose, the GMT in the two age subgroups was 1,183,066 and 3,638,522, respectively. After the second immunization, serum neutralizing activity was detected in all the participants by multiple methods. Binding- and neutralizing-antibody responses appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells.

CONCLUSIONS

In this small study involving older adults, adverse events associated with the mRNA-1273 vaccine were mainly mild or moderate. The 100-μg dose induced higher binding- and neutralizing-antibody titers than the 25-μg dose, which supports the use of the 100-μg dose in a phase 3 vaccine trial. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 Study ClinicalTrials.gov number, **NCT04283461. opens in new tab**.)