Accelerate COVID-19 Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines

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Dear Editor:

The epidemic of COVID-19 is far from over in the United States. Fortunately, vaccination with two mRNA vaccines, one from Pfizer/BNT Biotech[1,2] and one from Moderna[3,4] has begun in high risk groups including health care personnel and residents of old age homes, but supplies are not adequate for the entire population, all of whom deserve vaccine protection. Both vaccines are recommended to be given in two doses, three or four weeks apart, which gave about 95% efficacy.[2,3] Data from both of the pivotal trials revealed that a single dose induced considerable short term protection against COVID-19 disease. For both vaccines the curves of cases in the vaccine and placebo groups diverged at about 12 days after the first dose and few cases occurred in vaccinees thereafter. For the Moderna vaccine 35 cases occurred in the placebo recipients from 14 days after the first dose until the second dose compared to 2 in the vaccine recipients for an efficacy of greater than 90%. The Pfizer study reported an efficacy of 52% from the time of the first dose until the second dose, but the efficacy from 12 days after the first dose can be estimated to be similar to the Moderna vaccine from the curves. Both vaccines induced neutralizing antibodies after the first dose which were boosted by a second dose and the longer-term efficacy was approximately 95%. Although much more work is necessary to define correlates of protection, induction of neutralizing antibodies appeared to be protective. Other vaccines produced by other methods may soon achieve emergency authorization in the United States, but their efficacy after one or two doses, and adequacy of supply are unknown.

Authorities in the UK have argued that the protection following one dose of these mRNA vaccines and the Astrazeneca vaccine that is approved in the UK is sufficient to

encourage a strategy of giving a first dose to as many as possible in order to confer significant initial protection, but to hold the second dose until up to 12 weeks after the first dose as supplies improve. [5]

As the two mRNA vaccines are in short supply, the question is should the American authorities insist on giving two doses of the mRNA vaccines at the prescribed intervals of three or four weeks, or should the emphasis be to provide single doses to the greatest number of people, delaying the second doses by several months for people not at the highest risk. Judgment on this issue appears to rely on the answers to three questions: will one dose protect more people than two doses?; will antibodies and efficacy persist for several months after single doses?; and will a second dose give a boost if delayed?

To give an answer to the first question, suppose that 1 million people are to be vaccinated but only 1 million doses are available. If two doses are given to each vaccinee and the efficacy is 95%, 475,000 people will be protected. If single doses are given and the efficacy is 80%, 800,000 people will be protected. To answer the second question, we do not have data on persistence of antibodies, but in view of the apparent low level of antibodies that correlated with protection by the mRNA vaccines[2,3] we think efficacy is likely to last for several months. As for the third question, B cell memory after mRNA vaccination has been clearly demonstrated, which supports the idea that antibodies will be boosted by a second mRNA dose given months later.[6]. Priming of the immune system generates good responses to second doses of most vaccines for at least six months and perhaps longer[7]. Three doses of hepatitis B vaccines administered at yearly intervals were equally effective as the recommended 1, 2, and 6 weeks schedule[8]. CDC recognizes that there are delays for some doses of vaccines and has had a policy of not restarting

immunization schedules because of delays for at least 20 years. For the available mRNA COVID 19 vaccines the policy reads:

> "There is no maximum interval between the first and second doses for either vaccine. Therefore, if the second dose is administered >3 weeks after the first Pfizer-BioNTech vaccine dose or >1 month after the first Moderna vaccine dose, there is no need to restart the series."[9].

We urge consideration of interim use of single doses in the United States in order to extend vaccination to as many people as possible. Based on immunologic principles, sensitization with single doses would still allow boosting with a second dose several months later, when supplies improve. Israel is also following this strategy and has vaccinated a much higher percentage of their population with at least one dose than countries trying to adhere to strict schedules.[10] Health care workers and first responders in the United States are getting two doses now, but as long as there is a shortage of mRNA vaccines the general public would benefit from widespread use of at least one dose. We urge serious consideration of this step until supplies are adequate for two dose vaccination without leaving large numbers of susceptible individuals at risk. Of course, the licensure of additional vaccines would help alleviate the shortage, although most leading candidate vaccines require two doses, and the same issues will apply if supplies are insufficient and the efficacy data support short term protection from one dose. Whenever supplies become adequate, shorter intervals between the first and second doses can be instituted. The issue here is to protect the largest number of people in the shortest possible time.

Potential Conflicts of Interest:

Stanley Plotkin is a consultant to Moderna for Cytomegalovirus; consultant to Sanofi and Merck unrelated to Coronavirus; consultant to Valneva, and Codagenix.

Neal Halsey is serving on data and safety monitoring boards for a COVID 19 vaccine developed by INOVIO, a meta-DSMB for multiple COVID 19 vaccine trials sponsored by the Coalition for Epidemic Preparedness, and he served on mock Vaccine and Related Biologic Products Advisory Committee for Pfizer's COVID 19 vaccine.

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