AN ALTERNATIVE VACCINE STRATEGY TO REDUCE COVID-19 MORBIDITY AND MORTALITY

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An Alternative Vaccine Strategy to Reduce COVID-19 Morbidity and Mortality
There are two known pathways to immunity:

- previous infection with the SARS CoV2 virus
- inoculation with an effective vaccine.
SHOULD PERSONS WITH PRIOR COVID-19 BE IMMUNIZED?

- Among more than 90 million confirmed COVID-19 cases worldwide, there are only 31 (0.000034%) documented reinfections.

- Harvey et al reported on 3.2 million subjects, 88.3% with a positive antibody test and 11.6% with a negative antibody test, who were followed at 30-day intervals. They found that positive antibodies persisted and were associated with a 90% reduced risk for SARS-CoV-2 over 90 days.

- Lumley et al similarly showed a 90% reduced risk in 112,541 healthcare workers in the UK. In the latter study, among the 1177 workers who were seropositive at baseline, only 2 became PCR positive, and both remained asymptomatic.
COVID LiveUpdate: Dr. Anthony Fauci states that people infected with the coronavirus need to wait 90 days for the vaccine.
100 MILLION DOSES IN FIRST 100 DAYS

• With 100 million doses, we could:
  • Offer a high level of protection to 50 million people with two doses, or
  • Offer what appears to be very good protection to 100 million people with one dose, followed by a second dose after 90 days
WHEN SHOULD THE BOOSTER DOSE BE GIVEN?

• We suggested that the interval between doses be widened to 90 days

• Who disagrees with us?
  • Anthony Fauci
  • Paul Offit

• Who agrees with us?
  • The UK National Health Service
  • The US CDC (as of January 22) suggests the second dose can be delayed up to 6 weeks
MOST DOSES ARE NOW BEING USED FOR BOOSTERS

• Stanford Vaccine Clinic

Availability: Jan 24-Feb 18
ARGUMENT IN FAVOR OF MAINTAINING THREE WEEK (PFIZER) OR 4 WEEK (MODERNA) SCHEDULE

- In theory RNA vaccines require two doses to achieve durable immunity.
- These were the intervals used in the clinical trials. Because they were not tested using longer intervals, there is “no evidence” they will work if the second dose is delayed.
ARGUMENT AGAINST MAINTAINING THREE WEEK (PFIZER) OR 4 WEEK (MODERNA) SCHEDULE

- Phase 1 studies of these two mRNA based vaccines show the antibody response to a single dose is similar to convalescent plasma and natural infection shows prolonged immunity.

- Proponents of strict adherence to the two-dose schedule point to estimates that the first dose is only about 50% effective for preventing COVID-19 infections. But these analyses fail to exclude the 14-day post inoculation period when neutralizing antibodies are being established.

- The Moderna trial showed that the first dose was 94% effective for the interval 15-30 days after the first injection, exactly the same efficacy as for the period following the second dose.
ANALYSES FAIL TO EXCLUDE THE 10-DAY POST INOCULATION PERIOD WHEN NEUTRALIZING ANTIBODIES ARE BEING ESTABLISHED. THE MODERNA TRIAL SHOWED THAT THE FIRST DOES WAS 94% EFFECTIVE FOR THE INTERVAL 15-30 AFTER THE FIRST INJECTION, EXACTLY THE SAME EFFICACY AS FOR THE PERIOD FOLLOWING THE SECOND DOSE.
THE INTERVAL BETWEEN DOSES HAS BEEN STUDIED, ALTHOUGH NOT UNDER IDEAL STUDY DESIGNS

- Data from the AstraZeneca trial suggest delaying the second dose results in more rather than less durability of the immune response.
- An evaluation from in Brazil showed that the Chinese Sinovac Biotech vaccine was 20% more effective in a sub-group of patients who waited longer for their booster dose.
- Similarly evidence from other non-COVID vaccine trials suggest durability is stronger with wider intervals between doses.
## FINDINGS FROM ASTRazeneca TRIAL (Lancet, 2021, 397, 106)

<table>
<thead>
<tr>
<th></th>
<th>Total number of cases</th>
<th>ChAdOx1 nCoV-19</th>
<th>Control</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COV002 (UK), age 18–55 years</strong></td>
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<tr>
<td>LD/SD recipients</td>
<td>33</td>
<td>3/1367 (0.2%)</td>
<td>30/1374 (2.2%)</td>
<td>90.0% (67.3 to 97.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>SD/SD recipients</td>
<td>49</td>
<td>14/1879 (0.7%)</td>
<td>35/1922 (1.8%)</td>
<td>59.3% (25.1 to 77.9)</td>
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<tr>
<td><strong>COV002 (UK), age 18–55 years with &gt;8 weeks’ interval between vaccine doses</strong></td>
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<tr>
<td>LD/SD recipients</td>
<td>33</td>
<td>3/1357 (0.2%)</td>
<td>30/1362 (2.2%)</td>
<td>90.0% (67.3 to 97.0)</td>
<td></td>
</tr>
<tr>
<td>SD/SD recipients</td>
<td>24</td>
<td>8/1467 (0.5%)</td>
<td>25/1512 (1.7%)</td>
<td>65.6% (24.5 to 84.4)</td>
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<tr>
<td><strong>All SD/SD (UK and Brazil)</strong></td>
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<tr>
<td>&lt;6 weeks’ interval between vaccine doses</td>
<td>28</td>
<td>9/1702 (0.5%)</td>
<td>19/1698 (1.1%)</td>
<td>53.4% (-2.5 to 78.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;6 weeks’ interval between vaccine doses</td>
<td>70</td>
<td>18/2738 (0.7%)</td>
<td>52/2757 (1.9%)</td>
<td>65.4% (41.1 to 79.6)</td>
<td></td>
</tr>
</tbody>
</table>

Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body mass index. Model adjusted for BMI (<30 vs ≥30 kg/m²), health-care worker status (yes vs no), and ethnicity (white vs non-white). Model adjusted for BMI (<30 vs ≥30 kg/m²), health-care worker status (yes vs no), ethnicity (white vs non-white), age (<55 years vs ≥56 years), and study (COV002 vs COV003).

Table 3: Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population.
• The second dose should be administered as close to the recommended interval as possible. However, if it is not feasible to adhere to the recommended interval, the second dose of Pfizer-BioNTech and Moderna COVID-19 vaccines may be scheduled for administration up to 6 weeks (42 days) after the first dose. There are currently limited data on efficacy of mRNA COVID-19 vaccines administered beyond this window. If the second dose is administered beyond these intervals, there is no need to restart the series.
SIMULATION

• Based on an average of 200,000 cases of COVID-19 per day, X .95% vaccine efficacy = 2.63 million persons would avoid COVID-19 with this strategy.

• The alternative strategy would immunize 100 million persons with one dose, excluding persons with prior COVID-19. With this strategy, 5.85 million persons could avoid COVID-19. Thus, an additional 3.22 million persons would avoid infection compared to the standard strategy.

• 15% of COVID-19 patients are hospitalized and 1.7% die from the disease. The alternative strategy could prevent (.15) x (3.22 million) = 480,000 hospitalized cases and (.017) x (3.22 million) = 54,400 deaths by April 30.
• Considering limited vaccine availability, in the short term there is little benefit from vaccinating either people with a prior infection or those who have already had a first dose.

• Using the limited supply for these two groups would cause harm by depriving fully vulnerable persons of needed protection.