Week in Review: 7 – 11 December 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Phase III SARS-CoV-2 vaccine trial results appear in a medical journal for the first time.

Vaccines are hoped to be the cornerstone in helping to control the covid-19 pandemic. Vaccination outside of clinical trial settings began in the United Kingdom on December 7th and will likely begin in the United States next week, assuming that the US Food and Drug Administration grants emergency use authorization for the Pfizer vaccine.

Until now, publicly available phase III vaccine trial data has been limited to press releases and slide decks furnished by the vaccine manufacturers. Released in the *Lancet* is data from four studies involving the ChAdOx1 nCoV-19 vaccine being conducted in the UK, Brazil and South Africa. (This is the vaccine sometimes referred to in the press as the Oxford vaccine or the Oxford/AstraZeneca vaccine). The data reports slightly more favorable data than findings made public recently, with higher efficacy for test subjects who were enrolled in the primary dosing strategy than initially reported. The manuscript also adds important details.

Early news about the phase III trial data was puzzling because the vaccine showed greater success when the initial dose given was half of the standard dose. Now we have more complete data and we can try and tease out what really happened.

Enrollment began in April and the data published cover up through early November. Data analyzed in this paper included almost half of the 23,848 patients enrolled in these trials. These studies include adults who were randomly assigned to receive the study vaccine or a control vaccine (a meningococcal vaccine or just saline). Most participants received a "standard dose" followed by a second standard dose but as mentioned, a subset in the UK received a "half dose" as their first dose followed by a standard dose as a second dose. The half dose regimen had not been planned. Why a subset of volunteers received a half dose is explained in this manuscript. The authors state "a lower-than-anticipated reactogenicity profile was in the trial, and unexpected interference of an excipient with the spectrophotometry assay was identified." In other words, the half dose was a manufacturing error. That error, it turns out, may have been a stroke of luck.

Overall, after two doses, the vaccine was shown to have an efficacy of 70.4 percent after both doses. The vaccine even provided protection of 64.1% after a single dose. This efficacy was seen across all study sites. But those who received half dose followed by a full dose had 90% protection against covid-19. The early reports of 90% efficacy seen in the half dose subgroup was felt to not be due to statistical chance, although some statistical uncertainty (i.e. large confidence intervals) require more investigation. This half dose data has already attracted a great deal of attention; but it should not be the big takeaway and much remains to be learned. For example, the half dose group also did not receive their second dose in the same time window as other test subjects with <1% getting the second dose in 8 weeks. It remains to be seen whether the timing is what made a difference or the dosing regimen itself. The implications for possible greater efficacy in the half dose group could translate to a massive public health benefit especially as officials try to vaccinate the entire global population.

Meanwhile, the manuscript provides much-needed detail on a variety of outcomes. Most strikingly, *all hospitalizations* for covid-19 occurred in the control arms and accounted for 10 patients. Adverse effects reported in the studies included high fever in one patient and one case of transverse myelitis attributed to the vaccine. Four deaths occurred (1 in the study arm) but none were thought to be vaccine related. Three of the deaths were related to trauma and thus not covid-19 itself.

A larger number of test subjects and follow-up will be needed to glean whether the vaccine prevents mortality. It remains possible that the vaccine renders covid-19 disease less likely, but the very few who do become gravely ill have poor outcomes. But with such a high reduction in covid-19 illnesses, it seems likely that mortality rates will also improve with the vaccine. It is very promising to see data that

largely matches previous manufacturer press releases. The Oxford/AstraZeneca efficacy may not be as high as those quoted by the Pfizer and Moderna vaccine manufacturers, but these results exceed expectations that we might have had several months ago, and this vaccine is far more affordable. *Abbreviated from Brief19 for 8 December 2020. —Christopher Sampson, MD, FACEP*

Expert analysis briefing: I don't think you can claim an overall efficacy of 70% by just combining the very efficacious low-dose/standard-dose regimen with the successful but less efficacious standard-dose/standard-dose regimen in a "post-hoc" and unplanned analysis. Therefore, it is a little misleading to claim an overall 70% efficacy, if the protection will be lower than that (including in some subgroups) for those who receive the standard-dose/standard dose regimen. This vaccine is promising but I wish they would have included an explanation of their plans to evaluate the low-dose/standard-dose regimen going forward, since it appears to be much more efficacious than the fully standard-dose regimen. It would be desirable to move ahead getting approval for the most efficacious regimen. Also, reviewing the safety data suggests that this vaccine may be fairly "reactogenic," with a high rate of adverse events (i.e. it causes a fairly high number of immune system side effects). The safety profile is acceptable, but to increase uptake among the general population, it will be crucial to communicate the expected rates of these side effects to the public so they know what to expect. People will need to be reassured that they cannot get covid-19 from the vaccine, even though some of the side effects may resemble flu-like illnesses. *9 December 2020.* *—Angela Rasmussen, PhD*

Unemployment insurance helps individuals throughout the covid-19 pandemic. New evidence suggests that individuals with unemployment insurance during the covid-19 pandemic have fared better than those without, according to a new paper in *JAMA Internal Medicine*. The role of unemployment insurance is threefold, as it covers social needs, healthcare expenses and can, in turn, reduce daily stress. The researchers used a national survey called the Household Plus Survey, which is conducted by the U.S. Census Bureau. The study outcomes assessed access to food and healthcare, ability to pay rent and missing payments, and symptoms of anxiety and depression. Nearly 70,000 individuals completed the survey representing over 34 million unemployed individuals living in the US. Survey respondents were younger (average age of 34 years) and primarily women (51 percent). Thirty six percent of respondents reported use of unemployment insurance. When compared to individuals without insurance, those with unemployment insurance felt more confident they would be able to obtain food, pay rent, were less likely to miss housing payments, and were significantly less anxious and depressed. Individuals with unemployment insurance also reported better health care access compared to those without. Although this large, nationally represented survey study has limitations including possible selection bias, response rate and an inability to determine causation, the research is important as it has obvious face validity. In other words, access to unemployment insurance is good policy, and we should have a nationwide safety net in place for those who have suffered profound economic disruption from the necessary city- and state-wide quarantine measures. *7 December 2020.* *— Joshua Niforatos, MD, Research Section Editor*

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Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.