Week in Review: 11 – 15 January 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Johnson & Johnson publishes early data for its covid-19 vaccine candidate. The vaccine is a few months behind the mRNA options but may eventually offer advantages.

The past month has been a busy one on the coronavirus vaccine front. With the US FDA granting emergency authorization of the Pfizer and Moderna covid-19 shots, rollouts have begun among healthcare workers and other high-risk persons. We've been able to examine data from both of these mRNA vaccines as well as a third option, the Oxford-AstraZeneca candidate (the current DNA-based vaccine frontrunner).

This week, new data published in *The New England Journal of Medicine* on the Ad26.COV2.S coronavirus vaccine, being developed and tested by Johnson & Johnson. This vaccine is a "recombinant adenoviral vector" vaccine, and it uses a mechanism similar to the Oxford-AstraZeneca approach. Scientists spliced a small piece of the SARS-CoV-2 genetic material in a harmless version of an adenovirus (naturally occuring adenoviruses can and do cause flu-like illnesses; the strains used for vaccines do not). One administered, the vaccine generates an immune response from the body.

These results are from the Phase 1-2a trial of 805 participants which took place at multiple sites across the United States and Belgium. Three main cohorts were established and studied. Data from two of those cohorts were reported: subjects between 18 and 55 years of age and those greater than 65 years of age. (Data from another cohort which will allow long term comparisons between one and two dose regimens were not reported in this new paper). The two cohorts in this study received either a low or high dose intramuscular shot in either a single dose or in a two-dose regimen scheduled 56 days apart. Participants were randomized to one of five groups: low dose followed by low dose, low dose followed by placebo, high dose followed by high dose, high dose followed by placebo and placebo followed by placebo. The main goal of the study was safety and reactogenicity (Phase 1 and Phase 2 trials are not adequately large enough to study efficacy). This differs from the recent vaccine studies which focused on efficacy and made global headlines when they were found to be around 95 percent effective in preventing covid-19 disease.

At day 29 after the first dose, neutralizing antibody levels (titers) were detected in 90 percent or more of all participants. That number increased to 100 percent by day 57. These titers remained stable until day 71. Of note, the second booster dose was associated with antibody levels that were 2.6-2.9 times above levels after the first dose. This implies that a booster shot might provide a great deal of protection, but this study was not designed to study outcomes. Therefore, we do not know whether these higher titers mean greater and longer durability of protection, though it certainly implies that advantage.

Meanwhile, side effects were similar to the mRNA vaccines, with most common complaints being fatigue, headache, myalgia and injection site pain. These effects were reported more often in the high-dose groups.

Similar to the mRNA vaccines, adenovirus-based vaccines cause our cells to produce just the spike protein of SARS-CoV-2 (which our body then generates antibodies to), but not the rest of the virus. In addition, adenovirus itself is "replication incompetent," meaning it has been engineered so that it can't replicate and spread in our bodies. Unlike mRNA vaccines, adenoviruses have been used in the past. A current example of an adenoviral vaccine is the rabies vaccine.

One criticism of adenoviral vaccines is that booster shots may be required, given a waning response over time. Another is that since in general, adenoviruses are common, some individuals may already have immunity prior to vaccine administration. In other words, if someone is immune to the adenovirus itself, the vaccine might fail to work because our body would neutralize it before it gains entry into our cells, a necessary step in order for the coronavirus spike protein to be manufactured and to then trigger an immune response.

However, adenovirus vaccines have a major advantage: storage. Unlike the mRNA vaccines, the Johnson and Johnson vaccine is expected to be stable at normal freezer temperatures for two years or longer. Even at refrigerator temperatures, the vaccine is thought to have a three-month shelf life. The mRNA vaccines require freezers that are so cold that even most pharmacies don't have them, and transportation requires dry ice or unusually cold (and hard-to-come-by) freezers. So if this vaccine works as well as the mRNA options do, it will have substantial appeal.

It must be cautioned that these data reflect early research of Phase 1-2a trials. The report provides information that supports further development of this method as a future vaccine candidate. Phase 3 trials will assess whether this vaccine is as protective as the current available options. While these initial results are promising, nothing can replace Phase 3 data, which we await with anticipation. *14 January 2021*.

—Christopher Sampson, MD, FACEP

Covid-19 symptoms at 6 months. New research on what we've learned about the long-haul.

Covid-19 is not the only acute illness that can cause long-term suffering. Far from it. As medical care has become more advanced, and more patients survive previously universally fatal ailments, a condition known as post-intensive care syndrome has become more common and better understood. When we are fighting for our lives, the body becomes a battlefield. Often, what is left behind in the aftermath is a kind of scorched Earth.

New research in *The Lancet* followed-up with over 1,700 covid-19 patients who were hospitalized and then released. Six months later, the frequency of bothersome and disabling symptoms, findings on CT scans of the lungs, and pulmonary function severity was reported. Researchers grouped these results into three categories according to the severity of the patients' initial illnesses: patients who did not require supplemental oxygen, patients who did, and patients who needed more intense oxygen such as high-flow nasal oxygen, non-invasive devices (similar to CPAP machines), and invasive mechanical ventilation (i.e. intubated and on breathing machines).

At six months, 76 percent of all patients had at least one of the listed symptoms, which range from fatigue/muscle weakness (63 percent), difficulty sleeping (26 percent), hair loss (22 percent), difficulty with smell and taste (11 and 9 percent), and trouble with mobility (7 percent). When comparing the sickest patients to those who did not require supplemental oxygen, Fatigue/muscle weakness was 2.7 times more likely. Chest pain was also more likely (2.6 times). Mobility was compromised in 14 percent of the sickest group, 2.5 times more likely than the least sick group. Of note, anxiety and depression was present in 23 percent of these survivors, and nearly one third of the sickest cohort had these symptoms at 6 months. Among all of these symptoms disease severity and female gender were the most meaningful predictors.

Radiographic findings and pulmonary function tests were also impressive, though these by themselves do not necessarily mean that patients continue to suffer. Some patients have clear CT scans and feel terrible, while for others the opposite may be true. Symptoms that patients notice tend to be more meaningful than these "doctor-centered" findings, though they may portend to long-term lung problems. We just do not know.

Of interest, this study also studied levels of immunity. While blood levels of many types of antibodies dropped, giving the researchers concern that re-infection may eventually be possible, there is no known threshold for this. It is possible that even very low levels of antibodies and other immune markers may still provide protection.

This study adds to a growing body of literature about long-term symptoms after covid-19. Earlier studies looked at two-month outcomes. That so many patients have symptoms at six months is concerning. But it is not surprising, It is likely that similar findings would be found as a result of a great many number of severe acute illnesses. The problem is that SARS-CoV-2 is so out of control, that these findings appear to be far more frequent. Though a comparison to a group of similarly ill non-covid-19 patients would be informative, that was not provided in this study, which is a major weakness in its design and therefore in what we can say we have learned about covid-19 from it.

Why is all of this happening? We are only beginning to ask the question and answers are not available. But in an effort to explain the mental health findings, the authors posited that the "underlying mechanism of the psychiatric consequences of COVID-19 is likely to be multifactorial and might include the direct effects of viral infection, the immunological response, corticosteroid therapy, ICU stay, social isolation, and stigma." But in reality, the very same thing could easily be said of almost all long-term covid-19 symptoms, not just those related to mental health. When the body combats a serious illness, the ramifications don't simply cease to exist just because the first and most important battle has been won. *12 January 2021*. —*Jeremy Samuel Faust, MD MS*

Covid-19 associated with major increase in hospitalizations for pediatric patients.

Hospitalization indicates a certain level of morbidity or sickness. To be admitted to hospital for an in-patient stay, a patient's needs must go beyond requiring Tylenol (i.e. acetaminophen) or Motrin (i.e. non-steroidal anti-inflammatory) for fever, aches, and pains. This is especially true for children. Children often get sick from viruses. They only need to be hospitalized if there are services that cannot safely be achieved elsewhere. Hospitals provide vital sign monitoring, oxygen, intravenous medications, and hands-on care from a multidisciplinary professional team. Long-story-shot: if a child is being hospitalized, a physician has determined that they are already quite sick, or at risk for progressing to serious illness in a short period of time.

A new research letter out in *JAMA Pediatrics* looks at trends in pediatric hospitalizations for covid-19 in 2020. The data came from researchers at the University of Minnesota which tracked hospitalizations in 22 US states. (Only the states that collected hospitalizations by age could be included in the analysis. This paper assessed overall hospitalizations for adults, and those for patients under 19 years of age from May to November 2020.

Out of over 300,000 hospitalizations for covid-19, 5,364 of them were for children. Over the course of the study, overall hospitalization of children increased from a rate of 2 per 100,000 children in the state population to 17 per 100,000 children, an impressive jump. There was variation seen between states, and for two of the states in May there were no pediatric hospitalizations specifically recorded as being related to covid-19. By the end of the study period, though, every state had pediatric covid-19 hospitalizations, and the 20 states who had previously reported them in May showed increases in pediatric covid-19 admissions ranging from 42 percent to 5,067 percent.

By now, it doesn't matter what state you live in; children are suffering from this disease across the United States, though fortunately at rates far lower than adults and with far fewer serious outcomes.

Pediatricians are accustomed to counseling families on managing viral symptoms at home, but covid-19 has started pushing children into hospital beds. It has forced families to reconsider visits to pediatric offices, and continually and increasingly threatened the health and safety of our children in a variety of ways. Uncontrolled spread has meant school closures, as well as complications like MIS-C, a post-covid-19 inflammatory syndrome. Is this data finally enough for us to realize how much our youth are affected by this deadly virus? At a minimum it should raise our concerns, especially as we learn more about the B.1.1.7. variant, which many believe is causing an increase in infections among children. Regardless, say it with me now: children are not immune to covid-19. *11 January 2021*.

—*Joanna Parga-Belinkie*

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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.