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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Moderna vaccine phase III trial results released in *New England Journal of Medicine.*

The phase III randomized double-blinded multi-center trial of the Moderna vaccine against SARS-CoV-2 has now been published. The trial enrolled 30,420 volunteers, randomly assigned to receive either two doses of the vaccine 28 days apart or a placebo injection. None of the study subjects who received the vaccine developed severe covid-19 (needing hospitalization). Among volunteers who received the mRNA vaccine, only 11 out of 15,210 developed covid-19, versus 185 out of 15,210 in the placebo group. This means that the vaccine was 94.1 percent effective in preventing covid-19 illness (though we do not know whether infections were prevented). Severe illness was only detected among test subjects in the placebo group, another promising sign. Subjects older than 65 years and those who had evidence of previous coronavirus infection also fared similarly.

Of note, an assessment of outcome 14 days after the first dose indicates early effectiveness. However, we do not yet know whether one dose would provide long-lasting immunity, which means that for now, the two-dose strategy must be continued. Data given to the FDA earlier this month suggested that one dose provided 92 percent efficacy compared to placebo, but only out to 28 days. Much longer follow-up is needed on this aspect in particular.

Side effects have been a closely watched area. Soreness or pain at the injection site was equally frequent in those who received the vaccine and those who received the placebo. Those who received the vaccine were more likely to report fever and generally feeling ill. No severe adverse events were reported in either group.

The Moderna vaccine (mRNA-1273) is a lipid nanoparticle that contains mRNA that encodes the virus's spike protein. The Moderna and Pfizer vaccines were developed using a novel strategy, using mRNA instead of a weakened, killed, or gutted virus, which are the usual mechanisms of action for vaccines in use for a variety of other diseases. Both the Moderna and Pfizer vaccines include the genetic code for just one part of SARS-CoV-2, the spike protein. Once injected, the human cells create that single viral protein (but not the 28 other proteins that would be needed for a complete and infectious viral particle) which is then recognized as "unusual" by our own immune systems. That our bodies "know" to turn around and make antibodies to a protein that it just manufactured itself is one of the remarkable achievements of our own immune systems. The rationale is that including part of the virus might limit side effects such as rash, fever without reducing effectiveness. Also, using mRNA instead of DNA eliminates the chance of the viral genetic material being incorporated a person's own DNA.

These results demonstrate that the Moderna vaccine is safe to administer and effective at preventing covid-19 serious enough to require hospitalization. It cannot assess for adverse events that occur more rarely than in 1 in 15,000 patients nor does the study speak to whether the vaccine reduces other complications such as an increased risk of blood clots in the lungs or persistent neurologic or psychiatric changes. The study did not analyze if there was a difference in vaccine efficacy for different strains of SARS-CoV-2, though experts believe that there is little cause to worry that it would not be effective against new strains such as the B.1.1.7 mutant which has now been detected in the US.

—Michael Chary, MD PhD

POLICY BRIEFING

Understanding vaccine hesitancy as public health experts consider a vaccine mandate. Schools will be a major battleground.

Vaccine hesitancy is already a well-documented and closely studied phenomenon, mostly encountered in the world of pediatrics. But in anticipation of more widespread covid-19 vaccination rollouts and the exploration of a possible vaccine mandate, a discussion of the logistics is now more relevant than ever. Ground zero for the brewing controversies: schools. It is certain that no matter how safe and effective these vaccines turn out to be, some parents will desire exemptions. The deadly American trope of pitting individual autonomy against public health is poised to play out yet again, with higher stakes than ever before.

With multiple SARS-CoV-2 vaccines now available, a recent viewpoint in *JAMA* explored how adults might respond to a vaccine mandate. Hesitancy already exists for the covid-19 vaccine; 39 percent of Americans intending to wait on getting it, and 15 percent saying they wouldn't take it at all (thought that number has fallen steadily from 50 percent last summer). Given the current climate, and the fact that the vaccines are only approved via emergency use authorization, passing a mandate would be difficult. Before that could happen, a full biologics license application approval would have to be obtained through the US Food and Drug Administration. Mandates for emergency use authorized vaccines would have no legal standing.

Requiring a vaccine for millions of Americans who expect protection of their individual liberties is daunting. The *JAMA* viewpoint explores what a mandate might look like for specific populations, starting with places the mandates already exist—schools. All states require vaccination to enter schools, but medical exemptions are permitted. The troubling aspect for healthcare professionals is that the many states allow for religious exemption and a few also allow exemption for philosophical reasons, though rules have tightened in recent years. Predictably, the areas with less stringent policies are where outbreaks of preventable disease occur. Given a national desire to return to in-person classroom learning, it is likely the covid-19 vaccine will eventually be added to the list of required childhood vaccinations. But aside from a FDA approval, more testing in pediatric populations will be needed. Pediatric organizations have been vocal in calling for these trials.

While healthcare workers are required to get the influenza vaccine (or wear a mask for the duration of flu season), given the stresses of the pandemic and the available shots, it may be a while before they are required to get the covid-19 vaccine. Healthcare institutions are working to track vaccine hesitancy within their clinics and hospitals. Currently, many healthcare workers have expressed enthusiasm for the vaccines, heralding vaccination as a necessary step to return to pre-pandemic normalcy and hoping the general public will be reassured by their example.

Businesses are another area of interest, particularly in instances where in-person work, or vulnerability of clients comes into question. Our hope is that exemptions policies will be strict.

Immunizations have a long and excellent record of safely saving lives. Vaccine mandates may become a key and necessary tool in restoring life-as-we-once-knew-it. Vaccine hesitancy will need to be overcome by having trusted medical professionals discuss the benefits and address their patients' concerns. While a mandate may be needed, targeted and thoughtful education from within communities would be more helpful in getting the public to accept vaccines as the pandemic-defeating innovations that they may turn out to be.

—Joanna Parga-Belinkie, MD

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