28 July 2020

BRIEF19

A daily review of covid-19 research and policy.

BREAKING NEWS RESEARCH BRIEFING

Primate study suggests mRNA vaccine effective in fending off SARS-CoV-2.

The great hope in getting society "back to normal" in the face of the covid-19 pandemic is the development of herd immunity through vaccination. A new publication reporting research conducted at the National Institutes of Health was released today in *New England Journal of Medicine*. The study assesses Moderna's mRNA vaccine, which is currently entering Phase III human trials.

Meanwhile, researchers studied viral replication in the upper and lower airways of a well-known port of entry for SARS-CoV-2: angiotensin-converting-enzyme 2 (ACE2) receptors. Non-human primates (rhesus macaque) were used, given that species' similarity to humans with respect to immune response to this and other viruses. Typically, when infected with SARS-CoV-2, these animals develop lung disease resulting that resolves within 14 days.

The non-human primates were randomized to receive 10 or 100 *micrograms* of a messenger RNA vaccine mRNA-1273 or a sham injection with no vaccine (fluid only). The vaccine mRNA-1273 encodes parts of the surface spike protein of SARS-CoV-2 which cells then manufacture and the immune system recognizes by making antibodies and other immune cells and proteins. The vaccine was administered intramuscularly twice, four weeks apart. Antibody and T-cell responses were assessed initially and then the airways were "challenged" with SARS-CoV-2 (i.e. high quantities of virus were placed) eight weeks later. The challenge consisted of 3 milliliters of virus, delivered endotracheally and 1 milliliter given intranasally. Bronchoalveolar lavage (BAL, which removes fluid and cells from the lower airway tract) was then performed. Thee fluid was analyzed for viral replication and viral genomes. Nasal swab specimens were also obtained for genetic analysis and quantifying. Specimen were obtained on days 1, 2, 4 and 7 after the viral challenge. Post-mortem lung tissue was also examined.

Did it work? Results suggest the answer is yes. The vaccine was found to induce antibody levels that exceeded those found in samples taken from forty-two humans who had recently recovered from SARS-CoV-2 infection. The vaccine induced antibody levels in the non-human primates that were 12 to 84 times higher than those found in the "convalescent-plasma serum" samples from the recovered humans. (Giving convalescent plasma to patients with covid-19 is a therapy that is currently used to treat some patients, though results from clinical trials have been mixed.) By the second day after the vaccine was giving to the primates, SARS-CoV-2 viral replication was not detectable in the fluid taken from the lower respiratory tract of the animals ("broncheoalveolar lavage" fluid in) seven of the eight animals in both the low and high dose vaccine groups. Among the animals that received 100 *micrograms* of vaccine group, no detectable viral replication was found in the noses of the 8 animals two days after the challenge. Animals that did not receive the vaccine had measurable viral replication for far longer. Pathologists then

assessed tissues taken from the lungs of the animals. No pathological changes were found in the lungs of the vaccinated animals—but disease-like changes were seen in the control animals.

These results show promise for this candidate mRNA vaccine. The published data suggest that vaccination at the higher dose in particular was effective in offering protection to the upper and lower airways of non-human primates against SARS-CoV-2. However, given other recent studies that have shown rapid decline in antibodies of infected humans by 30 to 90 days, the looming question is how long this vaccine offers protection. Another unresolved question regards the potential development of vaccine-associated enhanced respiratory disease, a fatal complication seen during H1N1 vaccine development. The final and most crucial question however is whether this non-human primate vaccine and infection model will translate to humans.

-Christopher Sampson, MD, FACEP