

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

A major clinical trial finds no benefit of hydroxychloroquine in treating covid-19.

A newly published [study](#) out of the United Kingdom has found that hydroxychloroquine is not effective in the fight against covid-19. The study was performed by the RECOVERY research team, the same collaboration that published the ground-breaking randomized clinical trial on the use of dexamethasone in covid-19, the first treatment shown in a clinical trial to improve mortality among patients who required oxygen or mechanical ventilation (though no benefit was found in patients without those needs, with a suggestion of potential harm among those patients). This new randomized clinical trial was conducted across 176 hospitals in the U.K. Patients included in the study were diagnosed with SARS-CoV-2 infection and the primary outcome of interest was mortality after 28 days. A total of 1,561 and 3,155 patients were randomized either to hydroxychloroquine (HCQ) plus standard-of-care treatments (such as oxygen as needed, and other non-specific supportive treatments) or standard-of-care treatment only, respectively. The results of the study were sobering. The mortality rate from covid-19 was 26.8% in the HCQ group and 25% in the standard-of-care group—which was not a statistically significant difference. Not only did a quarter of subjects die, but HCQ provided no mortality benefit. Interestingly, those who received HCQ had longer lengths of stay in the hospital and were also more likely to reach what researchers call a “composite endpoint,” of two outcomes (in this case the need for mechanical ventilation or death) when compared to patients who did not receive HCQ (29.8% vs. 26.5%; with a risk ratio 1.12. (Risk ratios refer to the probability of a certain outcome in one group compared to the probability of the same outcome in another group, in this case, receiving HCQ or not) The statistical analysis suggests that the researchers can be 95% confident that the true number is somewhere between 1.01 and 1.25. The one silver-lining of the study is that high-doses of HCQ did not confer an excess risk of side effects (i.e., new major cardiac arrhythmia, which is a known risk associated with the medication).

There are a few major takeaways from this study. First, this study represents the largest and most important randomized clinical trial on the use of HCQ in hospitalized covid-19 patients to date. Patients receiving HCQ were randomized to the drug or not, whereas in previous observational studies (in which researchers looked back at charts of previous cases) sicker patients were often exposed to HCQ, thereby introducing selection bias (in other words, it is possible that patients who received HCQ in those studies fared worse because they were more seriously ill at the outset). In the final analysis, these new results from the RECOVERY study highlight a lack of mortality reduction among patients who received HCQ, and an apparent association with (if not a direct cause of) increased hospital lengths of stay and the need for mechanical ventilation. The argument for HCQ use in covid-19 is quickly dying. [17 July 2020](#).
—Joshua Niforatos

Coronavirus vaccine based on genetic material reports Phase 1 results.

The authors of [a new study](#) appearing in *The New England Journal of Medicine* published evidence that an mRNA vaccine made by Moderna Therapeutics did not show signs of being toxic, was well-tolerated, and induced the production of antibodies against the Spike protein, a component of the virus thought to be responsible for the virus’ increased virulence. In this Phase 1 trial, 45 volunteers with no detectable coronavirus received two shots 28 days apart. The 45 participants were divided into three groups depending on whether they received 25, 100, or 250 micrograms of the vaccine. Three out of 15 participants in the highest dose group had severe adverse effects, including a large red rash and one episode of passing out.

An [mRNA vaccine](#) is a novel approach. Moderna's vaccines would be the first approved for human use based on this recent technology. Instead of the usual approach of baiting the immune system with a weakened form of a virus, mRNA vaccines act like a software update for the genome of immune cells. One upside of mRNA vaccines is that they do not integrate into the DNA of the host's cells. This means they are less likely to have the side effects associated with similar vaccines that are made from DNA. A downside is that mRNA vaccines are less likely to give a provide long-lasting immune responses precisely *because* they don't fully integrate into the host's DNA.

One major gap in the data: the vaccine was not was not studied in older individuals with pre-existing medical conditions, the part of the population most at risk for death or disability from covid-19. Older individuals may not respond as briskly to these doses of the vaccine, which could force a choice between higher doses which would be accompanied by more adverse effects and lower doses that are less likely to confer immunity, though would have fewer side effects.

The results of this study are encouraging, though successful Phase I trials only indicate that a vaccine is not immediately toxic among a small group of healthy volunteers. Even if the phase II and phase III trials are less promising, the development of preliminarily safe mRNA vaccine is a substantial achievement. *Abbreviated from Brief19 for [15 July 2020](#). —Michael Chary, MD, PhD*

Has covid-19 affected the prison population?

One of the foundational mitigation principles in the covid-19 pandemic is social distancing. Unfortunately, the prison system makes social distancing uniquely difficult. Given this context, an interesting [paper](#) was recently published in *JAMA* that examined covid-19 case rates and deaths among federal and state prisoners. The researchers used data from the UCLA School of Law "COVID-19 Behind Bars Data Project," an extensive and nationally [comprehensive database](#) of the prison system in the United States, covering March 31, 2020, to June 6, 2020.

Astonishingly, by June 6 there were 42,107 cases of covid-19 among U.S. prisoners with a SARS-CoV-2 case rate of 3,251 per 100,000 prisoners. This case rate was approximately 5.5 times higher than that measured among the general U.S. population, a case rate of 587 per 100,000 persons during the same time period. The crude death rate was also higher in the prison population compared to the U.S. population at 39 deaths versus 29 deaths per 100,000 persons, respectively. When accounting for age and sex differences between the prison population and the general population, the adjusted death rate from covid-19 was three times greater for prisoners than the general U.S. population. Finally, the mean daily case growth rate was 8.3% per day in prisons versus 3.4% per day in the U.S. population.

This study had a few limitations that say more about the prison system in the U.S. than the research itself. First, officially reported data are the only available data on prison disease and deaths. Transparency could be an issue, though it is unknown if such issues had any effect on the data. Second, comprehensive data on testing rates were not made available. Finally, Departments of Corrections generally do not report demographic data on individuals who died. In this context, it is possible and even likely that the real covid-19 case rates and death rates are in reality substantially higher among the prison population than even these numbers suggest. National policies that improve prison conditions to prevent such outcomes are urgently needed. [13 July 2020](#).

—Joshua Niforatos, MD Research Section Editor.

Kane Elfman PhD, Publishing and design.

Anna Fang, Week in Review.

Jeremy Samuel Faust MD MS, Editor-in-Chief.

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Twitter: [@brief_19](#)

submissions@brief19.com

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.