

## **BRIEF19**

*A daily review of covid-19 research and policy.*

### **RESEARCH BRIEFING**

#### **Diversity, Representation and Covid-19 Clinical Trials.**

Racial minorities have a fraught history of inclusion in unethical clinical trials in the United States, and covid-19 has the potential to further complicate the story. One example of exploitation of minorities in clinical trials were the Tuskegee Syphilis experiments, during which Black men were used as subjects to study the natural course of syphilis, despite readily available penicillin.

Meanwhile, contemporary examples of racial injustice in clinical trials include *underrepresentation* of Black and other minorities. This is where covid-19 is relevant. Despite a disproportionately high covid-19 disease burden amongst the Black, Latinx and Native American populations, these groups are disproportionately underrepresented in ongoing drug trials. This ultimately asks: will such treatments be generalizable and effective across all populations if studies aren't performed in a population representative of the U.S. as a whole?

In a perspective piece [published](#) in the *New England Journal of Medicine*, this continued lack of minority representation in clinical trials is highlighted. In the Adaptive Covid-19 Treatment Trial (ACTT-1), which enrolled 1063 patients, Black, Latinx and Native Americans accounted for only 20%, 23%, and 0.7% of the patients in this study, respectively. Meanwhile, only 11% of 397 patients in the Gilead funded Remdesivir study were Black. The crux of the disparity lies in the fact that these studies were conducted in areas where covid-19 related deaths affected these groups at a disproportionately high rate, and their inclusion in these trials were, “substantially underrepresented,” according to the article. The authors suggest the lack of diversity in these clinical trials is multifactorial and includes an understandable history of mistrust of the medical community from the perspective of minority communities, as well as the financial cost associated with participating in clinical trials. These problems are further compounded by poor health literacy and language barriers. An additional factor is a lack of diversity amongst the principal investigators. It should also be noted that Remdesivir’s “compassionate use” program provided no racial or ethnic data for the 53 patients treated, so no conclusions could be drawn from that subset of patients.

Nevertheless, National Institutes of Health (NIH) policy and federal laws mandate the inclusion of racial minorities in NIH funded clinical trials, as well as transparency of racial and ethnic data in phase 3 clinical trials. And yet the Remdesivir studies failed to have adequate representation or even report proper data. While the ACTT-1 did include demographics for patients enrolled, it still failed to provide outcome data linked to gender, race and ethnicity.

When diverse populations are not adequately represented, it is difficult to extrapolate data to the general population. The authors of this article advocate for prioritizing “inclusion of patient populations that reflect the demographics of the ongoing pandemic.” Further, they emphasize the importance of increasing funding for scientists belonging to underrepresented ethnic groups and standardizing the reporting of race and ethnicity data. The authors firmly believe that regulatory agencies, medical journals, funders and peer reviewers have the obligation to ensure that clinical trials meet the standards set in place, not only by federal law but also with respect to NIH policy. Future proposals and manuscripts must be able to account for the demographics of their subjects and commit to reporting more nuanced data. *NEJM. 13 August 2020.* —Onyeka Otugo, MD, MPH

**Experiments with Icatibant show promise in treating covid-19 lung disease.** As the U.S. awaits a safe and effective vaccine to combat SARS-CoV-2, researchers have continued to explore the use of pre-existing medications to treat the virus. A group of scientists in the Netherlands have conducted

one such trial to explore whether Icatibant, a drug approved to treat hereditary angioedema would be successful in reducing fluid accumulation in the lungs of patients suffering from covid-19. Hereditary angioedema is a genetic condition in which those affected lack or have dramatically decreased activity of an enzyme called C1 esterase *inhibitor*. When C1 esterase inhibitor is offline, C1 esterase runs overtime, leading to a buildup of two other chemicals, bradykinin and kallikrein. These chemicals cause remarkable swelling, most notably in the mouth, throat and areas lined with mucosa, including the intestines and parts of the lungs. Meanwhile, ACE2 receptors promote the degradation of bradykinin and kallikrein. SARS-CoV-2 uses this very same receptor to enter human cells, thereby preventing the ACE2 receptors from carrying out their usual functions. Because of this connection, researchers hypothesized that Icatibant might be able to reduce lung swelling in covid-19 patients by compensating for the loss of ACE2 function. They gave one dose of Icatibant to nine patients requiring oxygen support and found that four out of nine patients needed less supplemental oxygen. However, of those four, the improvement in two lasted only a few hours. In sum, this trial hints that Icatibant may help patients in covid-19 whose disease involves swelling and accumulation of fluid in lung tissue. But it is not a large enough of a study to provide strong evidence. There is still much to be learned. *Abbreviated from Brief19 for [14 August 2020](#)*. —Michael Chary, MD PhD

**New research suggests that nurse staffing shortages result in increased cases in nursing homes.** Nursing homes have accounted for an incredibly high number of covid-19 fatalities in the United States outbreak. As covered [previously](#) in *Brief19*, nursing homes accounted for 45% of the deaths in the U.S. as of late June, despite the fact that that residents of these long term care facilities make up less than 1% of the nation’s population. A new [article](#) published in *JAMA* looks at potential drivers of disparities across nursing home facilities during the covid-19 pandemic. The researchers looked at the association between nursing home ratings by the Centers for Medicare & Medicaid Services (CMS) and covid-19 case load. These researchers looked at data from eight state health departments to determine the total number of covid-19 cases in nursing homes between January 1 to June 30, 2020. Nursing home ratings, quality measures, and nursing home staffing were extracted from CMS Nursing Home Compare, a database that tracks facilities performance. Over 4200 nursing homes were included in the study. ‘High-performing’ nursing homes had fewer cases of covid-19 compared to ‘low-performing’ nursing homes. Perhaps most interestingly, after statistical adjustment the only other factor associated with covid-19 caseloads appeared to be facilities with high ratings of performance by nursing staff; these facilities were less likely to have a high burden of covid-19 cases. No other quality measure domain was associated with an increase in the number of covid-19 cases in a particular nursing home. The authors conclude, “These findings suggest that poorly resourced [nursing homes] with nurse staffing shortages may be more susceptible to the spread of COVID-19.” The major limitation of this study, however, is the absence of a denominator: how many residents were there per nursing home. Also missing was information about the presence or frequency of demographic characteristics that may predispose nursing home residents to developing symptomatic covid-19. Nevertheless, this paper provides evidence that appropriate staffing of nurses and other staff in nursing homes appears to be helpful in preventing increased covid-19 burdens in individual facilities. [11 August 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.