BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Vaccine acceptance and disparities among incarcerated people.

A new correspondence in *The New England Journal of Medicine* measured vaccine acceptance among incarcerated people in the California Department of Corrections and Rehabilitation. The covid-19 vaccine rollout has been seen as a crucial endeavor given that prisons and jails have been disastrous hot zones. In fact, the authors note that more incarcerated people have died of covid-19 than have died by capital punishment in the US during the last seven decades combined.

In California, a shocking 97,779 people were inmates in prisons or jails during the study period, or one in around 400 California residents. This alone is its own scandal, unsurprising though it may be. Of the 97,779 incarcerated people in California at the time these data were collected, 64,633 (66.5 percent) were offered vaccines, of whom 42,952 (44 percent) accepted at least one dose.

The rates of vaccine acceptance varied by age and race. Older people were more likely to take the vaccine. Hispanic and White inmates were the most likely to accept the vaccine at approximately 72-73 percent. Black inmates were the least likely to accept the vaccine, at around 55 percent. The authors explicitly state a likely explanation for this latter finding, saying that lower rates of vaccine interest among Black inmates "may reflect mistrust in correctional authorities and clinicians or a lack of access to reliable information on vaccine safety and efficacy." Indeed, the corrupt legacy of the Tuskegee experiments and other blemishes in our nation's history continue to cast a harmful shadow, even today.

That said, a more uplifting observation was also noted. Nearly 2,000 residents who initially declined an offer to be vaccination were subsequently asked if they had changed their mind. Of these, nearly 46 percent said yes to vaccination at the time of the second offer. This suggests that some people may change their minds, especially after seeing others get vaccinated without incident. It may be that repeatedly asking people who initially decline vaccination is a worthwhile endeavor in many environments. *13 May 2021*. *—Jeremy Samuel Faust, MD MS*

Study claiming smokers less likely to get covid-19 retracted.

Almost a year ago, a paper was published in the *European Respiratory Journal* which caused a lot of head scratching. The authors of the study claimed that smokers were 23 percent less likely to be diagnosed with covid-19 compared to non-smokers, implying a *protective* effect from cigarettes or vaping. This finding seemed to go against mountains of previous research of smokers and respiratory illnesses where increased illness and mortality is often seen. The article was initially released as a preprint in July 2020 and then given "early view" status by the journal. Now, that article has been retracted.

The justification for retraction comes not as a result of its questionable findings, but newly identified conflicts of interest among its authors. The research team came from the University of Piraeus in Greece and University of Utah. But the members also had troubling ties. One of the authors is a fairly prominent name in vaping research. Another of the authors, served as a consultant for the tobacco industry (related to harm reduction). Another author, was a principal investigator for a Greece-based non-profit organization, also funded by the tobacco

industry. In the article, none of the authors reported conflicts of interest. Medical journal standards dictate that such conflicts be stated overtly in any manuscript.

The journal clarified that according to the bylaws of The European Respiratory Society, which creates it, its mission is to promote lung health. Specifically, individuals with ongoing relationships in the tobacco industry are barred from taking part in the society's activities, includes professional and academic meetings and any relevant publications. Nevertheless, the senior author of the smoking and covid-19 paper released a statement on the *Retraction Watch* (a website that monitors retracted paper) justifying the omissions, saying that "conflicts were irrelevant to the study's main aims and objectives."

This topic was also addressed in the journal *BMJ Evidence-Based Medicine* not long after publication of the initial article. Titled "Is there a smoker's paradox in covid-19?" the authors of the *BMJ EBM* article performed an evidence-based analysis of the available data. These authors did point out that the "smoker's paradox" concept is not a new idea and has been around since 1995 when a junk theory was floated that smoking decreased short-term mortality after heart attacks and stroke. The authors of the *BMJ EBM* article ultimately concluded that, "reported data are questionable and a protective effect should not be inferred."

One unanswered question is why it took so long for the authors' conflicts of interest to come to light and for the *European Respiratory Journal* to respond. The important lesson from this retraction is that if something appears too good to be true a dose of skepticism must always be maintained, and post-publication scrutiny is in order.

The covid-19 pandemic has tested the limits of junk science, with poorly vetted research too often being pushed out as fact. Now, the cleanup begins. *12 May 2021*.

—Christopher Sampson, MD, FACEP

Ibuprofen and other "NSAIDs" appear safe in patients with covid-19.

Early in the pandemic there was widespread concern that use of nonsteroidal anti-inflammatory medications (NSAIDs) such as ibuprofen, Aleve, Motrin, Advil, might lead to worse outcomes for patients with covid-19. A new article published in *Lancet Rheumatology* suggests that these concerns appear to have been unfounded.

In a large, multicenter study in the United Kingdom, which included 255 healthcare facilities and 78,674 patients hospitalized with confirmed or highly suspected SARS-CoV-2 infection, researchers followed the outcomes of a cohort of patients as they progressed through their disease (i.e. the study was prospective, not retrospective). The project sought to characterize what effect, if any, NSAID use had on in-hospital mortality for covid-19 patients. Patients were included in the study if they reported NSAID use within two weeks of the hospital admission.

Just over 5 percent of patients were taking NSAIDs prior to hospitalization. When comparing these patients to others who were similar (in terms of demographics and severity of disease at the time of hospitalization, as determined through a process called "propensity score matching analysis"), NSAID use was *not* associated with an increased in-hospital mortality. Furthermore, use of NSAIDs was not associated with increased need for escalating oxygen therapy, mechanical ventilation, kidney injury, or the need for intensive care.

Let's dig into the methods for a moment. There is debate in the health services research community regarding pros and cons of the "propensity scoring" methods that were used for this study. The key question is whether this procedure—which amounts to finding a matching patient to serve as a "control" every time you find a patient in the group who "received the drug"—sufficiently mimics a randomized clinical trial in which some patients are randomized to receive a medication and others are not. While that's a black box, this study has many features to

recommend it: it was prospective (i.e. it was not a chart review of cases whose outcomes were already known), and it involved patients from several hospitals. The limitations of the small retrospective studies that preceded it—including some that had the opposite finding—were far greater. In sum, this is the best study on this topic we know of to-date.

At this time, if a patient's symptoms can be adequately treated with NSAIDs and there are no other contraindications to its use, the presence of covid-19 should not deter using this effective class of fever and pain-reducing medications.

As ever, the covid-19 pandemic has been humbling for healthcare providers and researchers. Over and over, we have seen that concrete data from robust studies (i.e. not relying on retrospective studies) are needed before making conclusions both about which medications to give our patients and which ones we need to avoid. *10 May 2021*. *—Joshua Niforatos, MD, MTS*

Pfizer/BioNtech vaccine data indicates 100 percent reduction in SARS-CoV-2 among US children ages 12-15. Will it save any lives? Almost certainly.

The US Food and Drug Administration extended the Emergency Use Authorization for the Pfizer/BioNtech vaccine to adolescents ages 12-15 on Monday. The FDA published data on the safety and efficacy of the mRNA-based vaccine, which has been administered to millions of adults in 93 countries without any major safety concerns so far.

The short of it is that the vaccine performed well, according to data that followed the outcomes of adolescents who received either the vaccine or a placebo. There were 16 cases of covid-19 among adolescents who received placebo and *zero* among those who received the Pfizer/BioNtech vaccine. We do not know how serious the cases in the placebo group were.

But first and foremost, this was a safety assessment. Over half of the adolescents who received the vaccine experienced headache or fatigue after the first dose and nearly 2/3 of recipients had these symptoms after the second dose. As with the adults, a lower but still impressive number of people who received a placebo shot also reported these symptoms (around 35-40 percent). Interestingly, the number of subjects with these symptoms was *lower* after the second placebo dose, implying that psychological effects of were higher after the first sham shot than the second. In fact, rates of most side effects were higher after subjects got their second "real" dose, while almost all of those same side effects went down the second time among those getting placebo. (As a sidebar, I add that the human mind is never ceases to amaze). The rate of severe symptoms was generally under 1 percent, though for a few systemic reactions like headache, up to 2 percent reported a "severe" instance, and 2.3 percent reported fevers as high as 102-104F (38.9C-40.0C).

But what about "serious adverse events," define as death, a life-threatening adverse event, hospitalization (or prolonging of an existing hospitalization), disruption of the ability to conduct normal life functions, or any "important medical event"? In the place group 0.1 percent of the 1,100 subjects (or around 1 person) reported such an occurrence, compared to 0.4 percent (4 people) in the vaccine group. We were not given granular details on these 5 events, but it's more likely that the events were of the milder nature of these "severe adverse events" (i.e. prolongation of existing hospitalization as opposed to death), both by virtue of the odds of death in general being low, and the absolute scandal that it would be if 4 deaths out of 1,100 kids in the vaccine arm were not mentioned to the FDA. The FDA document states that there were "no notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine."

Meanwhile, antibody levels taken one month after the second dose were excellent among 12-15-year old subjects included in the dataset. In fact, the levels were more robust than those seen among 16-25-year old test subjects from previous studies.

So far, in the US, 282 children ages 0-17 have died from covid-19. If the vaccines are 95-100 percent effective in reducing deaths among this group, as they appear to be in younger adults, the new data mean that vaccinating kids could save hundreds if not thousands of pediatric lives in the United States in the coming months. Just how many remains unknown. However, we can make some educated guesses. If it is the case that 50 percent of US children have already been infected with SARS-CoV-2, then fully vaccinating the entire pediatric population would effectively safe 282 pediatric lives (since half remain unexposed and we assume that the mortality rate would apply if the kids were not vaccinated). If merely 20 percent of US children have been exposed (which is possible, given school closures), vaccines would be poised to save over 1,100 more lives of US children. These numbers, of course, do not take into account the suffering related to far higher rates of hospitalization and other complications such as the multi-system inflammatory syndromes in covid-19 (MISC), which according to the US Centers for Disease Control and Prevention has affected over 3,000 US children as of April 2021.

Pediatric vaccinations appear safe in the short-term. Assuming this continues to be the case in the longer run, vaccinating kids will remain an important tool in ending the covid-19 pandemic. *11 May 2021*.

—Jeremy Samuel Faust MD MS

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