*19 March 2021*

# ***BRIEF19***

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

## ***RESEARCH BRIEFING***

***Brief19* turns one. What we've learned and how our guiding principles have worked. (And yes, a little new research on Vitamin D as well).**

This weekend marks the one-year anniversary of *Brief19*. We've produced a daily briefing five-days per week for the entire year, without missing a day (not even for holidays), plus breaking news, and week-in-reviews on Saturday (Research) and Sunday (Policy). Covid-19 has not taken a break, so neither have we.

Looking back on our briefs over the last year, there is very little I would change. In my view, we've been on the right side of virtually every major research and science question. That's because we've stuck to some key principles which apply both to covid-19, and medical and scientific evidence in general:

1. Correlation is not causation. Anecdotes are not only not evidence; they're often the inverse of reality.
2. Good ideas are not enough. Convalescent plasma sounds like a great idea. Give patients with covid-19 a boost of antibodies taken from a recovered patient. The problem is, when scientists performed clinical trials, it almost never worked. A recent study found a subset of patients who benefit, but only under rarified conditions. On the other hand, great harm can ensue, and sometimes in ways we do not expect. That's why giving treatments on a "what's the harm" basis are intellectually destitute, and potentially dangerous.
3. Covid-19 is likely to unveil some of medicine's greatest weaknesses. When that occurs, we highlight it. This has meant putting racial disparities and structural racism on equal footing with other risk factors for serious covid-19 illness.
4. Therapeutics that have long been used by the medical profession are highly unlikely to be game-changers. Why? Because thousands if not millions of healthcare professionals have been fighting infectious diseases with the benefit of modern medicine for decades or longer. If there were something under our noses that could knock out coronaviruses (or any respiratory virus), we would likely know about it and would have studied it properly. That said, exceptions occur and randomized controlled (and ideally blinded) trials are the only way to reliably detect these rare wins. Dexamethasone, a steroid long in use for a variety of conditions, remains the only drug we know of with high quality evidence that it lowers mortality.
5. Novel therapeutics (i.e. drugs) may turn out to play some role in treating covid-19, but we are highly skeptical; we assume nothing works *unless* there is compelling high quality, non-anecdotal, non-retrospective data to show us otherwise (the same principle applies to repurposed therapeutics described above). When pharmaceutical companies deploy their "usual tricks," we become *extremely* wary. By "usual tricks" I mean that researchers who are being paid by pharmaceutical companies to study their own drugs do things that undermine our confidence in the results. The most glaring and frequent problems are: 1) changing the primary outcome of a study in the middle of the study. This suggests that an initial and often loftier goal is not being achieved and there is a salvage mission underway; 2) the outcomes being measured are "strange bedfellows." If a trial is measuring whether a drug decreased hospitalizations *or* deaths (i.e. combining those two outcomes), we wonder why the trial does not just measure one or the other? Usually it is because without the statistical combination, the "positive finding" disappears. And

indeed, spending the night in the hospital and *dying* are not exactly interchangeable outcomes. This is why despite some signal of benefit for some of the designer monoclonal antibodies in one of the recent studies, we remain underwhelmed.

6. We've been bullish on vaccines from the get-go. Why were we cautiously optimistic (and then jubilantly so) about vaccines, when we were so pessimistic on most therapeutics? Because of a simple difference in the way vaccines work as compared to therapeutics. Therapeutics more or less try to add a weapon to our immune system's response to infection. It's like adding a gun to the armamentarium. But it's rare that a drug is strong enough to make a difference without scorching the Earth. But vaccines in essence trick the body into thinking it has been infected. This one act of biological trickery coaxes the immune system into mounting a multi-pronged attack. If a drug is akin to adding one weapon to the battlefield, vaccines are more like activating an already fully functional army that has been lying in wait. Once we saw data that the vaccines could elicit strong immune responses in people, and showed some clinical efficacy in animals, we felt confident that vaccines would work to some degree. That said, the extent to which the vaccines turned out to work were a pleasant surprise, almost surpassing our highest hopes.
7. Preprints (scientific manuscripts that are posted online but have not undergone peer review) are no better or worse than peer-reviewed studies. We look at data with the same critical eye, regardless of whether it is in a top medical journal or not. Many of the best preprint manuscripts we have covered have gone on to publication in influential and prestigious publishing houses.
8. Go beyond what research says and dive into what it means. Yes, we describe the latest data from top medical journals. But we try to emphasize a fair and measured interpretation. Our recent coverage of coronavirus variants has been a case-in-point. We've described the fact that the variants seem to avoid neutralization by antibodies derived from vaccinated peoples' blood. But we've also pointed out that the lower levels are still *well* above the boundary for therapeutic effect. So while the numbers sound scary, we place numbers in context. Similarly, the B.1.1.7 (United Kingdom) variant was described in the media as increasing mortality by 64 percent. But we noted that the death rate in the cohort studied went from around 3 to 4 deaths per 1,000 infections. That's real, but not a doomsday outcome.

Do we get it right every time? No. But these principles have helped us bring you level-headed perspectives and we hope they will continue to do so.

And sure. I can't help myself. There's always some new information to share. Today in *JAMA Network Open* there's a new study on Vitamin D and the risk of SARS-CoV-2 infection. The researchers found an increase in test positivity (i.e. how many positive tests there were divided by the number of tests performed) among Black people with low Vitamin D levels, compared to those with normal levels. The finding was not present in White people. This was not a clinical trial though. It was an observation study. If you've been reading our blog all year, you know what that means: the findings could be a proxy for something entirely unrelated to Vitamin D, though the investigators attempted to control for potential confounders such as other medical comorbidities. Alternatively, the findings could be a real reflection of something about low Vitamin D and the immune system. A randomized study, designed similarly to a vaccine trial following uninfected patients over time to track for future infection, would be helpful.

Thanks for reading *Brief19*.

*—Jeremy Samuel Faust, MD MS*

## ***POLICY BRIEFING***

**Interim guidance on changes in CDC procedures.**

Back in February, *Brief19* reported on efforts announced by the US Centers for Disease Control and Prevention (CDC) to depoliticize the agency and focus on promoting evidence-based and scientifically-validated recommendations. As a result, the CDC recently released its review on changes being made across the board at the agency.

The Principal Deputy Director for the CDC, Dr. Anne Schuchat, conducted interviews with incident managers of various Emergency Response task forces within the CDC, public health stakeholders, and career staff. The general findings of existing materials were that many documents were not primarily authored by CDC staff, relied on more suggestive (versus directive) language, and that the data to support some decisions was not consistently readily apparent. The report also included the following changes to existing documentation.

Guidance removed:

- "The Importance of Reopening America's Schools this Fall."
- "Overview of Testing for SARS-COV-2."
- "Opening Up America Again," linked on the CDC's website.

Also included were several reports recently (or soon to be) released, covering phased prevention, school guidance, targeted testing, exemption from quarantine following natural exposure versus inoculation, masking, and travel.

As data on potential and currently authorized vaccines are published, the agency will monitor and update its recommendations accordingly.

With regards to science, the CDC's website has been overhauled to make landing pages cleaner, easier to understand, and optimized to make the supporting science more evident. Overall, this iteration of the agency seems committed to removing or minimizing politics from its process and increasing the transparency of the factors guiding their decisions. *The Centers for Disease Control and Prevention.*

*—Brief19 Policy Team*

*Kimi Chernoby, MD, JD, Policy Section Founder, Joshua Niforatos, MD Research Section Editor, Frederick Milgrim, MD, Editor-at-Large, Joshua Lesko, MD Lead Policy Analysist, Barb Cunningham, Copy-editor, Benjy Renton, Thread-of-the-Week, Anna Fang, Week-in-Review. Megan Davis, social media. Kane Elfman PhD, Publishing and Design. Jeremy Samuel Faust MD MS, Editor-in-Chief. http://www.brief19.com/ 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 and public policy.*