Lax peer review + social media + confusing and misinterpreted data: Why so many COVID-era studies presented incomplete science

The pandemic has upended many practices, among them peer review of technical medical and scientific articles.

Lax peer review + social media = misunderstanding science

Pre-COVID, the preprint sites bioRxiv.org (“bio-archive,” founded in 2013) and medRxiv (“med-archive,” founded in 2019) were mainly the province of science and medical journalists, and of course researchers. Preprints are technical papers that haven’t yet been peer-reviewed, a process that can take months. Preliminary screens remove outrageous claims and check for plagiarism.

Until a few months into the pandemic, the warning on both sites not to report on these papers was hard to navigate to, but seasoned journalists knew to respect the conditions. With general assignment reporters suddenly covering a health care crisis that increasingly required knowledge of virology, immunology, and biotech, medRxiv and bioRxiv became great sources of news.

The disclaimer was moved to the opening page:

> Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information.

The warning hasn’t helped.

Skipping peer review leads to confusion and the spread of misinformation, especially through the echo chamber of social media. “COVID Vaccine Preprint Study Prompts Twitter Outrage,” for example, details the hoopla over a medRxiv preprint that, according to experts on the statistics used, grossly overestimates the risk of heart inflammation in male teens after taking the Pfizer-BioNTech vaccine. The yelling continues.

Clinicaltrials.gov as a crystal ball for countering COVID

I still hesitate to use preprints as sources for my articles – this is my 79th on COVID. But I do indulge in looking ahead, by perusing clinicaltrials.gov. Anyone can register a clinical trial at this site – the intent to run one, as well as detailed protocols as experiments proceed through the 3 phases (safety, safety and efficacy, safety and efficacy on more people).

Credit: NLM

My main interest in ongoing and upcoming COVID clinical trials is to follow the retooling of vaccines to cover new viral variants, for SARS-CoV-2 will continue to mutate and spread as long as pockets of vaccine hesitancy and refusal persist. The nucleic acid sequences that lie at the core of the vaccines must correspond to the exact ways new variants differ. That's what a team of 16 experts writing in a Viewpoint in *The Lancet* concluded, including the two officials who recently resigned from FDA in the wake of the too-soon presidential booster announcement:

> The effectiveness of boosting against the main variants now circulating and against even newer variants could be greater and longer lived if the booster vaccine antigen is devised to match the main circulating variants. There is an opportunity now to study variant-based boosters before there is widespread need for them.

They then compare the situation to the yearly development of new flu vaccines.

So I thought I'd peruse the thousand or so entries that pop up at clinical trials.gov searching under "COVID" and "vaccine." It's an eclectic list.

1. The number of studies exploring old vaccines, like the old TB vaccine BCG, has dropped, as things haven't panned out.

2. Many investigations are evaluating the existing vaccines in various populations, based on geography, age, and combinations of co-morbidities, for example.

3. Several studies “mix and match” vaccine types (Pfizer for one, Moderna for the other, while some pit vaccines against each other, like 40,800 people in Turkey who got either an experimental inactivated vaccine (TURKOVAC) or Sinovac, an approved inactivated vaccine from China.

4. Some new studies look for unusual vaccine side effects, like in the mouth, and vaccine distribution, such as in milk.

5. Lots of texting is going on. Mebo Research’s COVID-19 Back-to-Normal Study is tracking bad reactions to vaccines in 1,000 people for a year, while UCLA researchers are texting 400,000 people, urging them to get vaccinated. Ascension South East Michigan’s “Text Message Nudges for COVID-19 Vaccination” are going to 1500 health care employees, and “Vaccine Acceptance Intervention for Veterans” is deploying “motivational interviewing” for 2500 veterans. Efforts at the University of Massachusetts in Worcester and in Ontario help primary care providers fight vaccine hesitancy.

6. Some clinical trials are testing vaccines delivered to different body parts. Immunizing in the nose, throat, and/or mouth would increase production of IgA antibodies, to complement the IgG antibodies that the approved vaccines elicit, but by themselves aren’t powerful enough. CyanVac’s entrant is a nasal spray that targets the viral spike, but is hooked up to a parainfluenza vaccine – a dog distemper shot. The vaccine elicits antibodies and killer T cells.

I’m most intrigued by a vaccine candidate from ImmunityBio. It’s being tested on people who’ve had their 2 Pfizer or Moderna shots, 20 participants receiving it under the tongue and another 20 under the skin. The third dose targets the spike as well as the nucleocapsid proteins that hug the virus’s genetic material, and also includes an “enhanced T cell stimulation domain” to hike T cell production. The T cell response, only recently demonstrated for the first vaccines, is a much more telling measure of durable protection than antibody ups and downs.

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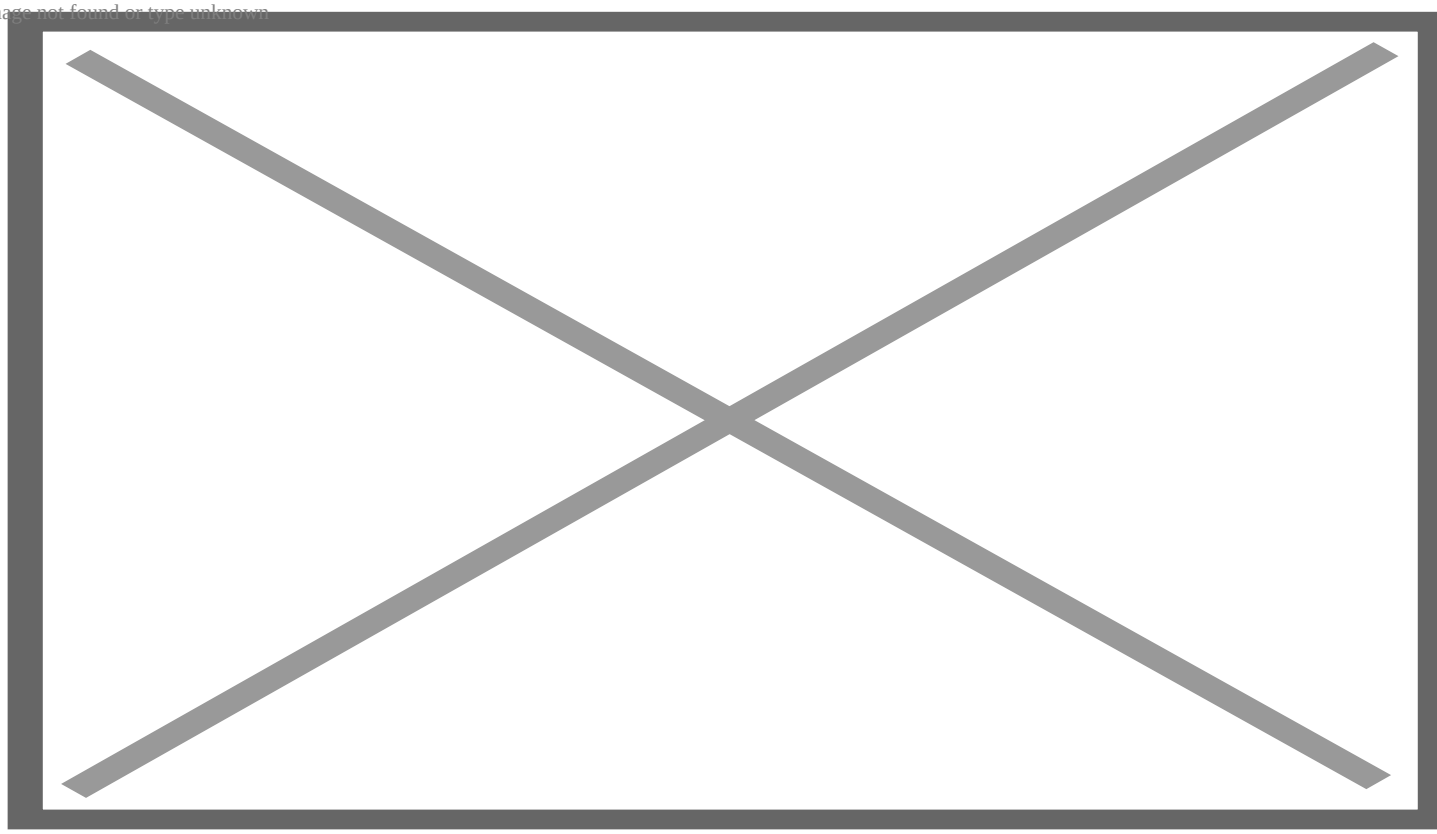

Credit: VectorStock

Leonard Sender, Chief Operating Officer of ImmunityBio, announced preliminary findings. “Our U.S. data show that just a single prime subcutaneous vaccination with our COVID-19 vaccine candidate induces a 10-fold increase in T cell response—equivalent to T cell responses from patients previously infected with SARS-CoV-2. The T cell responses are maintained against variants, which is critical to providing protection against this ever-changing virus.”

7. Moderna and Pfizer and others have been tweaking their vaccines to cover additional viral antigens for months, since the variants began sweeping the planet. Moderna’s trial of a vaccine against the B1.351 variant (South Africa) is set to conclude next August, with efforts against delta not far behind.

8. Some vaccine manufacturers are anticipating COVID becoming endemic – a constant presence everywhere. Novavax, for example, is testing it’s COVID-flu combo in Australia.

9. Magical mystery trials. How about passive immunity from antibodies in horse serum? Or the “universal anti-viral vaccine for healthy elderly adults,” aka AlloStim, from Immunovative Therapies. It’s an elixir of donor memory T cells to replace a person’s tired ones, oozing cytokines such as gamma interferon early in viral infection. The cells protect against “any future variants, strains, mutations of the causative SARS-CoV-2 virus as well as protection from any future currently unknown newly emergent novel viruses.” Wow.

The failure of the entire United States to get behind the vaccine effort is going to keep COVID among us

for longer than might have been, a tragic lost opportunity that I just can't wrap my head around. I think we have another two or three years until SARS-CoV-2 settles down and becomes endemic, a seasonal infection about twice as deadly as influenza. It's good to know that so many anti-COVID products are in the works.

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