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Why clinical trials during disease outbreaks may need a new approach

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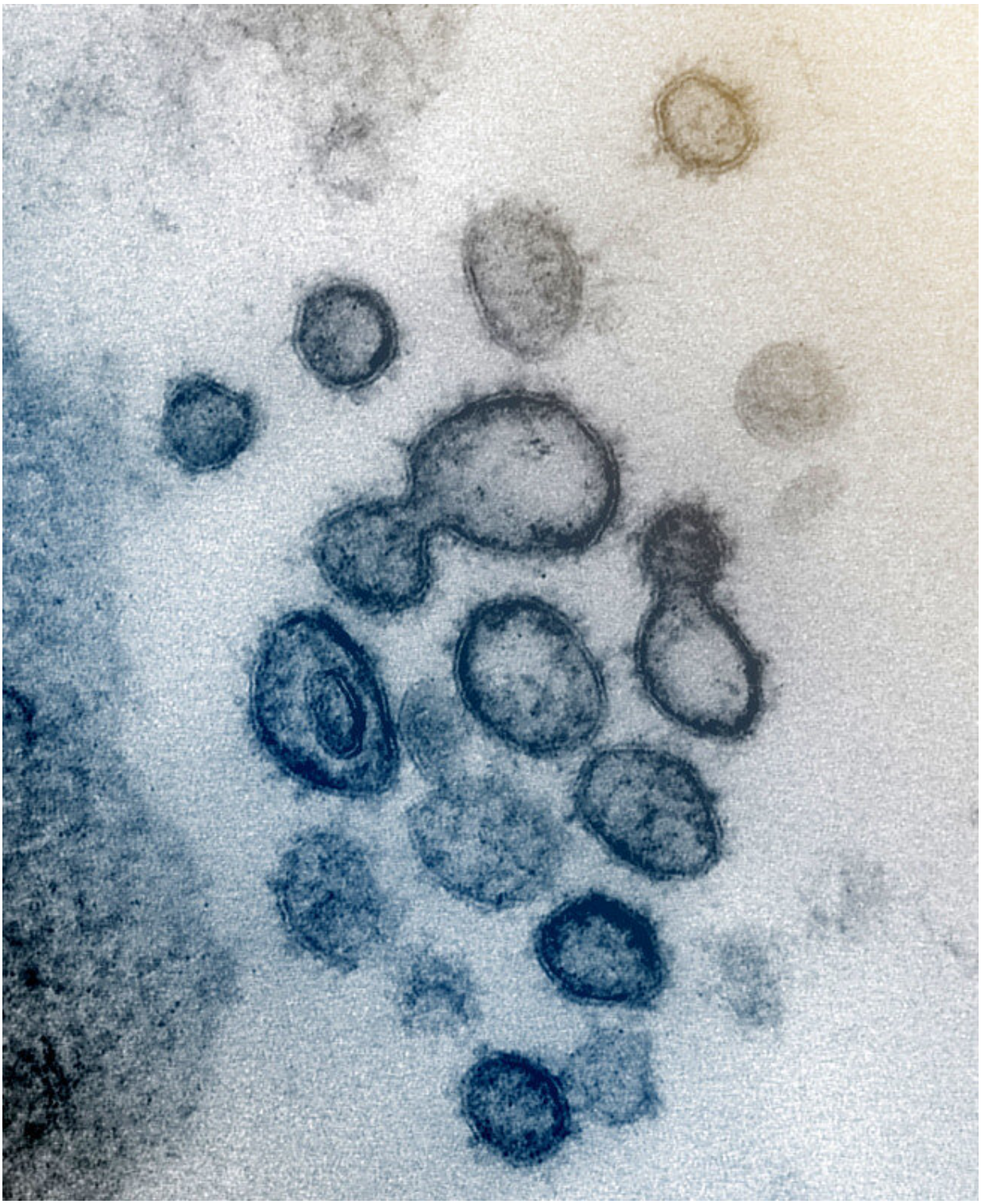

This transmission electron microscope image shows SARS-CoV-2 -- also known as 2019-nCoV, the virus that causes COVID-19 -- isolated from a patient in the US. Virus particles are shown emerging from the surface of cells cultured in the

lab. The spikes on the outer edge of the virus particles give coronaviruses their name, crown-like. Credit: NIAID-RML

Scientists around the world are racing to develop vaccines and treatments for the novel coronavirus in an effort to halt the global COVID-19 pandemic. While recognizing the need for speed, the scientific community is committed to ensuring these treatments are safe and effective through randomized clinical trials—the only proven path to that end.

However, during infectious disease outbreaks, a clinical trial, by design, can have drawbacks that may stand in the way of generating reliable evidence. As trials for COVID-19 treatments, like the drug Remdesivir, are already underway, researchers are hoping to avoid mistakes made during the West African Ebola epidemic, in which incomplete studies led to inconclusive results.

To that end, in a new paper published in the *New England Journal of Medicine* (*NEJM*), public health experts call for the implementation of a new kind of model during such epidemics: a so-called "core protocol," which would allow a single clinical trial to extend across multiple infectious disease outbreaks.

"The idea is that a trial might start as soon as possible once an outbreak was underway, but if the outbreak tailed off before enough information was collected, the data would be stored, rather than reported, and the trial would continue the next time another outbreak appeared," explained co-author Susan Ellenberg, Ph.D., interim chair of Biostatistics, Epidemiology, and Informatics at the University of Pennsylvania's Perelman School of Medicine.

As members of the World Health Organization's Research and Development Blueprint Working Group on Clinical Trials, Ellenberg and colleagues from around the world are tasked with addressing approaches to testing new therapies and vaccines in the context of infectious disease outbreaks. The authors did not specifically write the NEJM paper in the context of COVID-19, but Ellenberg said that a core protocol could and should be applied to clinical trials conducted during this pandemic.

"Let's suppose that within two weeks, the COVID-19 outbreak in Wuhan had become contained. Whatever trial that may have started there may not be able to finish. But there is disease in other areas. So, the idea is that the results of that initial trial would not be published, but the trial could be continued in other locations," she said.

The concept for the core protocol paradigm stems, in part, from lessons learned during the Ebola outbreak that took place in 2015 in West Africa. During the 2015-16 outbreak, a clinical trial to test the effects of the therapeutic ZMapp was underway. When the outbreak ended, the trial (called PREVAIL II) also ended abruptly and study results were published—even though they were not definitive. The authors of that study concluded that "although ZMapp appeared to be beneficial, the results did not meet the pre-specified threshold for efficacy," and the evidence of efficacy clearly did not meet the conventional standards for licensure.

Nevertheless, in 2018, when a large Ebola outbreak emerged in the Democratic Republic of the Congo (DRC), many doctors chose to treat patients with ZMapp based on its preliminary promise, even though it wasn't thoroughly proven. That included doctors conducting a new randomized study—the PALM trial—that used ZMapp rather than a placebo as the control group against which to compare other Ebola therapeutics. Releasing promising but inconclusive results from partially-completed trials, and then leaning on that shaky knowledge during future

outbreaks "can create a state of perpetual uncertainty" when it comes to both the drug whose effectiveness was not yet proven (in this case, ZMapp) as well as the new drugs it's being compared to, Ellenberg and the WHO committee authors write in their new paper.

How do you prevent this kind of uncertainty and potential adverse consequences? The WHO committee authors say that "core protocols," in contrast, should specify that data from a trial that has not yet been completed due to insufficient enrollment should not be released. They argue that this approach can speed the implementation of clinical research in successive outbreaks—such as from the transition of Ebola research efforts in West Africa in 2015 and 2016 to those in the DRC in 2018.

"Although the PALM trial was successful in identifying two promising therapeutics, there were limitations resulting from the use of ZMapp as the comparator group, because its clinical benefit had not been definitively established during the PREVAIL II trial," the researchers argue. "These challenges could have been largely avoided if the PREVAIL II trial had been designed under a core protocol."

In fact, although two therapeutics outperformed ZMapp in that study, we still do not know whether ZMapp has any effect at all—something that would be useful to know if combination regimens are developed, or if some patients develop intolerance to the superior treatments, Ellenberg noted.

A challenge with this kind of approach, Ellenberg said, is that during an infectious disease crisis, there will always be public and political pressure to release interim results of these kinds of studies.

"In the early days of the AIDS epidemic, people said, 'Whatever it is, let's try it. I don't care if it's only been through a Phase I trial.' But the

thoughtful activists recognized that having hundreds of drugs out there is not going to help you if you don't know which ones are going to work, and, eventually, AIDS activists became the strongest advocates for rigorous trials," she said.

"You can certainly understand the position of people who want to do anything they can—as soon as they can—to try a treatment that might work. But if we give in to that, we may never know what will really work, and that will disadvantage everybody."

More information: Natalie E. Dean et al. Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks, *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMsb1905390

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