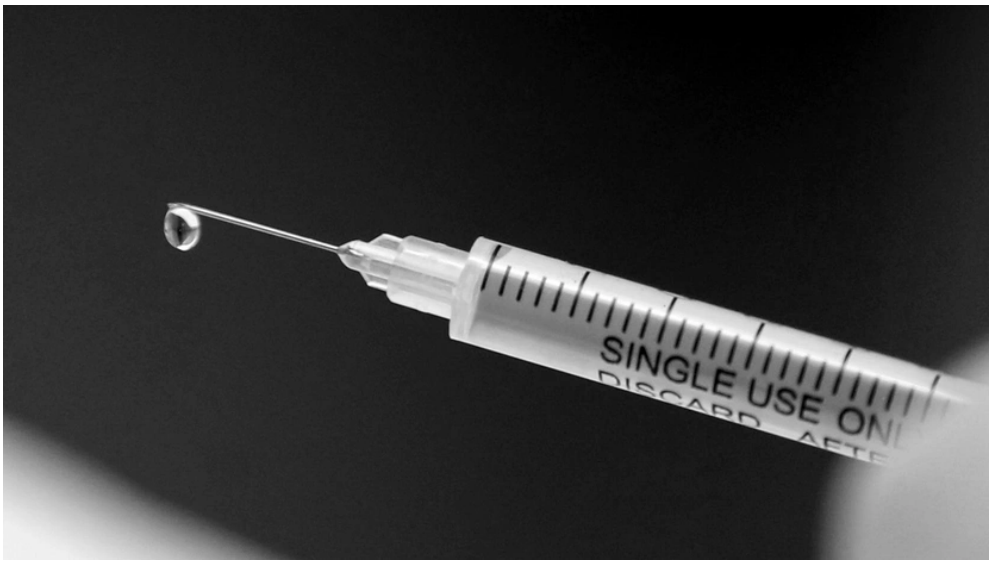
The Atlantic

HEALTH

The Long Haul of Vaccine Results Is Just Beginning

The initial results of the AstraZeneca/Oxford vaccine trials were unexpected and confusing, but there's more data to come.

SARAH ZHANG **DECEMBER 1, 2020**



SIPHIWE SIBEKO / REUTERS

The first two coronavirus-vaccine trials ran as smoothly as anyone could hope. And when the results from both Pfizer/BioNTech and Moderna came back with more than 90 percent efficacy, easily surpassing the FDA's bar of 50 percent, even people like me—who kept telling you to temper your vaccine expectations—reacted with uncharacteristic and unrestrained optimism. These results really were about as good as it gets.

Then came the results for a third vaccine, from AstraZeneca, developed in collaboration with Oxford University. At a glance, these looked good, if not spectacular: an average of 70 percent efficacy. But that top-line result obscured a strange divide between a full, two-shot regimen, which showed 62 percent efficacy, and a half-dose shot followed by a full-dose second shot, which showed 90 percent efficacy. Those split results were immediately confusing—was less vaccine more effective?—but became even more so as more information came to light.

The half dose actually began as a manufacturing mistake, and the volunteers who received it were all younger than 55, and younger people often have better responses to vaccines. Plus, the 90 percent efficacy is based on a small number of cases—possibly small enough to create a statistical fluke. The workings of the human immune system are especially un-intuitive, and scientists have offered plausible biological reasons why a half dose might be superior. But given the data

available so far, "it's basically uninterpretable at this point," Shane Crotty, an immunologist at the La Jolla Institute for Immunology, says. Several scientists said they were glad that these muddled and confusing results from AstraZeneca/Oxford were not the first COVID-19 vaccine data to be released.

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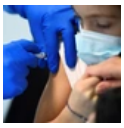

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Nevertheless, the news here is good: Another vaccine works. Although Pfizer/BioNTech's and Moderna's trials went about as perfectly as possible, AstraZeneca's announcement demonstrates how an honest mistake, a confusing trial design, and a lack of transparency can compound one another to create unnecessary confusion at a time when vaccines are under heightened scrutiny. "At the scale at which we're planning to deploy these vaccines, we don't want to leave any room for doubt," says Natalie Dean, a biostatistician at the University of Florida who specializes in infectious disease and vaccine-study design. In an ideal world, many effective vaccines, deployed in tandem, would bring the global pandemic to a timely end, but each vaccine candidate is unique and needs to be evaluated individually.

[Read: The end of the pandemic is now in sight]

Before vaccine manufacturers can give any experimental shots, they have to decide the number of people they will enroll in the trial, their definition of effectiveness (for example, will the vaccine be judged on its ability to prevent symptoms, or severe death, or transmission?), and the statistical analyses they will use. Changing the study protocol after it's set is usually frowned upon because it can muddy the results, which is exactly what happened with the dosing error in AstraZeneca/Oxford's vaccine. After U.K. scientists discovered the manufacturing error that created the weak doses, they got permission to modify the protocol and keep going.

This unusual change might require extra transparency, but that didn't happen here. The original press releases neither acknowledged that the half dose was originally a mistake nor explained the full data behind the 90 percent–efficacy number. A company spokesperson said that a peer-reviewed study with more details is forthcoming. But even in these very splashy initial press releases the company has

been less transparent, Dean notes, than Pfizer/BioNTech and Moderna. Those companies released results based on predetermined milestones laid out in published and detailed U.S. trial protocols; AstraZeneca has shared similarly detailed protocols for its U.S. trial, but the data undergirding last week's announcement came from the U.K. and Brazil. The U.K. component of this vaccine trial alone has 28 arms, an unusually large number, where participants are divided by age and various dosing regimens. The Brazilian trial has a simpler design. (Moderna's trial, in comparison, has two arms: vaccine and placebo.) The AstraZeneca announcement pooled data from the U.K. and Brazil without specifying how the groups might be different.

Thus the confusion when more information began to trickle out—but not from the company itself. On Tuesday, the day after AstraZeneca's announcement, Moncef Slaoui, the head of Operation Warp Speed, the U.S. government's vaccine effort, told reporters that only people younger than 55 got the half dose, while the full-dose group included people older than 55. That presented a problem: Younger people have immune systems that tend to respond more robustly to a vaccine, so the 90 percent and 62 percent efficacy rates in those two groups are not directly comparable. Moreover, only 2,741 of the more than 23,000 people whose data were included in the announcement got the half dose, so it's unclear if the seeming benefit of the smaller dose will hold up in a larger trial. AstraZeneca is now eyeing a new trial to validate its half-dose regimen.

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If the effect of the half dose is real, the type of vaccine that AstraZeneca and Oxford made might help explain that. It's a vector vaccine, which uses a more innocuous cold virus, called an adenovirus, to deliver instructions to the body for making a key coronavirus protein. But the immune system might also learn to recognize and attack the adenovirus vector, making the second shot less effective. Perhaps a smaller first dose can mitigate that effect. (Pfizer/BioNTech's and Moderna's vaccines use a different technology, called mRNA.) But without more data, this is just a hypothesis.

The manufacturing error that led to the half dose will probably go down as a fortuitous mistake. Even if the half dose is not *more* effective, it certainly doesn't seem to be *less* effective. A smaller effective dose means you need to manufacture less vaccine per person, which would be cheaper—and AstraZeneca/Oxford's vaccine already is cheaper to make and easier to store than Pfizer/BioNTech's or Moderna's. This, again, is good news, which might have gotten lost in the confusion over the data.

As more trials conclude in the coming months, there will be more news like this—sometimes good, sometimes confusing, and sometimes disappointing. But setbacks for individual vaccines shouldn't make us lose sight of the big picture: Less than a year into the discovery of a new virus, we already have three effective vaccines against it. More vaccines could help, but these three alone will make a big difference in our lives over the next year.