An Ethical Path to a Covid Vaccine

Carl Elliott
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Adverse Events: Race, Inequality, and the Testing of New Pharmaceuticals
by Jill A. Fisher
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When will we get a vaccine? That's the question Americans have been asking since the novel coronavirus shut down much of the country in March. Dr. Anthony Fauci says it could happen this year. Others think it will take a lot longer. The HPV vaccine took fifteen years to develop. The chickenpox vaccine took twenty-eight. No widely effective vaccine has ever been developed for many life-threatening viruses, including cytomegalovirus and HIV.

Ted Warren/AP Images

Jennifer Haller, the first person to be injected in a clinical trial of a potential vaccine for Covid-19, Seattle, March 2020

One potential way to speed up the development of a vaccine for Covid-19 is a "challenge study," in which researchers give healthy subjects a prospective vaccine and then infect them with the coronavirus. In conventional trials researchers typically give subjects either a test vaccine or a placebo and follow them over time in their ordinary living conditions to see if the vaccine is effective. But there's no need to wait for a naturally occurring infection in a challenge study, which allows it to be shorter and to require far fewer subjects. Yet such a study would also require deliberately giving those subjects a potentially deadly illness for which there is no good treatment, and for some observers, that's a deal-breaker. A joint statement by the AIDS Vaccine Advocacy Coalition and the Treatment Action Group says, "Until there is an approved treatment, a challenge trial with a potentially fatal and as-yet untreatable pathogen is unacceptable."

Nonetheless, the drumbeat for Covid-19 challenge studies is growing louder, and some of the most energetic drummers are bioethicists. Nir Eyal, a bioethicist at Rutgers, was one of the first to call for them.[1] His proposal, cowritten with the epidemiologists Marc Lipsitch of Harvard and Peter Smith of the London School of Hygiene and Tropical Medicine, appeared online in late March. Challenge studies have also been endorsed by the NYU bioethicist Arthur Caplan and the vaccinologist Stanley Plotkin.[2] Julian Savulescu and Dominic Wilkinson, bioethicist-physicians at Oxford, have raised the moral stakes even higher by proposing not just that researchers conduct Covid-19 challenge studies but that the first human subjects could be elderly nursing home patients. "Their motives might be purely altruistic," Savulescu and Wilkinson wrote. "Or they may be fatalistic or wish to die, or at any rate not care if they die sooner rather than later."[3]

The utilitarian argument for challenge studies is straightforward: calculate the number of lives risked and compare it to the potential number of lives saved. Backers of challenge studies point to a study (based on data from China) that estimates the risk of death from Covid-19 for a healthy adult between the ages of twenty and twenty-nine at 0.03 percent.[4] And if subjects are recruited from hot spots where the risk of getting Covid-19 is very high anyway, they argue, infecting them deliberately wouldn't put them at much greater risk. At least in a challenge study their medical condition would be closely monitored.

Challenge studies are troubling, of course, because many of us recoil at the thought of infecting healthy human subjects with a pathogen. But such studies are not unusual. Nor are they limited to the annals of past research abuses such as the Guatemala syphilis study in the late 1940s, in which US Public Health Service workers gave syphilis and gonorrhea to Guatemalan prisoners, soldiers, prostitutes, and psychiatric patients.[5] Not only have infectious disease researchers in the modern era intentionally infected people with pathogens ranging from influenza to malaria and cholera, but they have done it with the approval of institutional review boards charged with protecting human subjects. Defenders of challenge studies argue that there is nothing wrong with infecting subjects as long as they have consented, the risks are minimized, and the studies are held to the same established ethical standards as others are.

Many people are convinced that Covid-19 challenge studies should proceed. Thirty-five members of the US House of Representatives have called for them. The World Health Organization has not explicitly endorsed challenge studies, but it has published guidelines for how they might be ethically conducted. Among the strategies the WHO recommends to minimize risk to the initial subjects is to expose them to the virus "one by one, with meticulous titration of viral dose." Some scientists worry that a small study may not reveal all the potential side effects of a vaccine, and that the results of a study on young healthy people may not be relevant to older, less healthy patients. Nevertheless, a website for a nonprofit group called 1DaySooner says it has signed up over 26,000 volunteers for Covid-19 challenge studies.

A useful comparison is Phase I drug trials, which are usually conducted to determine if experimental drugs are safe. As in challenge studies, researchers in Phase I trials intentionally expose their subjects to potentially serious risks not in exchange for any potential benefit to the subjects themselves but rather for the advancement of scientific knowledge. Research sponsors typically pay subjects between $200 and $250 a day to check into a locked research unit for several weeks while they are given an experimental drug. Researchers usually monitor their blood, urine, and vital signs, and some studies require invasive procedures such as lumbar punctures, biopsies, or endoscopies.

Because Phase I trials are such a routine part of drug development, bioethicists and social scientists have subjected them to far more scrutiny than challenge studies. In *Adverse Events*, the sociologist Jill Fisher has provided the most thorough examination yet.[6] What can we learn from the way these trials are done?

Until the late 1970s most Phase I trials were done on prisoners.[7] Today they are done mainly on poor people. A subject Fisher calls "Bob" was unemployed and on probation in St. Louis when he began doing paid studies at Washington University. They didn't pay much, and some of them were grueling. One required him to ride a stationary bike with an endoscopy tube down his throat. When his probation ended, Bob began traveling around the country doing better-paid studies and competing in poker tournaments. By the time he spoke to Fisher he had done drug studies in seventeen different states. "That's my golden vein," he said, pointing to a scarred hole on his inner elbow where his blood had been drawn. "You can see I got, you know, a cavern there. Been stuck many times."

Like prisons, poultry processing plants, and funeral homes, Phase I trial sites occupy a segment of the American economy that is not so much hidden as overlooked. If the world that Fisher reveals in *Adverse Events* is unsettling, it is mainly because of the routinized, factory-like conditions under which Phase I trials are conducted. The effect is a little like that of *Titicut Follies*, Frederick Wiseman's 1967 documentary about the Bridgewater State Hospital for the criminally insane. What stands out is not the casual cruelty (although it is occasionally evident) but the institutionalized indifference to the humanity of vulnerable people.

Fisher did fieldwork in six trial sites across the country. One was an academic site in a hospital, one was associated with a pharmaceutical company, four were commercial sites (two of which were independent and two affiliated with contract research organizations). The pharmaceutical company site was a state-of-the-art unit, but conditions at some of the commercial sites were grim. One was located in a former manufacturing facility, another in a converted warehouse. The largest was capable of housing three hundred subjects and included a vast space with over eighty beds lined up in rows. On Fisher's first visit to the site, these beds were occupied by healthy subjects lying on their backs with their arms at their sides. "Many stared blindly at the ceiling," she writes.

Several sites were located miles away from any hospital emergency room. Fisher compares them to "overcrowded prisons." Yet many subjects had seen far worse. "We had dogs—bedbug sniffing dogs—come in because there were bedbugs in the facility," one subject said. "Air conditioners were broken. The beds would stink…. It was horrible."

Some of us may imagine that research subjects take part in studies for humanitarian reasons. But in Phase I trial sites this is rare. "I wanted to make some money," one subject told Fisher. "It's definitely not because I want to save the world. Let's get that on the record right now." While some of those Fisher talked to have enrolled in the occasional trial to make extra cash—to finance a vacation or an expensive engagement ring—most are serial research subjects with few alternatives. "What are we gonna do?" said a Native American man in his late twenties. "If I don't pay my parole, I'm gonna go back to prison." A young Hispanic woman whose husband had also done studies for money told Fisher, "Because we are not here legally, we don't have another option left."

Many of the subjects felt so ashamed of their participation that they hid it from their friends. "Once they call you a lab rat, you're done," a subject said. "You're like a roasted duck. It's over." The shame frequently came on top of other stigmatizing conditions: unemployment, poverty, a criminal record, lack of immigration papers.

Of the 235 research subjects Fisher interviewed, over 60 percent were minorities and 35 percent were African-American. Over a third of African-American subjects had done more than ten studies, and six African-American men had done over fifty. Fisher didn't ask subjects specifically about their income or health insurance, but the answers would likely have been depressing. A survey of a Pfizer trial site in Connecticut found that only 12.5 percent of the subjects had full-time employment.[8] Nearly half had household incomes below $25,000 a year, and over 38 percent had no health insurance. These figures raise troubling issues. Even if the drugs in Phase I trials are eventually approved, many of the subjects who have tested them may not be able to afford them if they get sick.

If all goes well in a study (as it generally does), subjects experience no side effects or only minor ones, such as nausea, headaches, or a rash. Yet many of Fisher's subjects had disturbing stories. One told her about a study in which the majority of participants experienced sleep paralysis, a frightening state of being conscious but unable to move or speak, which can include vivid hallucinations. A subject who tested a drug for ADHD described the effects as something out of a horror movie. "I thought that I was going crazy," she said. Another took part in an antibiotic study in which the subjects lost control of their bodily functions. "So, at the same time we were throwing up, everything else was releasing," she said. "It was like a scene out of *Poltergeist*."

Some of the subjects Fisher interviewed avoided Phase 1 vaccine trials, worrying that they were too dangerous or that long-term side effects would disqualify them from doing more

trials. And indeed some Phase 1 vaccine studies have had serious problems. In 2004 an Alabama physician paid twenty-one clients of a homeless center to test an experimental smallpox vaccine. Two had to be hospitalized and a third contracted pericarditis.

Only rarely do subjects in Phase I trials die. Traci Johnson, a nineteen-year-old student, committed suicide in 2004 during an antidepressant study at an Eli Lilly facility in Indianapolis. A mentally ill veteran, Walter Jorden, died of a heart attack at a New Jersey trial site in 2007 while testing an antipsychotic medication. In 2016 a previously healthy volunteer died and several others were severely injured while testing an experimental drug at a Biotrial facility in France. In 2006 six healthy subjects at a trial site at Northwick Park Hospital in the United Kingdom came very close to death after an experimental monoclonal antibody sent them into multisystem organ failure.

Most of the subjects Fisher interviewed had been desensitized to the risks they were taking, mainly out of sheer repetition. “The reason why I don’t too much think about the risk [is] because I’ve done it so many times,” a Pakistani immigrant said. “If something was supposed to happen to me, it would have done happened already.” Some subjects even claimed that the studies were good for them. “I know what my labs look like, and I’m more healthier now doing clinical trials than I’ve ever been in my life,” said one subject.

Staff members were skeptical. With near unanimity they told Fisher that the informed consent process for the trials had serious problems. Fisher interviewed one subject who had turned down an infection challenge study after reading in the consent form that participants had to drink feces-tainted water. An acquaintance who had consented to the study didn’t understand what “feces” or “excrement” meant. “He was like, ‘What does that [word] mean?’” the subject said. “I had to be like, ‘Look, dude, like they want you to drink dookie in a cup of water!’”

One of the most revealing stories in *Adverse Events* took place at the gleaming pharmaceutical industry clinic. An Alzheimer’s study required subjects to undergo a procedure that many of them dreaded like no other: a lumbar puncture, or “spinal tap.” While lumbar punctures are routine procedures in skilled hands, they can sometimes cause bleeding, infections, piercing headaches, and, in rare cases, brain herniation. Two anesthesiologists had been hired to place a catheter in the spines of subjects so their cerebrospinal fluid could be collected over a period of several hours.

A nurse brought Fisher into the research subject’s room. Five staff members were there, all white. The subject was black. He sat hunched and silent on the bed. (Fisher calls him “Devon.”) Without speaking to Devon, a white anesthesiologist injected his back with lidocaine and threaded a hollow needle through his vertebrae. But the anesthesiologist hired to place the catheter had not arrived, so everyone waited. More than twenty minutes after the appointed starting time, the second anesthesiologist finally turned up.

Without a word to Devon, the second anesthesiologist threaded a catheter into the hollow lumbar needle and the cerebrospinal fluid began to flow. But the catheter was not connected to a collection container, so the fluid just spilled out. Finally a staff member noticed and connected it to a specimen tube.

Devon endured the procedure unflinchingly, yet it never even occurred to the researchers to speak to him. They might as well have done the lumbar puncture on a plastic dummy. The routine use of Phase I trial subjects for purely instrumental purposes is one reason Fisher compares them to "model organisms" such as fruit flies or guinea pigs: "Like a laboratory animal in an experiment, Devon was a mere object of the procedure, providing the biological material that needed to be sampled without regard to informing him what was happening to his body."

In 1969 the philosopher Hans Jonas tried to pinpoint exactly what is morally disturbing about the use of human subjects in medical research. "What is wrong with making a person an experimental subject is not so much that we make him thereby a means," Jonas wrote, "as that we make him a thing—a passive thing merely to be acted on."[9] Jonas thought the way to right this fundamental wrong was to bolster the subjects' agency. They should not merely consent to an experiment, Jonas argued, but embrace its purpose as their own.

The things that disturbed Jonas most about medical research have become a routine part of Phase I drug trials. The research subjects are treated as instruments for purposes they don't identify with, they are drawn from the most vulnerable segments of American society, and the research is often conducted under grim, dehumanizing conditions. Yet this doesn't have to be the case for Covid-19 vaccine challenge studies. The pandemic has created a sense of urgency and shared purpose that is rare for medical research. Many idealistic young people not only embrace the purpose of Covid-19 vaccine studies but seem willing to risk their health for the common good. The question is how to make those studies safe and fair.

Imagine volunteering for a challenge study and the very worst happens: you die or are permanently disabled. What conditions would need to be in place for you or your family to conclude that you had been treated fairly? It goes without saying that you should have the rights elaborated in the Declaration of Helsinki, such as informed consent and the minimization of risk. But you might also ask that the study sponsor pay for your medical bills if you become ill. You might believe you deserve financial support if you are injured so badly that you could never hold a job again. You might ask for a promise that the vaccine developed from the study would be priced fairly and made available to everyone who needs it. At a minimum, you might want a guarantee that the data from the study would be made available to the scientific community and not hidden, spun, or declared proprietary.

Unfortunately, research subjects in the United States are not guaranteed any of these things. Research sponsors have no legal obligation to pay for the medical care of subjects who have been injured or sickened in a study.[10] This sets the US apart from every other developed country. According to *The New England Journal of Medicine*, a 2005 report for the Department of Health and Human Services found that only 16 percent of academic medical centers in the US made it a policy to pay for the care of injured subjects.[11] A 2012 survey found that over half of research institutions offered no compensation for research-related injuries, and only 1.2 percent offered any compensation beyond payment for immediate medical care.[12] The US does maintain a National Vaccine Injury Compensation Program, but it excludes payment for experimental vaccines.

Nor does the US have a stellar record when it comes to paying restitution to mistreated research subjects. This includes subjects injured in challenge studies. President Obama apologized for the Guatemala syphilis study in 2011, but the US government has refused to pay any compensation to the victims or their family members. Between 1951 and 1974 Dr. Albert Kligman, a dermatologist at the University of Pennsylvania, deliberately infected inmates at Holmesburg Prison with herpes simplex, herpes zoster, vaccinia, papillomaviruses, staph aureus, and ringworm. Not only has the University of Pennsylvania never paid any compensation to the victims for their suffering, it honored Kligman with two endowed professorships and a lectureship in his name.[13]

It would also be a mistake to assume that drugmakers will be honest and open about their research results. It is not just that many have repeatedly failed to publish unfavorable data. As the former editor of *The BMJ* has written, many have simply designed their research studies to produce the results they want. Medical journal editors have been raising the alarm about this for over fifteen years now.[14] Between 1991 and 2010, according to Public Citizen, the pharmaceutical industry was the leading defrauder of the federal government, as measured by penalties paid for violating the False Claims Act. The worst scandals have involved prescription drugs such as Paxil and Bextra, but many of the companies accused of burying or manipulating research results are now racing to produce a Covid-19 vaccine.

The barriers to creating ethical Covid-19 vaccine challenge studies are not insurmountable. Some problems could be solved easily. For instance, research sponsors could eliminate many of the more exploitative elements of Phase I trials simply by limiting Covid-19 vaccine challenge studies to unpaid volunteers. Other problems, such as the issue of compensation for research-related injuries, would require major legislative or policy changes. Yet the bioethicists calling for Covid-19 challenge studies have not mentioned these issues, which are so deeply entrenched in the system that they are viewed as the normal state of affairs.

The World Health Organization lists a number of potential risks for challenge studies, among them a loss of public trust in vaccines and medical research if a research subject were to die. That risk is not unique to challenge studies, of course. But it would probably be far worse if the subject had been intentionally infected. While defenders of challenge studies argue that there is nothing intrinsically wrong with intentionally exposing willing subjects to harm, the public hasn't always seen things that way. For instance, until the early 2000s many psychiatric researchers conducted psychosis challenge studies on mentally ill patients. They typically used ketamine, amphetamines, or other drugs to make patients severely psychotic. Many psychiatrists saw no ethical problem with this, since mentally ill patients would probably experience psychotic episodes in the course of their illness anyway. It was only after patients and their advocates subjected the challenge studies to blistering criticism in the press that they were finally stopped.

The Covid-19 crisis has presented the medical research community with a rare opportunity. At no time in recent memory has the importance of research subjects been so evident. If a nonprofit organization can sign up over 26,000 volunteers for challenge studies in a matter of months, it should be possible to reform the oversight system so that research subjects are treated fairly. But those reforms would entail structural changes that unfortunately neither the research community nor those of us who benefit from medical research have shown any interest in making.

—*June 3, 2020*

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6 I am a member of the advisory board for a National Institutes of Health grant for which Fisher is a principal investigator, and I have provided a quote for the book cover. ↩

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