How human challenge trials accelerate vaccine development

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Anna Durbin was in Brazil in December 2015 when the Zika virus erupted in the country's northeast. Although she'd flown to São Paulo to work on a dengue vaccine, Durbin returned to Baltimore preoccupied with Zika.

For most adults, the mosquito-borne infection causes mild symptoms, or none at all. But for babies born to infected mothers in Brazil, Zika was proving catastrophic. As many as 15% of newborns exposed to the virus in utero had microcephaly—abnormally small heads. In just four months, 3,500 Brazilian babies were born with microcephaly.

In February 2016, WHO declared the epidemic a public health emergency of international concern. By then, Durbin, MD, was already working on Zika.

As director of the Johns Hopkins Center for Immunization Research (CIR), Durbin designs and oversees human challenge trials that fast-track vaccine development. By vaccinating a few dozen healthy human volunteers and then intentionally infecting with them with a virus or bacterium, CIR researchers determine whether a vaccine candidate works well enough to merit an expensive and time-consuming phase 3 efficacy trial. Human challenge models save time, money, and effort.

Durbin acted quickly. With her long-time collaborator, NIAID virologist Stephen Whitehead, Ph.D., she initiated the months-long process of designing a Zika vaccine trial. Meanwhile, Whitehead began testing a potential vaccine on nonhuman primates. (The CIR itself does not create vaccines but rather has contracts to test vaccines developed by the NIH and biotech and pharmaceutical companies.) By spring 2016, the epidemic had waned, and Durbin and Whitehead realized that infection numbers were likely too low for a traditional phase 3 efficacy trial. But they had an alternative: vaccine trials using human volunteers sequestered in CIR's 30-bed unit at Johns Hopkins Bayview Medical Center in Baltimore, the largest such facility in the U.S.

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This plan faced several vexing delays, not least of which were caused by

the coronavirus pandemic: CIR suspended inpatient research, and Durbin and colleague Kawsar Talaat, MD, ran outpatient COVID-19 vaccine trials for Pfizer and AstraZeneca.

Finally, this January—seven years after she began working on Zika—Durbin started recruiting volunteers for human challenge trials targeting the disease. Her team enlisted the first of up to five 14-person cohorts of healthy adult women willing to spend 16 days confined to the top floor at Bayview. (The trial excludes men because the Zika virus can persist in semen, potentially putting sexual partners at risk.)

This first human challenge trial for Zika is a virus dosing study that will determine the minimum number of Zika virus particles needed to infect the volunteers. The researchers' goal is to find a dose that reliably infects 80% of the volunteers. Testing the efficacy of a potential vaccine will come later, on other volunteers.

Human challenge trials have a long history. We're all beneficiaries of a famous one, conducted in 1796 by Edward Jenner. The British physician infected his gardener's son with cowpox and then smallpox. The cowpox protected the 8-year-old child from smallpox. Vaccines based on Jenner's discovery eradicated smallpox worldwide by 1980. (The late D.A. Henderson, MD, MPH '60, led WHO's successful global campaign and later served as dean of the School.)

Human challenge trials have played a key role in the development of vaccines and therapies for typhoid, malaria, cholera, and tuberculosis. Talaat views such studies on humans as more useful than experiments on animals, because, as she puts it, "Animals lie." She adds, "Animals are inbred, genetically similar. We're outbred. We're much more complex." She learned this lesson after working for years on an intranasal flu vaccine that induced robust immune response in mice and ferrets—but failed in humans.

Researchers increasingly use human challenge models to vet vaccine candidates and learn more about host-pathogen interactions. A 2022 systematic review in *Clinical Infectious Diseases* found 308 such studies between 1980 and 2021, with 15,046 volunteers. Among 94 studies that rated adverse events among volunteers, between 5.6% and 15.8% of participants underwent "severe" events, ranging from a relapse of vomiting in an E. coli study to acute myocarditis in a respiratory virus study. No volunteers died. At CIR, study participants have 24-hour access to medical care, and it's not rare to give IV fluids to a volunteer in a diarrheal study. A few times, a volunteer has been taken to the hospital across the street for an "unrelated event," but no one has been seriously ill.

Unlike the gardener's son, 21st-century human challenge volunteers first give informed consent. Ethical guidelines—from the WHO on down—stipulate that researchers must inform participants of the study's purpose, its benefits, the guarantee of privacy, the right to withdraw, the amount of compensation, and the demands on volunteers. In addition, says Durbin, "We give them really clear instructions about the risks." For a study of bacterial intestinal illness, for example, volunteers may have to tolerate fevers, stomach cramps, bloody diarrhea, dehydration, headaches, nausea, and vomiting. "We spend time going over the likelihood each thing will occur," says Durbin.

And yet people still volunteer. Why?

"We're very friendly," says Sabrina Drayton, who coordinates volunteer recruitment for CIR with ads on Craigslist under "general labor" and "gigs." "We let volunteers know how important they are, and that goes a long way toward recruitment."

Some volunteers need no encouragement. "We do have regulars," Drayton says. One of them has participated in eight studies and come in

for screening 20 times since 2006.

But it takes a certain personality to spend days or weeks sleeping in a four- or six-person room, unable to leave the unit or see visitors for the trial's duration. Something as simple as a private phone call might require hiding out in the laundry room.

Some people work remotely during their stints. And everyone can enjoy amenities that include large-screen televisions, foosball and air hockey tables, crafts supplies, and games; some dominoes matches become fierce. Lunch and dinner are catered. "We do have healthy food—Mexican, Lebanese, Chinese," says Talaat. "But the one you have to guard is Chick-fil-A, to make sure everybody gets a chance to get some."

Of course, money is an important inducement for volunteering, Drayton says. An upcoming CIR study on the clinical presentation of Zika virus disease and on virus shedding will pay volunteers up to $5,525 for several screening sessions, a 16-day inpatient stay, and 11 follow-up visits. A study on the intestinal illness shigellosis is paying $4,950 for a 10-day stay and four or five follow-up visits.

A few people make volunteering for studies a way of life, traveling from study to study, while others are motivated by having lived in a place with a disease such as dengue or Zika. The nonprofit 1Day Sooner, says Durbin, promotes volunteering for human challenge studies as an expression of altruism, akin to donating a kidney.

"A lot of research shows altruism is a very important factor when people sign up for clinical trials and challenge studies," says Jake Eberts, 1Day Sooner's communications director. He tried it himself in 2022, drinking a "dysentery smoothie" for a Shigella trial at the University of Maryland. After enduring three days of intestinal distress, Eberts got so interested

in challenge studies that he left his policy job to work for 1Day Sooner.

He describes his mix of motivations this way: "A, I was getting paid; I'm not a saint—I had to take unpaid time off. But the thing that really made me pull the trigger was that I was born in the U.S., my father was a doctor, and by some cosmic lottery I never had to worry about disease."

This year CIR researchers have marked progress on two vaccines they helped develop.

A Shigella vaccine trialed by Talaat's team is in a phase 3 efficacy trial on children in Kenya. Children are particularly vulnerable to the diarrheal illness caused by the bacterium. Globally, Shigella was the second-leading cause of mortality from diarrheal illness in 2016 among all ages, causing 212,000 deaths.

And in January, Durbin and Whitehead learned that the dengue vaccine they'd worked on together for 20 years was 80% effective in a phase 3 trial in Brazil—with sustained immune response two years post-vaccination. Durbin's team at CIR ran the human challenge trials that determined which formulation of the vaccine worked best against the four dengue strains.

Dengue is already endemic in 127 countries, and scientists predict that climate change will expand its reach. It hits Brazil hard. "Think of the early days of COVID when [U.S.] hospitals were overrun," says Durbin. Every dengue season in Brazil, she says, the scene is the same.

Now several pharmaceutical companies have licenses from NIH to produce the single-dose dengue vaccine: including Instituto Butantan in Brazil, Merck & Co. in the U.S. and beyond, and companies in India and Taiwan.

These successes grew out of the contributions of volunteers, Talaat says. "We've learned so much from studies. Without volunteers, we wouldn't have these answers."

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