posed of the entire virus, inactivated with chemicals, Sinovac announced this week it is collaborating with the Butantan Institute, a major research institution in São Paulo that manufactures vaccines. “We are working very hard to start the trial in July,” says Sinovac Senior Director Meng Weining.

WHO proposes a different solution for Solidarity’s efficacy trials. The agency hasn’t yet announced which candidates Solidarity will test, but, unlike Warp Speed—which won’t consider Chinese-made vaccines—it is open to products from every country and has made public detailed criteria for how it will prioritize vaccines. To cope with the patchiness of the pandemic, Solidarity will adopt a strategy Henao Restrepo helped develop for Ebola vaccine trials in Guinea in 2015 and, 3 years later, in the Democratic Republic of the Congo (DRC): setting up vaccination teams that can quickly mobilize to localized outbreaks.

“We did this in Congo despite the war,” Henao Restrepo says. “It’s not the traditional way, and some people think that we are crazy, but we have done it not once but twice.” In the DRC, about 20 teams with 15 members each drove around the affected regions and set up temporary sites, vaccinating and following more than 300,000 people.

Warp Speed, which could if needed expand its trials to international sites used for HIV drug and vaccine testing, also plans to form “surge clinics” to quickly recruit people in rural U.S. areas with big outbreaks or pockets of high transmission such as nursing homes. Models driven by machine learning will help Warp Speed forecast where infection will be highest, says Peter Gilbert, a University of Washington, Seattle, biostatistician. “There are risk predictors that account for space and geography and features that are more constant like race, ethnicity, or preexisting conditions,” Gilbert says. “It’s really complicated.”

One of the trickiest issues for trial designers is deciding what, exactly, represents success for a COVID-19 vaccine. “Is it an infection endpoint, a transmission endpoint, preventing moderate disease, or preventing severe disease?” Koff asks.

“There was a lot of debate on that question,” for Warp Speed, notes John Mascola, who heads NIAID’s Vaccine Research Center and contributes to the project. A COVID-19 vaccine that fails to prevent infection might still provide great benefit if it reduces symptomatic disease, so Warp Speed and Solidarity both ultimately chose that as the primary endpoint of the trials. Trial volunteers who develop fever, headache, dry cough, or other symptoms linked to COVID-19 will be tested for SARS-CoV-2, to see whether more people with confirmed infections develop symptomatic disease in the placebo arm of the trial than among those who received the vaccine.

To detect an efficacy signal, both Warp Speed and Solidarity estimate they will need to give each vaccine to 15,000 to 20,000 people in a population that has a 1% per year incidence of SARS-CoV-2 infection. If the vaccine prevents COVID-19 symptoms at least 50% of the time, its efficiency should be clear in 6 months, after about 150 infections have accumulated in the trial.

Both efforts will pit multiple vaccine candidates head to head. One difference is that Solidarity plans to compare all its vaccines against a shared placebo group, an approach that reduces the number of volunteers the researchers need to recruit and follow. “In the Solidarity trial, the philosophy is we have to make this thing really simple,” says Gilbert, who has worked with this effort, too. Solidarity trial sites have the option to do nuanced studies on immunity and other issues, but those are built into Warp Speed’s trials. They will do repeated blood draws and nasal or throat swabs to evaluate immune responses and viral levels. The data might help researchers understand why vaccines succeed or how they might affect transmission.

In addition to Solidarity, WHO is helping the Access to COVID-19 Tools (ACT) Accelerator, another global effort, which may stage its own vaccine efficacy trials if companies do not want to participate in Solidarity. “Companies may or may not be very enthusiastic about head-to-head comparisons,” explains Soumya Swaminathan, WHO’s chief scientist and top liaison to the ACT Accelerator. The ACT Accelerator has pockets as deep as Warp Speed: Countries and philanthropies in May pledged $8 billion, with a commitment that it would equitably distribute any proven COVID-19 products—vaccines, treatments, diagnostics—to rich and poor alike.

Buchbinder is impressed by the speed at which these massive efforts have gotten underway. “It’s unlike any other research I’ve undertaken,” she says. But she and others are careful to temper expectations. Even though she will oversee a Warp Speed trial site, for example, she doubts the U.S. effort will meet Trump’s goal of having a proven vaccine by October. Koff agrees; the failures of so many HIV vaccine trials have sobered him, he says. “We need to be really careful how we manage expectations,” he concludes. ■

**COVID-19**

**Can phone apps slow the spread of the coronavirus?**

Digital contact tracing is growing—and facing its first real-world tests

By **Kelly Servick**

Health departments around the world are betting on technology to help stem the stealthy spread of the coronavirus: cellphone apps that aim to identify and alert those who recently came into contact with an infected person.

By encouraging those potentially exposed to COVID-19 to self-isolate, the thinking goes, a phone app could swiftly cut off chains of transmission. Dozens of local and national governments have launched official apps or are developing them.

“It’s very appealing—that you have an app that does all this work,” says Hannah Clapham, an epidemiologist at the National University of Singapore. But she and others warn that an app can’t replace human contact tracers. “I worry that we think it’s going to save us.”

So far, only epidemiological models suggest apps can change a pandemic’s course. Ensuring that an app detects risky contacts without overwhelming users with false alarms is one challenge; getting enough people to download an app is another. As health officials weigh competing apps and prepare pitches to privacy-conscious citizens, epidemiologists, engineers, and behavioral scientists are considering how to put an app to the test.

People can apparently transmit the coronavirus for days before they develop symptoms, so by the time health departments learn of a case, they have precious little time before infected contacts start to spread the virus. “You have a couple days to chase people down,” says C. Jason Wang, a health policy researcher at Stanford University who works with health departments on COVID-19. And traditional contact tracing—interviewing the infected person, tracking down the recent contacts they can recall, and telling those people to self-isolate—is time consuming.

In contrast, phones could detect when two
Most apps keep users anonymous, health officials won’t automatically know who gets an alert or what they need to stay home, Wang says. And users might not dutifully check in with health officials when they get an alert. “That’s too optimistic,” he says. “We tell people to stay at home; they go to the beach.”

To test whether an app accurately flags risky encounters, health officials want to know the proportion of identified contacts who end up sick—the “secondary attack rate.” As a rule of thumb, if an app’s attack rate matches or exceeds that of traditional contact tracing, “we know the app is doing a really good job,” Salathé says.

Some app designs allow health officials access to anonymized ID codes of infected users and all their contacts. That means officials can calculate the secondary attack rate and fine-tune the app by checking how many notified users later report symptoms or a positive test through the app. In Norway, which launched such a centralized app in April, municipalities will compare how many, and how quickly, contacts are identified by the app versus through traditional contact tracing, says Emily MacDonald, an epidemiologist at the Norwegian Institute of Public Health.

Other apps, including Switzerland’s and one released this week in Germany, are decentralized, meaning data about interactions stay on a phone. Privacy advocates favor this design, and Google and Apple encourage it. Last month, they released technology to support Bluetooth tracking, but only for apps with a decentralized design. With these apps, health departments will know about potentially infected users only if they report getting an alert. Critics say that design could make it harder to evaluate the app’s performance.

The ultimate test, some researchers say, is a randomized trial to gauge whether using an app brings down rates of infection. But such trials “would be very costly and difficult,” says Oxford behavioral economist Johannes Abeler. Because COVID-19 is relatively rare, such trials would have to be large. And to gauge effectiveness, researchers would have to factor in the proportion of a participant’s contacts who downloaded the app—which might be nearly impossible to know.

Another possibility is to compare changes in infection rates between geographic areas or demographic groups with different levels of app use, suggests Rosalind Eggo, an epidemiologist at the London School of Hygiene & Tropical Medicine who hopes to study the impact of apps as data accumulate. “We have a lot of technology that can help us here,” she says. “There’s quite a lot of people saying, ‘Oh, it won’t work.’ I think we need to try.”
Can phone apps slow the spread of the coronavirus?
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