ture, whereas the Pfizer/BioNTech candidate appears to require ultracold freezers or dry ice to keep the product below –70°C.

Even –20°C is a challenge, and high-tech thermoses that were used to transport Ebola vaccines in sub-Saharan African countries at ultracold temperatures may be called into action. Longer term, Pfizer and BioNTech have said they intend to create a more stable freeze-dried powder formulation; another company, CureVac, said last week its COVID-19 mRNA vaccine remains stable at normal refrigeration and will soon start an efficacy trial.

Ruth Karron, who heads the Center for Immunization Research at the Johns Hopkins Bloomberg School of Public Health, notes another uncertainty: whether the mRNA vaccines prevent people from becoming infected in the first place, which is key to controlling the spread of the virus. "The data we have are that these vaccines protect you against severe illness, but it doesn't mean that you can't get infected and give it to your patient, your neighbor, your customer, or whomever." But Karron also says of the Moderna result: "Wow, fantastic, amazing."

Science's COVID-19 reporting is supported by the Pulitzer Center and the Heising-Simons Foundation.

Operation Warp Speed, the U.S. government effort to develop COVID-19 vaccines and rapidly move them into efficacy trials, has invested $1 billion in Moderna's COVID-19 vaccine R&D. (Pfizer did not take Warp Speed money for development.) This summer, Warp Speed committed another $1.5 billion to Moderna to purchase 100 million doses of its candidate and $1.9 billion to Pfizer for the same amount of its product, which was developed at BioNTech, a company that has focused on treating cancer with mRNA.

Small studies have shown mRNA vaccines can trigger immune responses and don't have obvious, significant safety issues, but the two efficacy trials are the first to report that they can actually protect people from a pathogen. The snippet of mRNA at the heart of both vaccines was initially designed by a team led by Barney Graham of NIAID's Vaccine Research Center. When he learned that the strategy worked, Graham says, "I had my moment of relief and sobbing tears."

Both mRNA vaccines have yet to complete their trials, which aim to accrue about 150 to 165 cases of COVID-19 to provide greater statistical certainty about efficacy. They should hit those targets by December, when the U.S. Food and Drug Administration plans to convene an advisory panel to review the data. Cases are accumulating fast because most trial sites are in the United States, where the epidemic has exploded. If the advisers recommend emergency use authorizations for the vaccines, Warp Speed plans to start to deliver them to U.S. pharmacies and clinics the next day.

Moderna projects it can have about 20 million doses for the United States by the end of the year. Pfizer, which has made sales agreements with several countries in addition to the one it negotiated with Warp Speed, projects it can supply a total of 50 million doses by the end of this year, with an unspecified number going to Warp Speed. The U.S. Centers for Disease Control and Prevention will prioritize who should receive the vaccine first, but the companies say there should be enough to vaccinate the entire United States by the spring.

Both vaccines require two doses separated by weeks. Pfizer says it will have 1.3 billion doses next year. Moderna's vaccine delivers more mRNA—100 micrograms of mRNA per dose, versus Pfizer's 30 micrograms—and it does not see a way to produce more than about 1 billion doses in 2021. "We don't have a billion-dose manufacturing capacity sitting idle somewhere. We are increasing our output more and more and all our key engineers are working to make that happen," says Stéphane Bancel, Moderna's CEO.

The cost of the vaccine—Warp Speed paid about $25 per dose, all told—may also be far too high for many countries. Bancel says his company is in discussions with the COVID-19 Vaccines Global Access Facility, a nonprofit set up to help resource-limited countries purchase the vaccine at discounted prices.

Once supplies are available, the question will become whether people who are hesitant about a COVID-19 vaccine—especially a novel type that has no long-term safety record—will roll up their sleeves. Still, Karron suspects hesitancy will drop if people see the vaccine works and no serious side effects surface. She also imagines pressure will build to contribute to the social good. "There's going to come a moment where you're going to be able to say, you know, we could open up our community, except for people like you," Karron says. "If you would get vaccinated, we could get back to some semblance of life as we knew it."

Fauci says a COVID-19 vaccine always looked like a solid bet. The fact that many infected people clear the virus without developing serious, if any, symptoms, shows that the immune system can beat it back. "I've been saying all along that when the body tells you that it's capable of making an adequate immune response against natural infection, that tells you you have a pretty good chance to get a vaccine." ■

With reporting by Jocelyn Kaiser.

COVID-19

Reinfections, still rare, provide clues on immunity

The growing group of people who get sick twice suggests protection can wane relatively quickly

By **Jop de Vrieze**

In late June, Sanne de Jong developed nausea, shortness of breath, sore muscles, and a runny nose. At first, she thought it might be lingering effects from her COVID-19 infection in the spring. De Jong, 22, had tested positive on 17 April and suffered mild symptoms for about 2 weeks. She tested negative on 2 May—just in time to say farewell to her dying grandmother—and returned to work as a nursing intern in a hospital in Rotterdam, the Netherlands.

But when her symptoms re-emerged, her doctor suggested she get tested again. "A reinfection this soon would be peculiar, but not impossible," she told De Jong, who by then had again lost her sense of smell and had abdominal pains and diarrhea.

The call from her municipal health service came on 3 July. De Jong had tested positive again. "You're kidding me!" she recalls saying.

Scientists are keenly interested in cases like hers, which are still rare but on the rise. Reinfections hint that immunity against COVID-19 may be fragile and wane relatively quickly, with implications not just for the risks facing recovered patients, but also for how long future vaccines might protect people. "The question everybody wants to answer is: Is that second one going to be less severe most of the time or not?" says Derek Cummings, who studies infectious disease dynamics at the University of Florida. "And what do reinfections teach us about SARS-CoV-2 immunity in general?"

South Korean scientists reported the first suspected reinfections in May, but it took until 24 August before a case was officially confirmed: a 33-year-old man who was treated at a Hong Kong hospital for a mild case in March and who tested positive again at the Hong Kong airport on 15 August after returning from a trip to Spain. Since then, at least 24 other reinfections have been officially confirmed—but scientists say that is definitely an underestimate.

To count as a case of reinfection, a patient must have had a positive polymerase chain reaction (PCR) test twice with at least one symptom-free month in between. But virologist Chantal Reusken of the Dutch National Institute for Public Health and the Environment (RIVM) explains that a second test can also be positive because the patient has a residue of nonreplicating viral RNA from their original infection in their respiratory tract, or because they had suppressed but never fully cleared the virus. So most journals want to see two full virus sequences, from the first and second illnesses, that are sufficiently different, says Paul Moss, a hematologist at the University of Birmingham. “The bar is very high,” Moss says. “In many cases, the genetic material just isn’t there.”

Even if it is, many labs don’t have the time or money to clinch the case. As a result, the number of genetically proven reinfections is orders of magnitude lower than that of suspected reinfections. The Netherlands alone has 50 such cases, Brazil 95, Sweden 150, Mexico 285, and Qatar at least 243.

The Hong Kong patient’s second infection was milder than the first, which is what immunologists would expect, because the first infection typically generates some immunity. That may explain why reinfections are still relatively rare, says Maria Elena Bottazzi, a molecular virologist at Baylor College of Medicine and Texas Children’s Hospital.

They could become more common over the next couple of months if early cases begin to lose their immunity. Reinfections with the four coronaviruses that cause the common cold occur after an average of 12 months, a team led by virologist Lia van der Hoek at Amsterdam University Medical Center recently showed. Van der Hoek thinks COVID-19 may follow that pattern: “I think we’d better prepare for a wave of reinfections over the coming months.” That’s “bad news for those who still believe in herd immunity through natural infections,” she adds, and a worrisome sign for vaccines.

Others are less pessimistic. Although antibodies can wane within months—particularly in mild cases—they sometimes persist. Neutralizing antibodies, the most important kind, as well as memory B cells and T cells seem to be relatively stable over at least 6 months.

And there are hints that people who

“You’re kidding me!” Sanne de Jong, a nursing assistant, said when she was told she had COVID-19 again in July.

PHOTO: MIRANDA DE JONG

have serious COVID-19 mount the strongest responses, just as in the two other serious human diseases caused by coronaviruses, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome. Both trigger high antibody levels that last up to 2 years, and T cell responses to SARS can be detected even longer. Because of these persistent immune defenses, “I expect that most reinfections will be asymptomatic,” says Antonio Bertoletti, an infectious disease specialist at the National University of Singapore. He says being reinfected might even be a good thing, “since you will continue to boost and train your immune system.”

Not all reinfections seen so far are milder. “We see all different combinations,” Reusken says. The second time Luciana Ribeiro, a surgeon in Rio de Janeiro, got sick, it was much worse. She was first infected by a colleague in March, developed mild symptoms, and tested negative afterward. Three months later, Ribeiro had symptoms again—she could no longer smell her breakfast, she says—but she didn’t immediately get a test because she thought she was immune. When she grew more and more tired, she requested a computerized tomography scan. “It showed that half of my lungs were affected,” Ribeiro says. “‘This clearly is COVID,’ the radiologist told me. I didn’t believe it, but I tested positive.”

Ribeiro thinks she was reinfected by a patient in the intensive care unit where she works, and that her second episode may have been worse because virus-laden aerosols produced during a medical procedure entered her lungs. But some scientists worry about another scenario that could make the second episode worse: enhanced disease, in which a misfiring immune response to the first infection exacerbates the second one. In dengue fever, for example, antibodies to an initial infection can actually help dengue viruses of another serotype enter cells, leading to a more severe and sometimes fatal second infection. In some other diseases, the first infection elicits ineffective, nonneutralizing antibodies and T cells, hampering a more effective response the second time around.

A recent preprint published by Chinese researchers suggested patients whose first COVID-19 infection is very severe may have ineffective antibodies, which might make them more prone to severe reinfections. But so far there's no evidence from reinfected patients to suggest enhanced disease is at work in COVID-19—although scientists haven't ruled it out either. Vaccination against some diseases can also trigger enhancement later—a known or suspected complication of vaccines against dengue and respiratory syncytial virus in humans and a coronavirus disease in cats. But there is no evidence that candidate COVID-19 vaccines do so, Cummings says. "Having worked with dengue I can say the empirical basis for enhanced disease is just not there, while it was very strong in dengue."

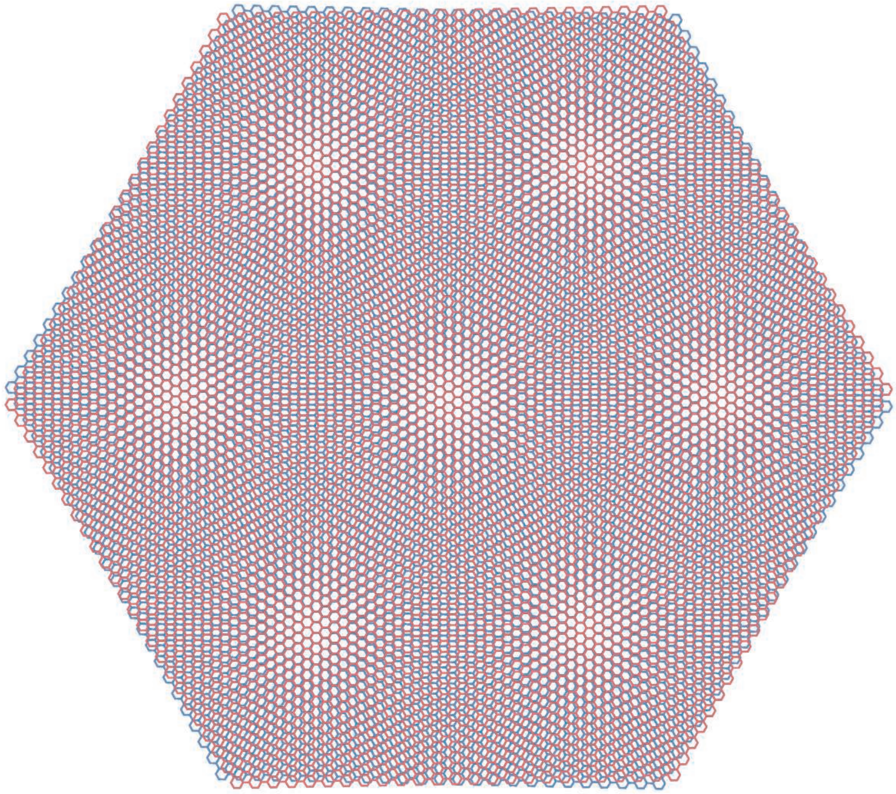
De Jong's virus samples were both sequenced in Reusken's lab, with a surprising outcome: The sequences were not identical, but showed so much similarity that RIVM virologist Harry Vennema says she probably she did not clear the virus in April and that it started to replicate again in June. "I did have a lot of stress after that first episode because my grandmother died," De Jong says. "Maybe that had an impact on my immune system."

That makes her case different from a true reinfection—although Vennema says perhaps they should be considered similar, because in both cases the immune system failed to mount a protective response. His lab has found at least one similar case, he says, suggesting some unconfirmed reinfections might actually be a resurgence of the original virus.

Other coronaviruses can also cause persistent infections, says Stanley Perlman of the University of Iowa. In 2009, his team showed that an encephalitis-causing mouse coronavirus can linger in the body and continuously trigger immune responses, even if it doesn't replicate. And in a preprint posted on 5 November, a team of U.S. scientists shows SARS-CoV-2 can persist for months inside the gut. Persistent infections, they suggest, may help explain the extraordinarily long-lasting symptoms that afflict some COVID-19 survivors.

De Jong is experiencing some of those symptoms. Although she tested negative in September and has high levels of neutralizing antibodies, suggesting she is protected for at least a couple of months, she still suffers from gastrointestinal complaints, fatigue, and cognitive impairment. De Jong says her story is a warning to people who had the virus and think they're now invulnerable: "Please be cautious. You can get it again." ■

Jop de Vrieze is a science journalist in Amsterdam.



MATERIALS SCIENCE

'Magic angle' graphene's next trick: superconducting devices

Twisted carbon sheets turned into switches that could make quantum computers smaller and more controllable

By **Charlie Wood**

In 2018, a group of researchers at the Massachusetts Institute of Technology (MIT) pulled off a dazzling materials science magic trick. They stacked two microscopic cards of graphene—sheets of carbon one atom thick—and twisted one ever so slightly. Applying an electric field transformed the stack from a conductor to an insulator and then, suddenly, into a superconductor: a material that frictionlessly conducts electricity. Dozens of labs leapt into the newly born field of "twistronics," hoping to conjure up novel electronic devices without the hassles of fusing together chemically different materials.

Two groups—including the pioneering MIT group—are now delivering on that promise by turning twisted graphene into working devices, including superconducting switches like those used in many quantum computers. The studies mark a crucial step for the material, which is already maturing into a basic science tool able to capture and control individual electrons and photons. Now, it's showing promise as the basis of new electronic devices, says Cory Dean, a condensed matter physicist at Columbia University whose lab was one of the first to confirm the material's superconducting properties after the 2018 announcement. "The idea that this platform can be used as a universal material is not fantasy," he says. "It's becoming fact."

The secret behind twisted graphene's chameleonlike nature lies with the so-called "magic angle." When researchers rotate the sheets by precisely 1.1°, the twist creates a large-scale "moiré" pattern—the atom-scale equivalent of the darker bands seen when two grids are juxtaposed. By bringing thousands of atoms together, the moiré allows them to act in unison, like super-

Science

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Science **370** (6519), 895-897.
DOI: 10.1126/science.370.6519.895

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