lurking in the vacuum. The original Muon $g-2$ experiment gave many physicists hope that new particles would soon be discovered.

Secret frequency

To verify the Brookhaven results, researchers rebuilt the experiment — which keeps muons running in circles around a superconducting ring magnet 15 metres in diameter — at Fermilab. They began collecting data in 2018, and have now presented the results from the first year of operations.

To avoid biasing its data analysis, the collaboration had blinded itself to a crucial parameter that is needed to calculate the $g-2$ constant — the exact frequency of a digital clock in the instrumentation. Two Fermilab physicists who are not collaboration members were entrusted with the missing bit of information. As a result, the team was able to conduct a lengthy study, but could initially plot its findings only on a graph in which the axes had slightly uncertain scales.

Then, at a 25 February online meeting that included most of the 200-plus team members, two leading members of the experiment opened an envelope that contained the secret clock frequency. When they plugged the number into their computers, it revealed the true value of their $g-2$ measurement. It was immediately obvious to the team that the result was consistent with the one recorded at Brookhaven more than 20 years ago.

"The agreement is excellent," says Lee Roberts at Boston University in Massachusetts, one of the original Muon $g-2$ team members. "People were clapping and jumping up and down — as much as you can do that on Zoom." The joyful reactions were obvious, even though "a lot of us were muted", adds Brynn MacCoy, a physicist at the University of Washington in Seattle. The result vindicates the claim of the original experiment, Roberts says.

Other physicists agree. The latest announcement gives "a nice, clear answer" to the riddle posed by the earlier results, says theoretical physicist Gino Isidori at the University of Zurich in Switzerland. "The experiment was correct."

But although the gap between the theoretical and experimental results has grown in statistical significance, it is still not unambiguous proof of the existence of new particles. "Those who were sceptical will probably stay sceptical," Isidori says. "At this point, the ball is in the theorists' court," he adds.

Quark calculations

The most widely accepted prediction for the muon's magnetic moment is a number that the theoretical community published last year in a 'consensus' paper[3]. But another study published on 7 April, this time in *Nature*[4], suggests that the gap between theory and experiment might not be as large as thought.

The hardest part to calculate is the contribution of quarks, the basic constituents of protons and neutrons, which is why physicists have conventionally supplemented their calculations with data from collider experiments.

In the *Nature* study, Zoltan Fodor at Pennsylvania State University in University Park and his collaborators recalculated the quark contributions from scratch with a simulation technique called lattice quantum chromodynamics (lattice QCD). The technique had not previously been used in $g-2$ predictions because it was not mature enough to give high-precision results. Fodor and his team managed to improve the precision, and found $g-2$ to be both larger than the consensus value and much closer to the experimental measurement. Other lattice QCD teams are working to match that precision so that the technique can be used in calculations for the consensus value, says Aida El-Khadra, a theoretical physicist at the University of Illinois at Urbana–Champaign. "The other collaborations are also working on reducing their errors, which requires significant computational resources," she says.

"There is not a single explanation which stands out as being far more elegant or compelling than any other."

The Muon $g-2$ team is now busy analysing some of the more recent data, as well as collecting more. The researchers ultimately expect the precision of their measurement to improve fourfold. If the discrepancy does turn out to be real, then the standard model will have to be updated to include new particles. One problem is that since 2001, many possible candidate particles that could have inflated the muon's magnetic moment have been ruled out in other experiments, mostly at the Large Hadron Collider outside Geneva, Switzerland.

Many theories that could explain the Muon $g-2$ results remain, but researchers see them as contrived. "To me, there is not a single explanation which stands out as being far more elegant or compelling than any other one," says Dominik Stöckinger, a theoretical physicist at the Dresden University of Technology in Germany who is a member of Muon $g-2$.

Since it was first put together in the 1970s, the standard model has passed all tests and has survived almost unchanged. But physicists are convinced that it must be incomplete, and some hope that muons will reveal its first failure. "If we confirm a difference with the standard model, that's what people have been searching for for 50 years," says Roberts.

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SCIENTISTS PROBE HOW A COVID VACCINE COULD CAUSE BLOOD CLOTS

Researchers are studying possible links between rare clots and the Oxford–AstraZeneca COVID-19 vaccine.

By Heidi Ledford

The very rare occurrence of a mysterious blood-clotting disorder among some recipients of the Oxford–AstraZeneca COVID-19 vaccine has got researchers scrambling to uncover whether, and how, the inoculation could trigger such an unusual reaction.

After weeks of investigation, the European Medicines Agency (EMA) announced on 7 April that it is possible there is a link between the clots and the vaccine. Even so, the clotting disorder — described in two reports in *The New England Journal of Medicine*[1,2] — is so uncommon that the benefits of the vaccine still outweigh its risks, EMA executive director Emer Cooke told reporters. "These are very rare side effects," she said. "The risk of mortality from COVID is much greater than the risk of mortality from these side effects."

But the finding leaves researchers wrestling with a medical mystery: why would a vaccine trigger such an unusual condition? "Of course, there are hypotheses: maybe it's something with the vector, maybe it's an additive in the vaccine, maybe it's something in the production process … I don't know," says Sabine Eichinger, a haematologist at the Medical University of Vienna. "It could be any of these things."

Eichinger was among the first to notice the

clotting disorder, a strange combination of blood clots — which can be dangerous, and potentially fatal, if they block blood flow to the brain or lungs — and a counter-intuitive deficiency of cell fragments called platelets that promote clotting. The clots also appeared in unusual parts of the body, such as the brain and abdomen, rather than in the legs, where most deep-vein blood clots form.

This rang alarm bells for Eichinger, who had previously encountered a similar phenomenon in a few people who had been treated with the blood-thinning drug heparin. Heparin is normally used to prevent clotting, but in very rare cases can trigger a syndrome called heparin-induced thrombocytopenia (HIT), which causes blood clots and low platelet levels.

By 22 March, the EMA had assembled 86 reports of people who had experienced blood clots in the brain or abdomen within two weeks of receiving a dose of the Oxford–AstraZeneca vaccine, developed in Britain by AstraZeneca in Cambridge and the University of Oxford. Some of the cases have been confirmed to bear the hallmarks of HIT, even though these people had not received heparin.

Risk factors

The EMA is asking AstraZeneca to conduct a number of investigations, including laboratory studies to determine the effect of the vaccine on blood clotting, and evaluations of data from clinical trials, to try to glean any further information about risk factors. Although there are reports that the syndrome is seen more often in women than in men, particularly in women aged under 60, the EMA was unable to conclude that women are at higher risk. Many countries prioritized health-care workers to receive the inoculations, and women comprise a larger segment of this workforce.

The EMA is also supporting studies by two academic consortia centred in the Netherlands, one led by Erasmus University Medical Center in Rotterdam and the other by investigators at Utrecht University and the University Medical Center Utrecht.

Their project list is ambitious. One of the consortia, co-chaired by virologist Eric C. M. van Gorp at Erasmus, consists of 22 hospitals that have been working together to study the effects of coronavirus on blood coagulation. The team will look for potential cases of HIT among people who developed blood clots after vaccination with the Oxford–AstraZeneca vaccine or other COVID-19 vaccines. It will also conduct lab studies to look for signs that the already-small risk could be cut further by reducing the amount of vaccine administered in each dose.

The team will also try to tease apart whether this problem is restricted to certain populations. "What we find in Western Europe will not automatically be true in South America or other populations," says van Gorp. "This is a worldwide problem; everyone is concerned."

CARLOS GIL ANDREU/GETTY

A nurse immunizes a teacher in Granada, Spain, with the Oxford–AstraZeneca vaccine.

And, crucially, van Gorp and his colleagues will try to further evaluate whether the "probable" association between the vaccine and the syndrome is real. It is notoriously difficult to confirm whether a suspected rare effect of a vaccine is truly linked to the vaccine — particularly when it is one that has been used in tens of millions of people. "Somebody who gets the vaccine could have a stroke or a heart attack a week later because they were already going to have a stroke or a heart attack," says cardiologist Behnood Bikdeli at Brigham and Women's Hospital in Boston, Massachusetts. "It's good to be vigilant about these things, but the absolute number of events and the event rate are so remarkably low."

"We are going to get new variants and develop new vaccines. We need answers for the future."

Bikdeli would also like to see researchers collect — and share — more data about the incidence of this clotting condition in unvaccinated populations. Heightened awareness of the possible link between vaccination and the syndrome could lead to increased reporting rates among those who have been vaccinated compared with those who have not, which could falsely inflate the perceived rate at which the syndrome occurs, he says.

Other researchers are keen to pick apart what triggers the syndrome. HIT is thought to be the result of an immune reaction to complexes formed when negatively charged heparin molecules bind to a positively charged protein called platelet factor 4, which is important for clotting. This activates platelets, kicking off a chain reaction. "Once you get the platelets activated, it's like putting a match to tinder," says John Kelton, a haematologist at McMaster University in Hamilton, Canada, who has been studying HIT for 40 years. "They recruit more and more platelets, and when they are activated, they explode and produce coagulant material. HIT is like a forest fire; it just self-perpetuates."

Although exceedingly rare, cases of 'spontaneous' HIT in the absence of heparin treatment have been reported before, with suspected triggers including infection, knee surgery and treatment with drugs that — like heparin — are negatively charged. Kelton recalls a case he worked on years ago of a woman in her forties experiencing catastrophic strokes who had not been treated with heparin. "We tested her blood and found reactions exactly the same as reported for the AstraZeneca reactions," he says.

Kelton's lab is now working full time to try to determine what might be causing HIT-like symptoms in vaccine recipients. It is a tricky phenomenon to study: its rarity makes patient samples difficult to come by, and there are no good animal models, Kelton says.

One result of all of this activity will be increased attention to the relationship between the immune system and blood coagulation, says van Gorp, and the results could inform further vaccine development. "We are going to get new coronavirus variants and are going to develop new vaccines," he says. "We need answers for the future."

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