Africa and elsewhere suggest that the variant is highly transmissible – spreading several times faster than Delta – and might be able to infect people who are immune to other variants.

Omicron carries a large number of mutations in its spike protein – the prime target of immune responses – and some of these changes, when present in other variants, affect the ability of antibodies to recognize the virus and block infection.

Scientists used two types of laboratory assay to test how well Omicron can evade neutralizing, or virus-blocking, antibodies. One approach uses infectious SARS-CoV-2 particles, typically isolated from individuals infected with Omicron. The other relies on pseudovirus particles – genetically modified versions of another virus (often HIV) that use the SARS-CoV-2 spike protein to infect cells.

The results from the four teams all suggest that Omicron blunts the potency of neutralizing antibodies more extensively than any other circulating SARS-CoV-2 variant. But the magnitude of Omicron's impact varied between the studies, which examined blood from people with different vaccination and infection histories.

A study led by virologist Alex Sigal, at the Africa Health Research Institute in Durban, South Africa, found that serum – the antibody-containing portion of blood – from 12 people who received the Pfizer–BioNTech vaccine was around 40 times less potent against Omicron, on average, than against an earlier strain of SARS-CoV-2. That finding was similar to the results from two other studies: one reported by Pfizer and BioNTech in an 8 December press release, and the other released on Twitter and later posted on medRxiv by virologist Sandra Ciesek at the Goethe University Frankfurt, Germany (A. Wilhelm *et al*. Preprint at medRxiv https://doi.org/g8sz; 2021).

A fourth study, led by Murrell and virologist Daniel Sheward, also at the Karolinska Institute, reported a smaller reduction in levels of Omicron-neutralizing antibodies in two groups of participants: 17 health-care workers, who had all been previously infected, and 17 Swedish blood donors. The researchers cannot determine the vaccine status of the anonymous blood donors, but say they will soon update their paper with vaccination information from the health-care workers.

Despite differences in results – which are common in such virus-neutralization assays – the labs' conclusions are similar, and show that Omicron's effects on neutralizing antibodies are "not complete knockouts", says Murrell. "The magnitude is still a little up for question."

Booster protection

The results suggest that vaccines' effectiveness is likely to be significantly modified by Omicron – but precisely how much is hard to say. Sigal's team found that people who had already been infected before vaccination tended to have higher levels of neutralizing antibodies against Omicron than vaccinated people with no known history of infection. "I think retaining some neutralization against Omicron can only be helpful," says Moore, a co-author on the study, whose lab is also working on neutralization experiments.

"Omicron is scarier than anything we've known before, because it's a little bit worse still than Delta."

A previous case of COVID-19 isn't the only way to improve antibody levels against Omicron. The Pfizer–BioNTech study found that people who had received a third dose of its vaccine had neutralizing antibody levels against Omicron comparable to those, triggered by two vaccine doses, against other SARS-CoV-2 variants. On the basis of those results, "we expect significant protection against any type of COVID-19 mediated by Omicron in individuals who have received the third vaccine", said BioNTech's chief executive, Uğur Şahin, at a press conference on 8 December.

Danny Altmann, an immunologist at Imperial College London, agrees that jacking up antibody levels with booster shots should help protect against Omicron, just as boosters have improved protection against the Delta variant. "Omicron is scarier than anything we've known before, because it's a little bit worse still than Delta. But we were in quite a bad situation with Delta in unboosted populations," Altmann says.

Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington, says that it will be important to determine the extent to which immune mechanisms other than neutralizing antibodies, such as T cells, ameliorate severe disease caused by infection.

It will also be important to see further studies confirming the latest results, because variables such as the type of cell used can affect conclusions, says Pei-Yong Shi, a virologist at the University of Texas Medical Branch at Galveston. "In the next week or ten days, there will be a lot of confirmatory results coming out," he says.

HALF OF CANCER STUDIES FAIL HIGH-PROFILE REPLICATION TEST

Barriers to reproducing preclinical results included unhelpful author communication.

By Asher Mullard

A US$2-million, 8-year attempt to replicate influential preclinical cancer research papers has released its final – and disquieting – results. Fewer than half of the experiments assessed stood up to scrutiny, reports the Reproducibility Project: Cancer Biology (RPCB) team in *eLife*[1,2]. The project – one of the most robust reproducibility studies performed so far – documented how hurdles including vague research protocols and uncooperative authors delayed the initiative by five years and halved its scope.

"These results aren't surprising. And, simultaneously, they're shocking," says Brian Nosek, an RPCB investigator and executive director of the Center for Open Science in Charlottesville, Virginia. Although initially planning to repeat 193 experiments from 53 papers, the team ran just 50 experiments from 23 papers.

The low replication rate is "frankly, outrageous", says Glenn Begley, an oncologist and co-founder of Parthenon Therapeutics in Cambridge, Massachusetts, who was not involved in the study. But it isn't unexpected, he agrees. In 2012, while at the biotech firm Amgen in Thousand Oaks, California, Begley's team helped to draw attention to growing evidence of a 'reproducibility crisis', the concern that many research findings cannot be replicated. Over the previous decade, his haematology and oncology team had been able to confirm the results of only 6 of the 53 (11%) landmark papers it assessed, despite working alongside the papers' original authors. Other analyses have reported low replication rates in drug discovery, neuroscience and psychology.

Double take

The RPCB – a partnership between the Center for Open Science and Science Exchange, a marketplace for research services in Palo

PATRICK HERTZOG/AFP/GETTY

Vague experimental protocols was one barrier to replication that researchers encountered.

Alto, California — launched in 2013. Funded by the philanthropic investment fund Arnold Ventures, headquartered in Houston, Texas, the collaborators set out to systematically reproduce experiments in 53 high-profile papers published during 2010–12 in journals including *Nature*, *Science* and *Cell*.

The project focused on preclinical cancer research because early hints at low reproducibility rates came from this space — animal studies, in particular, seemed difficult to reproduce. By selecting high-impact papers, the team focused on the research that most shapes the field.

The RPCB started publishing its findings in 2017, and these hinted at the messy results to come. The researchers now summarize their overall findings in two papers published on 7 December.

The first of these papers[1] catalogues the hurdles the researchers encountered. For every experiment they set their sights on, for example, they needed to contact the authors for advice on experimental design because the original papers lacked data and details. They deemed 26% of authors "extremely helpful", sometimes spending months tracking down answers and sharing reagents. But 32% were "not at all helpful" — often ignoring queries altogether.

"Everyone always talks about this problem. But here, we've actually got data on how prevalent it is," says Manoj Lalu, a clinician–researcher who studies data reproducibility at the Ottawa Hospital Research Institute in Canada.

This lack of cooperation, alongside the need to modify or overhaul protocols once experiments were under way, took a toll. On average, the team needed 197 weeks to replicate a study. And as costs added up to $53,000 per experiment — about twice what the team had initially allocated — the project's budget couldn't cover its original ambition.

The second study[2] delves into the overall results of these experiments in detail. By one analysis, only 46% of the attempted replications confirmed the original findings. And, on average, the researchers observed effect sizes that were 85% smaller than originally reported.

> **"You can never do experiments exactly the same."**

The experiments with the biggest effect sizes were those most likely to be replicated. Animal experiments fared worst, mainly because *in vivo* experiments tend to yield smaller effect sizes than do in vitro experiments.

Counterclaims

Not everyone is convinced that the study has merit. Pushback came especially from researchers whose findings were not successfully replicated.

"I'm not sure there is much value in these one-shot experiments," says Erkki Ruoslahti, a cancer biologist at the Sanford Burnham Prebys in La Jolla, California. In 2017, the RPCB team reported that it could not confirm a finding made by Ruoslahti's team, but Ruoslahti counters that external laboratories have replicated the disputed result at least 20 times. A drug candidate resulting from this work is now in phase II trials. "It's hard for me to believe that half of all papers out there would not be valid," he says.

Dean Tang, a cancer biologist at the Roswell Park Comprehensive Cancer Center in Buffalo, New York, is also circumspect. The RPCB reported[3] in 2019 that it could not replicate some work from his lab. But, he argues, the replicators deviated from their experimental plan, relied on fewer and different cell lines from those used in the original study, and didn't double-check their own work.

But replication is extremely hard, says Olavo Amaral, a coordinator of the Brazilian Reproducibility Initiative and a neuroscientist at the Federal University of Rio de Janeiro, Brazil. "You can never do it exactly the same," he says. Does it matter if you shake a tube up and down instead of side to side? How do you account for different baseline readings? Figuring out when and how to stay true to an experimental protocol is part of the emerging science of replication, he says.

Failure to replicate alone is not necessarily cause for concern, says Nosek. Some preliminary findings are distractions, but contradictory follow-up results can lead to deeper scientific insights. The RPCB was not set up to call out or invalidate specific studies, adds Nosek. Replication, like science, is about the total body of evidence. Rather, he says, the goal was to capture a snap shot of the drivers and the magnitude of the reproducibility crisis, with an eye towards system-level solutions.

The real problem is the time, money and effort that are wasted in finding the signals amid the noise, says Tim Errington, the RPCB's project leader and director of research at the Center for Open Science. "How well are we using our resources? And how are we learning new knowledge? This is the place to keep pushing, across disciplines."

Culture shift

There is no shortage of proposed fixes: for example, in vitro and animal studies can benefit from blinding, bigger sample sizes, greater statistical rigour and preregistration of study plans. Papers should make fewer claims and provide more proof, researchers suggest. Data sharing and reporting requirements need to be baked into scientific processes.

But stakeholders also need to address the incentives and research cultures that stand in the way of replication, says Nosek. Researchers who have published high-profile papers have little to gain from participating in confirmatory analyses, he points out, and much to lose. Replication attempts are often seen as threats rather than as compliments or opportunities for progress, he says. "That kind of culture does not help this ethos of self-correction. We are really about changing the entire research culture," says Nosek.

1. Errington, T. M., Denis, A., Perfito, N., Iorns, E. & Nosek, B. A. *eLife* **10**, e67995 (2021).
2. Errington, T. M. *et al. eLife* **10**, e71601 (2021).
3. Yan. X. *et al. eLife* **8**, e43511 (2019).