of memory B cells had risen, on average, nearly 10-fold, and their 'titres', or levels, of neutralizing antibodies had shot up around 50-fold. Those gains were apparent in previously infected participants whether they'd received one shot or two.

In fact, just one dose of vaccine generated titres equal to — or higher than — those produced by two doses of vaccine in people without previous infections. "It's really amazing," says virologist Theodora Hatziioannou, who co-led the study. "I wish everyone's titres were like this."

Memory booster

The findings from Hatziioannou and her colleagues also hint at the biological underpinnings of a single jab's effectiveness in exposed people. In the 12 months after participants were infected, their memory B cells had not been static. Instead, those cells spent the entire year evolving, which left them able to craft antibodies even more potent and versatile than those that they produced immediately after infection.

Other studies corroborate that thinking; some show that a single shot can spur the growth of both antibodies and infection-fighting T cells[6,7]. "We're all seeing pretty much the same thing," says John Wherry, an immunologist at the University of Pennsylvania Perelman School of Medicine in Philadelphia. After recovery from COVID-19, "the second shot doesn't seem to do a whole lot".

And although most research on the topic so far has focused on mRNA vaccines, preliminary evidence from studies done in the United Kingdom and India suggests that single-dose strategies could succeed if they rely on the shot from Oxford–AstraZeneca, which uses an engineered adenovirus (refs 8, 9). A study published last month, for example, showed[9] that one dose of the AstraZeneca jab produced a much more powerful immune response in health-care workers who'd been infected than in colleagues who'd escaped infection. The results "support a single-dose vaccination strategy for previously infected individuals to increase coverage and protect a larger number of populations", the authors write.

A one-jab policy for those who've been infected might even help to overcome vaccine apathy, says Stacy Wood at North Carolina State University in Raleigh, a marketing expert who has studied vaccine messaging. She argues that, rather than sowing confusion, outreach that accounts for individual characteristics can help convince people who feel that their own circumstances, including infection history, make them unique. Cutting down the number of shots — and all the attendant side effects, anxiety and time involved — can also be an attractive proposition to some who are on the fence about getting immunized.

"The more tailored approach is probably better at this point," Wood says.

The accumulating evidence has been enough to convince many scientists that second doses of precious vaccine should not be allotted to people who've been infected.

Stretching vaccine doses

Providing only one dose for those who've had COVID-19 "would free up many urgently needed vaccine doses. With the additional available vaccines, there would be no need to delay the second vaccine dose for naïve individuals," argues a letter[10] published in May in *EBioMedicine* and signed by eight COVID-19 scientists. And, increasingly, countries and regions that are short of vaccine are following the scientists' lead, at least for younger adults who do not have compromised immune systems.

But not all governments are on board with this approach. In the United States, for instance, where vaccine is relatively plentiful, officials still recommend two doses for all. Determining previous infection history "is not recommended for the purposes of vaccine decision-making", says Kate Grusich, a spokesperson for the US Centers for Disease Control and Prevention in Atlanta, Georgia.

Scientists also point out that some people who become infected with SARS-CoV-2 mount a relatively weak immune response. Such a response is especially common in people who don't develop COVID-19 symptoms. "There's a huge range of antibody generation and durability in those individuals," notes Wherry. "Making decisions based on previous PCR-confirmed infections might miss some people."

That's where diagnostic antibody testing could help.

Screening for antibodies to the hepatitis B virus is already routine in some settings to guide vaccination strategies against that infectious agent — and the same could be done with antibodies to the SARS-CoV-2 spike protein, a marker of both natural and vaccine-induced immunity, says Viviana Simon, an infectious-disease specialist at Mount Sinai and a signatory to the *EBioMedicine* letter.

"When in doubt, I'm all for a second dose," she says. "But I personally hope that we can move eventually to more personalized schedules and recommendations."

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ALZHEIMER'S DRUG APPROVAL COULD AFFECT OTHER DISEASES

Aducanumab's controversial fast-tracking has researchers both worried and hopeful.

By Asher Mullard

The recent controversial approval of the Alzheimer's drug aducanumab by the US Food and Drug Administration (FDA) has raised the possibility that the agency could now be more willing to fast-track treatments for a swathe of neurodegenerative diseases. But an independent advisory panel fiercely questioned the new drug's effectiveness, and researchers are divided on whether the potentially smoother approval path that aducanumab has paved will really deliver useful therapies for people with conditions such as motor neuron disease (also known as amyotrophic lateral sclerosis, ALS), Huntington's disease and Parkinson's disease.

Drug developers including Amgen in Thousand Oaks, California, and Pfizer, based in New York City, have shut down their neuroscience programmes in recent years because of the difficulties of finding successful treatments for brain diseases. So Eric Siemers, a drug-development consultant in Zionsville, Indiana, thinks aducanumab's approval could bring renewed investment and innovation.

On the basis of conversations that he's had with investors and clients, he says, the tide is already turning. "There's a lot more interest now in research in neurodegenerative diseases," says Siemers, who is also chief medical officer of the Alzheimer's disease company Acumen Pharmaceuticals in Charlottesville, Virginia. Acumen filed paperwork for an initial public offering just days after the approval of aducanumab.

The news has also encouraged advocacy groups that are campaigning for people with

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People with Parkinson's disease often undergo therapy to improve their motor function.

few or no therapeutic options. "If the FDA can find a way to be flexible for Alzheimer's, maybe they can find a way to be flexible for ALS," says Neil Thakur, chief mission officer at the ALS Association.

But many researchers fear that this regulatory precedent puts false hope above solid clinical science. "Folks who are considering this approach should take a deep breath and a cold shower," says Fyodor Urnov, scientific director of the Innovative Genomics Institute at the University of California, Berkeley, and a former drug hunter at Sangamo Therapeutics in Brisbane, California. "I don't want a future where we have multiple prescribable medicines. I want a future where we have multiple prescribable medicines that work."

Reading between the lines

Aducanumab — developed by the biotechnology firm Biogen in Cambridge, Massachusetts — followed an unusual route to approval. In March 2019, Biogen halted two phase III trials of the drug candidate after an interim analysis showed that it was unlikely to improve cognition for people with mild Alzheimer's. But when Biogen re-evaluated the data and found that a subset of people in one of the trials might have benefited, it reversed course; the firm submitted aducanumab for approval in 2020.

The FDA's eventual decision to ignore the recommendation of its advisory committee and approve the drug, it says, was based on aducanumab's ability to lower levels of amyloid plaques in the brain — protein clumps that some scientists think cause Alzheimer's.

Instead of granting the drug a standard approval, which is typically reserved for agents that have demonstrated benefit for people in large phase III trials, the FDA opted to use its 'accelerated approval' pathway. This is for treatments that are "reasonably likely", but not certain, to help patients.

The agency has embraced this pathway in cancer, using results from small phase II trials to green-light drugs for narrow sets of patients with late-stage disease. With aducanumab, the agency has shown that it is willing to push the paradigm to a broader set of people. One reason that decision has attracted criticism is that decreased levels of amyloid plaques are an unvalidated and contentious marker of a drug's activity.

In large trials of other Alzheimer's drug candidates, amyloid lowering has not led to cognitive benefits, and this has made it a sticking point for researchers.

Biogen can now sell its US$56,000-per-year drug to 6 million people with Alzheimer's in the United States. As a condition of the accelerated approval, the firm has until 2030 to report the results of a 'post marketing' trial to prove the drug's cognitive benefit.

Internal memos released last week by the FDA shed some light on the decision. Clinical reviewers argued that aducanumab is likely to provide a cognitive benefit, whereas statistical reviewers said the data did not support approval.

Asked by *Nature* to elaborate on the implications for Parkinson's disease, Huntington's disease and ALS, an FDA spokesperson replied that "the FDA stands ready to work with research communities and drug developers to study more therapies for Alzheimer's disease and other neurodegenerative disorders".

Patrizia Cavazzoni, a high-ranking FDA official, has given a nod to aducanumab's broader impact. "The accelerated-approval pathway has been an incredibly useful tool," she said in a press meeting. "We believe it serves as a model that we hope can be replicated with neurodegenerative diseases."

Silver linings?

One neurodegenerative condition whose treatment could benefit from aducanumab's approval is Parkinson's disease, which affects around one million people in the United States. Although some drugs help to alleviate Parkinson's symptoms, none slow its progression. For Joseph Jankovic, a neurologist at Baylor College of Medicine in Houston, Texas, a more flexible approach to drug development might speed up progress.

The approval of aducanumab "is one of the worst decisions the FDA has ever made", says Jankovic, who is unconvinced that the drug's benefits outweigh its risks. But accelerated approval does have value, he argues. "I'm always looking at a glass half-full. I hope that this will soften the FDA when they review drugs for other diseases."

He has his eye on drug candidates that mop up α-synuclein, a protein that builds up in the brains of people with Parkinson's. A recent phase II trial of an α-synuclein-targeted antibody failed to make an overall dent in the symptoms of Parkinson's, Jankovic explains, but it delayed the worsening of people's tremors, stiffness and slowness of movement. Drug-development partners Roche, based in Basel, Switzerland, and Prothena in Dublin, have since launched a larger phase II trial to look at the motor-function benefits of the drug candidate. Results are expected in 2023, at which point this programme could test the FDA's resolve in relation to neurodegenerative diseases.

Huntington's disease — an inherited neurodegenerative disease that causes involuntary jerking movements and dementia — is another one to watch. People with this condition carry a mutant, toxic form of a protein called huntingtin (HTT), so researchers have developed drug candidates to lower its levels.

The most advanced of these had been tominersen, developed by Roche and Ionis Pharmaceuticals in Carlsbad, California, which lowers mutant HTT in the cerebrospinal fluid by 44%. Tominersen entered a phase III trial in 2018. Roche stopped that trial early, in March of this year, after patients worsened on treatment.

HTT-lowering drugs are not yet out of the running, however. Candidates that target other forms of HTT might still slow the disease. But for Urnov, the failure of tominersen is a prime example of why the FDA should not approve drugs using regulatory goalposts such as amyloid plaques or HTT.

"This is going to harm the prospects for safe, effective, approved medicines for neurodegeneration," says Urnov. "This is not how our field should be working."