for SARS-CoV-2, 4.4% had symptoms, such as headache, fatigue and loss of smell, that persisted; 1.6% had symptoms that remained for at least 8 weeks[5].

It will also be important to determine how long the condition lasts in children, says Armann. Headaches or trouble sleeping for just 6 months is a vastly different problem from having these symptoms all their life, even if it only happens for 1%, he says.

Buonsenso says that one of the challenges in working out how many kids develop long COVID is that there are no set diagnostic criteria in adults, let alone in children. Surveys to detect symptoms usually cast a wide net, and are not yet specific enough to tease out long COVID from other conditions, he says. Nevertheless, he is convinced that some children — perhaps 5–10% of those with COVID-19 — do develop the condition.

If psychological distress were a big factor in the symptoms he's seeing, as Armann has suggested, Buonsenso argues there would have been more children with symptoms from the first wave of infections in 2020, when restrictions were harshest in Rome. Instead, the second wave resulted in more cases of children with symptoms of long COVID, he says.

A proper definition of long COVID is urgently needed, says Hardelid, so that studies can determine how much of a problem it presents in children.

One suggestion, following a review of the literature in adults by the UK National Institute for Health Research, is that long COVID could be a collection of four different syndromes, including post-intensive care syndrome, post-viral fatigue syndrome and long-term COVID syndrome[6]. This could be the case in children, too, says Hardelid.

Buonsenso has also been looking at immunological changes that occur in people with long COVID, to see whether there are biological markers that could lead to treatments. In a small study posted as a preprint in May, he and his colleagues found that only the children with long COVID showed signs of chronic inflammation following infection[7].

Such investigations into the biological basis of long COVID could have far-reaching effects. In general, we know very little about chronic post-viral conditions, says Buonsenso, because most clinical attention, and funding, has focused on the acute phase of infections.


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# WHAT THE RISE OF 'ARPA-EVERYTHING' WILL MEAN FOR SCIENCE

## The renowned US Defense Advanced Research Projects Agency is inspiring science-agency mimics.

**By Jeff Tollefson**

US President Joe Biden's administration wants to create a US$6.5-billion agency to accelerate innovations in health and medicine — and revealed new details about the unit last month[1]. Dubbed ARPA-Health (ARPA-H), it is the latest in a line of global science agencies now being modelled on the highly regarded US Defense Advanced Research Projects Agency (DARPA), whose work a generation ago laid the foundation for the modern Internet.

With more DARPA clones on the horizon, researchers warn that success in replicating DARPA's hands-on, high-risk, high-reward approach is by no means assured.

"The ARPA model has been successful, and we've learned a lot," says Laura Diaz Anadon, who heads the Cambridge Centre for Environment, Energy and Natural Resource Governance at the University of Cambridge, UK. "But ARPA is not a magic bullet that will apply to everything."

Enamoured with the innovation that DARPA fostered in the United States, governments around the world, including in Europe and Japan, have attempted to duplicate the agency within their own borders. Most recently, the United Kingdom announced plans to create its version, the Advanced Research and Invention Agency (ARIA), with an initial allocation of £800 million (US$1.1 billion). And the Biden administration has proposed launching a second US agency, the $500-million ARPA-Climate (ARPA-C), to spur technologies for fighting climate change.

Scientists who have studied the DARPA model say it works if applied properly, and to the right, 'ARPA-able' problems. But replicating DARPA's recipe isn't easy. It requires the managers who build and run an agency's grant programmes to have the freedom to assemble research teams and pursue risky ideas in promising fields that have typically been neglected by conventional industrial research and development programmes. Critics aren't yet sure how ARPA-H, ARPA-C and ARIA will fare.

The US Department of Defense established DARPA in 1958, one year after the Soviet Union launched the world's first satellite, Sputnik 1. The goal was to ensure that the United States remained a world leader in technology. DARPA was instrumental in early computing research, as well as in developing technologies such as GPS and unmanned aerial vehicles.

DARPA functions differently from other major US science funding agencies, and has a leaner budget ($3.5 billion). Its roughly 100 programme managers, borrowed for


US AIR FORCE PHOTO/ALAMY

**DARPA investments have led to the creation of technologies such as unmanned aerial vehicles.**

stints of 3–5 years from academia or industry, have broad latitude in what they fund, and actively engage with their teams, enforcing aggressive deadlines and monitoring progress along the way. By comparison, projects funded by agencies such as the US National Institutes of Health (NIH) typically see little engagement between programme managers and the researchers they fund, apart from annual progress reports. Projects funded by these agencies also tend to be those that are likely to succeed — and thus typically represent more incremental advances, says William Bonvillian, a policy researcher at the Massachusetts Institute of Technology in Cambridge who has studied DARPA.

### Following the recipe

The DARPA model doesn't work if programme managers aren't given the space to fail, says Bonvillian. When the US government applied the model to developing national-defence technologies through the Homeland Security ARPA in 2002, he adds, this was the problem. The effort eventually collapsed. "If you don't get the culture right on day one, you have got a problem," says Bonvillian.

Researchers also point out that a successful ARPA needs a customer for the technologies it develops. In the case of DARPA, the US military was ready to purchase many promising inventions. ARPA-Energy (ARPA-E), which was launched in 2009 under former president Barack Obama to advance low-carbon energy technologies, addressed this challenge by helping grant recipients to develop plans for commercialization from the outset.

ARPA-E had the independence it needed to function well, researchers say. Still running today, the agency, housed within the US Department of Energy (DoE), has invested $2.8 billion in nearly 1,200 projects, which have attracted another $5.4 billion in private-sector investments and led to the creation of 92 companies.

Because it can take decades for new technologies to have commercial and societal impact, whether ARPA-E will transform the energy industry remains to be seen. But scientists have documented preliminary signs of its success[2,3], as measured by patenting, publishing and, in some cases, attracting venture capital for technologies originally funded by the agency.

"The answer is yes, the [ARPA] model works, or at least it did in this case," says Anna Goldstein, an energy researcher at the University of Massachusetts Amherst who has analysed ARPA-E's effectiveness. But that does not mean the model will solve all problems, she warns.

Researchers have responded to Biden's latest ARPA proposals with trepidation. Some scientists have questioned the need to create ARPA-C, rather than expanding ARPA-E. They point out that the two have similar missions, even though DoE secretary Jennifer Granholm has said they will not overlap. As planned, ARPA-C would seek to foster "game-changing" energy and climate solutions, including technologies such as small, modular nuclear reactors and low-energy buildings — innovations that also fall under ARPA-E's purview.

Questions also abound about ARPA-H. The Biden administration proposed that it should be housed within the NIH, which critics worry could stifle innovation.

In a guest editorial published in *Science* last month[1], NIH director Francis Collins and other administration officials acknowledged that the NIH tends to fund incremental research rather than bold new technologies that could transform the marketplace, and agreed that ARPA-H's organization must have a culture that values "bold goals with big potential impact".

The Biden administration is saying all the right things, says Bonvillian, although he still worries about whether ARPA-H will have the independence and the authority that it needs to operate within the biomedical-research behemoth. He also says the NIH will need to embrace the kind of interdisciplinary research that has been fundamental to technology development at agencies such as DARPA and ARPA-E. "If they set up an ARPA that is all biology all of the time, like NIH is, then they are going to radically limit its effectiveness," he says.

Others worry that the scope of ARPA-H's mission is too broad. Health care is a huge field. Given that there is already plenty of private investment in new drugs and medical therapies for prevalent diseases, Goldstein says, ARPA-H might be better placed to have an impact on neglected diseases that affect people living in impoverished and underprivileged communities. This area receives much less funding from other sources.

"The trick is setting the scope broad enough so that programme managers can wander intellectually and follow their noses, but not so broad that you try to boil the ocean," says Eric Toone, a chemist who helped to set up ARPA-E and now works for Breakthrough Energy Ventures, a venture-capital firm based in Kirkland, Washington. This is also a potential concern with the United Kingdom's ARIA, whose scope has yet to be defined, Toone adds.

Toone also recommends starting out small and letting new agencies grow over time. "The challenge you have with too much money is people's expectations wind up in funny places."


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# COVID AND THE BRAIN: RESEARCHERS ZERO IN ON HOW DAMAGE OCCURS

## Growing evidence suggests that neurological symptoms arise through multiple mechanisms.

**By Michael Marshall**

How COVID-19 damages the brain is becoming clearer. New evidence suggests that the coronavirus's assault on the brain could be multipronged: it might attack certain brain cells directly, reduce blood flow to brain tissue or trigger production of immune molecules that can harm brain cells.

Infection with the coronavirus SARS-CoV-2 can cause memory loss, strokes and other effects on the brain. The question, says Serena Spudich, a neurologist at Yale University in New Haven, Connecticut, is: "Can we intervene early to address these abnormalities so that people don't have long-term problems?"

With so many people affected — neurological symptoms appeared in 80% of the people hospitalized with COVID-19 who were surveyed in one study[1] — researchers hope that the growing evidence base will point the way to better treatments.

Early in the pandemic, researchers speculated that the virus might cause damage by somehow entering the brain and infecting neurons, the cells responsible for transmitting and processing information. But studies have since indicated[2] that the virus has difficulty getting past the brain's defence system — the blood–brain barrier — and that it doesn't necessarily attack neurons in any significant way.

One route by which SARS-CoV-2 might be accessing the brain, experts say, is by passing through the olfactory mucosa, the lining of the nasal cavity, which borders the brain. The virus is often found in the nasal cavity — one reason that health-care workers test for COVID-19 by swabbing the nose.

Even so, "there's not a tonne of virus in the