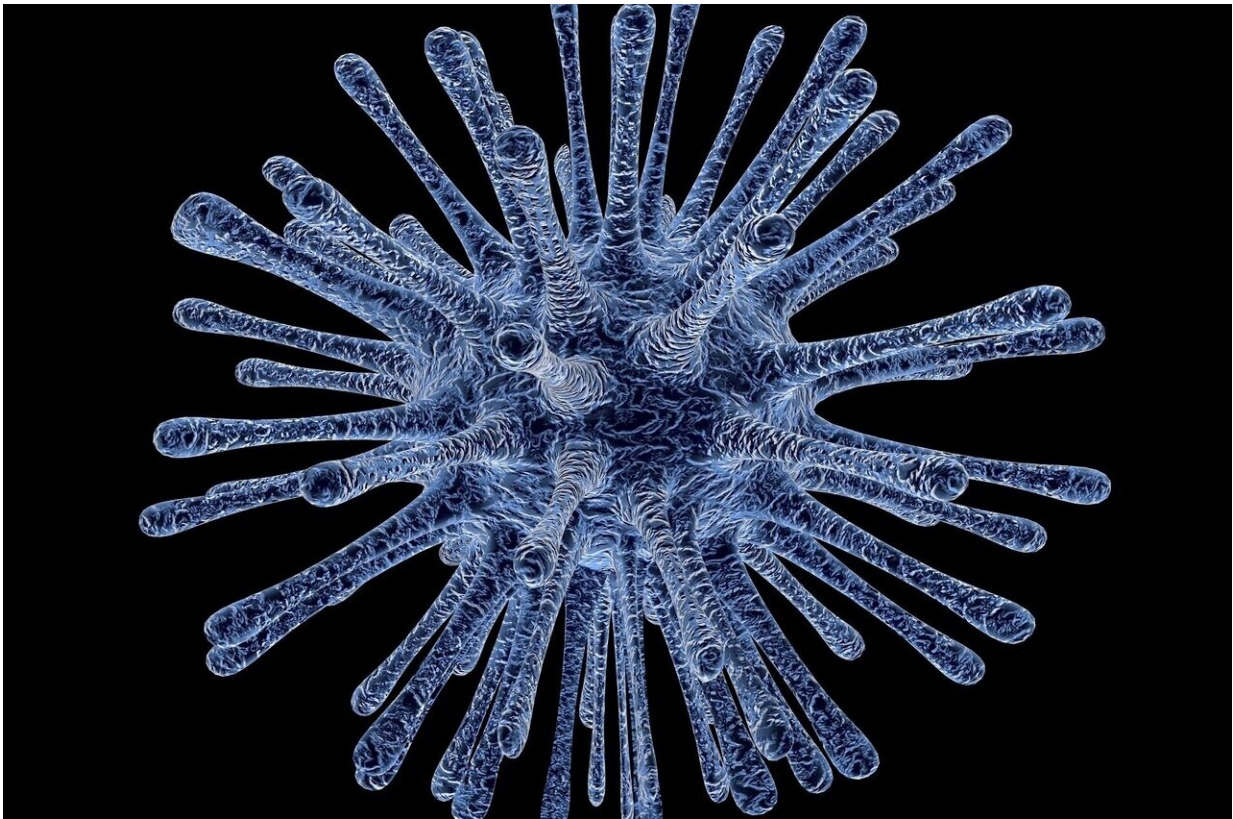


# 'Missing' virus detected in dozens of children paralyzed by polio-like illness

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Credit: CC0 Public Domain

A UC San Francisco-led research team has detected the immunological remnants of a common seasonal virus in spinal fluid from dozens of patients diagnosed with acute flaccid myelitis (AFM)—a polio-like

illness that causes permanent, sometimes life-threatening paralysis in young children. The findings provide the clearest evidence to date that AFM is caused by an enterovirus (EV) that invades and impairs the central nervous system.

The study was published October 21, 2019 in *Nature Medicine*.

AFM, which begins with cold-like symptoms and progresses to limb weakness and paralysis in a matter of days, was first documented in 2012. Since then, AFM outbreaks have occurred every other year, with more than 500 confirmed cases recorded so far. But because scientists have had trouble pinpointing a cause, AFM has been the subject of contentious debate within the medical community.

Mounting evidence implicated EVs as the likely culprit—specifically the so-called D68 and A71 strains of the virus. EV outbreaks are common and normally cause nothing more severe than cold-like symptoms or the rash-producing hand, foot and mouth disease.

Scientists started to notice, however, that EV outbreaks coincided with spikes in AFM. They also found that respiratory samples from children diagnosed with AFM often tested positive for EVs. Plus, [laboratory studies](#) found that these strains caused paralysis in mice.

But many experts remained skeptical of the enterovirus hypothesis, instead proposing that AFM is an autoimmune disorder or is caused by some other, as-yet-undiscovered virus. These EV skeptics argued that the evidence linking the virus to AFM was circumstantial, because the virus could not be found in 98 percent of AFM patients who had their [spinal fluid](#) tested. They maintained that until there was ample evidence of the virus invading the human nervous system, the link between EVs and AFM remained unproven.

"People were hung up on the fact that enteroviruses were rarely detected in the cerebrospinal fluid of AFM patients. They wanted to know how someone could get neurologic symptoms with no virus detectable in their central nervous system," said Michael Wilson, MD, associate professor of neurology, member of the [UCSF Weill Institute for Neurosciences](#), and senior author of the new study. "If we could detect something specific to a virus in the spinal fluid of AFM patients, we would feel more secure claiming that the neurologic symptoms of the disease are virally mediated."

The group first searched for the virus directly in spinal fluid using advanced [deep](#) sequencing [technologies](#), but this sort of direct detection of the virus failed, as it had previously. Therefore, to find evidence of the missing virus, Wilson and his collaborators—researchers at the Chan Zuckerberg Biohub, the Centers for Disease Control and Prevention, the California Department of Public Health, the University of Colorado, Boston Children's Hospital and the University of Ottawa—used an enhanced version of a virus-hunting tool called VirScan, first developed at Harvard Medical School in the laboratory of Stephen J. Elledge, Ph.D.

VirScan, which is a customized version of a Nobel Prize-winning technique called phage (rhymes with "beige") display, allowed Wilson's team to probe the spinal fluid of AFM patients for signs of an immune response against enterovirus and thousands of other viruses simultaneously.

"When there's an infection in the spinal cord, antibody-making immune cells travel there and make more antibodies. We think finding antibodies against enterovirus in the spinal fluid of AFM patients means the virus really does go to the spinal cord. This helps us lay the blame on these viruses," said Ryan Schubert, MD, a clinical fellow in UCSF's Department of Neurology, a member of Wilson's Lab, and lead author of the new study.

The researchers created molecular libraries consisting of nearly 500,000 small chunks of every protein found in the over 3,000 viruses known to infect vertebrates (including humans), as well as those that infect mosquitoes and ticks (an effort to rule out disease transmission through their bites). They then exposed these molecular libraries to spinal fluid obtained from 42 children with AFM and, as a control, 58 who were diagnosed with other neurological diseases. Any chunks of viral protein cross-reacting with any antibodies present in the spinal fluid would provide evidence for a viral infection in the central nervous system.

Antibodies against enterovirus were found in the spinal fluid of nearly 70 percent of AFM patients; less than 7 percent of non-AFM patients tested positive for these antibodies. Furthermore, because spinal fluid from AFM patients did not contain antibodies against any other virus, every other known virus could be eliminated as a possible culprit. These results were confirmed using more conventional lab techniques.

"The strength of this study is not just what was found, but also what was not found," said Joe DeRisi, Ph.D., professor of biochemistry and biophysics at UCSF, co-president of the Chan Zuckerberg Biohub, and co-author of the new study. "Enterovirus antibodies were the only ones enriched in AFM patients. No other viral family showed elevated antibody levels."

Though the study provides the most robust evidence so far that enteroviruses cause AFM, many questions around AFM and these viruses remain unanswered. For example, though the AFM-causing enterovirus strains—EV-D68 and EV-A71—were identified decades ago, they only recently seemed to have gained the ability to cause paralysis, with the D68 strain in particular responsible for the most severe cases of AFM.

"Presumably there are changes that are causing the virus to be more

neurovirulent, but no one knows for sure what they are," Schubert said. "Because the virus is found in such low amounts, if at all, it's hard to zero in on the differences between an A71 virus that causes routine hand, foot, and mouth disease and one that causes AFM."

Also, because enteroviruses are extremely common, scientists are still trying to figure out why fewer than 1 percent of infected children get AFM, and they're also trying to understand why children are the only ones affected. "We don't know for sure why children get paralysis and adults don't," Schubert said. "The thinking is that young children have low immunity to the virus that increases as they get older, so we see the most severe effects in children around the age of two. But more work needs to be done to understand AFM."

For study co-author Riley Bove, MD, answering these unresolved questions is a deeply personal mission. Bove, an assistant professor of neurology and member of the UCSF Weill Institute for Neurosciences, is the mother of a child who was diagnosed with AFM.

In the summer of 2014, Bove's entire family came down with what seemed to be a severe cold. Everyone recovered except Bove's then four-year-old son. Just days after the onset of the cold-like symptoms, he started experiencing difficulty breathing. Soon, he was paralyzed from head to toe and had trouble breathing on his own.

Today, Bove's son is a thriving nine-year-old, but she says the physical and emotional effects of AFM will be with him the rest of his life. "For every family with a child diagnosed with AFM, the long-term consequences of the disease remain the top issue," she said.

Bove hopes that the new study will lead to a scientific consensus around enterovirus as the cause of AFM, since this a key step on the road to improved diagnostics and the development of a vaccine for the illness.

"Public health education is important, but it's not enough to prevent AFM," Bove said. "The [virus](#) is too common to avoid. A vaccine is the only way to meaningfully prevent the disease."

For now, there's no way to prevent or treat AFM. But if it follows the biennial pattern first established after the 2012 outbreak, AFM cases may spike again next year.

"We're all holding our breath for 2020," Schubert said.

**More information:** Pan-viral serology implicates enteroviruses in acute flaccid myelitis, *Nature Medicine* (2019). [DOI: 10.1038/s41591-019-0613-1](#) , [nature.com/articles/s41591-019-0613-1](https://www.nature.com/articles/s41591-019-0613-1)

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