# Outbreaks of acute flaccid myelitis? What neurologists need to know

**After a third apparent spike in cases of acute flaccid myelitis across the USA, the US Centers for Disease Control and Prevention is on alert. Neurologists worldwide should be aware of what might be an emerging disease. Adrian Burton reports.**


James Gathany/CDC

**The US Centres for Disease Prevention and Control**

For **information on the Task Force members** see https://www.cdc.gov/ddid/bsc/afm-biographies.html

For **weekly updates on the number of confirmed cases of AFM in the USA** see https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html

For more on the **differences between AFM andacute flaccid paralysis** see https://www.cdc.gov/acute-flaccid-myelitis/downloads/afm-presentation.pdf

For **information on the symptoms of children with AFM** see https://www.cdc.gov/acute-flaccid-myelitis/about-afm.html

For more on the **links between AFM and EV-D68** see **Articles** *Lancet Infect Dis* 2015; **15:** 671–82

For more on **cases of EV-D68-associated AFM** see *Pediatr Infect Dis J* 2018; published online September 18

For more on **European states engaged in EV-D68 surveillance** see *Eurosurveillance* 2017; 22 [45]

For more on **outcomes of AFM in children at 1 year** see *Neurology* 2017; **89:** 129–137

For more on **clinical, neuroimaging and functional profiles of children in the acute and convalescent stages of AFM** see *Dev Med Child Neurol* 2018; published online September 18. htpp://dx.doi.10.1111/dmcn.14030

A task force set up on Nov 14, 2018, by the US Centers for Disease Control and Prevention (CDC) with a remit that includes determining what lies behind a third biannual spike in cases of acute flaccid myelitis (AFM) across the USA, made its first report soon after on Dec 6. 460 confirmed cases have now been recorded for the period between August, 2014 and Nov 30, 2018; 134 of those in 2018, with more under review. You might be forgiven for thinking these numbers small for a population of some 327 million. Certainly, AFM remains a rare—although serious—disease. But every other year since 2014, the number of new cases has peaked between August and October, and those peaks appear to be getting bigger. The work being undertaken by the new task force is therefore vital: vital because we might one day have to deal with a larger epidemic; because we do not yet know how to prevent new cases; because it is associated with serious neurological and functional defects in the short and long term; because it can be fatal; and perhaps most poignantly, because it mostly affects children. Neurologists, especially paediatric neurologists, and family and emergency room doctors should therefore be aware of this potentially emerging disease. And not just those in the USA; although fewer in number, cases raising concerns in Europe and Asia have also been recorded.

Defined as acute flaccid paralysis of one or more limbs, or acute onset of bulbar paralysis, AFM specifically affects the grey matter of the spinal cord, thus distinguishing it from acute flaccid paralysis, an umbrella term covering a range of clinical entities affecting any area of the neuraxis from the anterior horn cells onwards. "Symptoms can include sudden weakness and loss of muscle tone, loss of the reflexes in the arms and legs, and possibly facial drooping, droopy eyelids, difficulty in swallowing and moving the eyes, or slurred speech", explains Benjamin Greenberg (Cain Denius Scholar in Mobility Disorders, University of Texas Southwestern Medical Center, Dallas, TX, USA). "Physicians who see any of these things should immediately suspect AFM, and under the present circumstances be very suspicious if the patient has recently experienced a mild respiratory illness or fever." For most people that cold is the end of the story, but a few seem to go on to develop AFM; certainly, the parents of some 90% of children with AFM report them having had a mild cold before noticing more worrying symptoms. "All patients with suspected AFM should undergo MRI of the spinal cord", insists Greenberg. "The detection of signal abnormalities, predominantly affecting the grey matter is highly suggestive of AFM and should prompt a thorough work-up. This evaluation should consider potential mimics of AFM, including vascular insults to the spinal cord and anti-MOG (myelin oligodendrocyte glycoprotein) antibody-mediated inflammation within the spinal cord."

Of course, AFM as a medical condition is nothing new; it has always been around. What is new is the apparent increase in its incidence. But is it entirely real? The possibility exists that, for whatever reason, physicians simply began to take more notice of AFM, leading to more vigilant surveillance, resulting in cases being reported that at other times went uncounted. The increase in numbers might therefore reflect a truly growing problem, a problem we never knew we had, or a mixture of both. Either way, it is bad news, and certainly not helped by the fact that "even though there is more awareness, there are still clinicians who aren't recognising AFM", explains Ruth Lynfield (Task Force Co-Chair, State Epidemiologist and Medical Director, Minnesota Department of Health, St Paul, MN, USA). "We need help to make sure that all clinicians are considering it as a differential diagnosis for patients presenting with limb weakness."

Determining the cause of these cases is a priority. Although the disease resembles polio, no polio virus has ever been recovered from any stool provided by any patient with AFM. And enterovirus EV-A71, a known causal agent of AFM, has only appeared in a minute number of spinal fluid samples. The front-running viral candidate for now is enterovirus EV-D68. Research has shown that the original Fermon strain of EV-D68 does not cause AFM in a mouse model, unlike the strain that appeared in 2014, when case numbers began to rise. The virus was also reported to meet the Bradford Hill criteria for establishing causality, with peaks in its presence matching the appearance of new cases. Certainly, cases of AFM apparently associated with EV-D68 have been noted in Europe: in a 2018 paper, 29 were reported from across France, Norway, Scotland, Spain, and Sweden.

People are not mice, however, and associations are not proof of causality. If EV-D68 epidemics occur around the same time as AFM peaks, it is unsurprising that patients might also

be independently infected with this virus. Moreover, EV-D68 is not found in everyone who develops the disease; indeed, in the majority of samples taken from patients with AFM, it has not been detected. Possible environmental causes still cannot be ruled out, and it is unknown whether those people who develop the condition are genetically predisposed to it. A further problem for the association between AFM and EV-D68 might lie in the short length of time over which data have been collected. Increased numbers of cases in the USA have only been recorded since 2014 and given the every-other-year appearance of peak AFM numbers and EV-D68 outbreaks, only three matching peaks are available (for 2014, 2016, and 2018). "More data are needed to see if this association holds over a longer time", says Bonnie Maldonado (Professor of Paediatrics [Infectious Diseases] and Health Research Policy, Stanford University School of Medicine, Stanford, CA, USA). "However, while the jury is still out on this virus, we have enough data for us to remain suspicious of a role for EV-D68 in AFM."

"There are many loose ends to tie up", agrees John F Modlin (Deputy Director, Polio at the Bill and Melinda Gates Foundation and Emeritus Professor of Paediatrics and Medicine, The Geisel School of Medicine at Dartmouth, Hanover, NH, USA). "Still, AFM fits an epidemiological and clinical pattern that is strikingly similar to the paralysis that results from infection with a number of known enteroviruses, and the burden of proof for other mechanisms of disease will be high." The European Centre for Disease Prevention and Control (ECDC) told *The Lancet Neurology* that it is now closely monitoring the situation in the USA and elsewhere. Although EV-D68 is not presently under EU-level surveillance, several European states that work with the ECDC already have specific reporting and surveillance systems for the virus in place, helping to examine that burden of proof.

Unfortunately, for now there are only very basic infection control practices recommended, like hand washing, to help protect against viruses like EV-D68. Neither is there any swift curative treatment for AFM. "Patients should receive supportive care in an appropriate medical facility", says Greenberg. "Treatment considerations should include high dose corticosteroids, intravenous immunoglobulin, or plasma exchange. There are no prospective trials of these therapies in patients with AFM and each should be evaluated based on risk versus benefit considerations. Early initiation of physical and occupational therapy, with a plan to continue therapy for a prolonged period after hospital discharge, must be pursued for every patient."

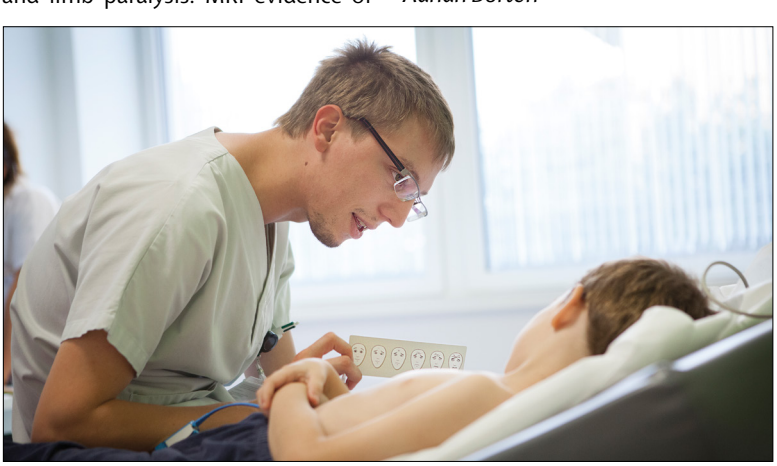
"The mortality rate in AFM is fortunately low during the acute phase", adds Carlos Pardo-Villamizar (Director, Johns Hopkins Transverse Myelitis Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA), "but almost 50% of patients require aggressive medical management in intensive care units during this phase, with many of them in need of mechanical ventilation support due to neuromuscular respiratory failure. Although the magnitude of paralysis and spinal cord involvement varies, almost 50–70% of the patients affected by AFM experience long-term consequences and neurological disability associated with weakness and limb paralysis. MRI evidence of long-term damage to the anterior horn of the spinal cord concurs with the residual muscle atrophy and limb paralysis observed in many children affected by AFM".

"Currently, we are working hard to figure out the cause of these clusters, markers that could help better diagnose the disease, risk factors for it, and treatments that might help those affected", says Jill Taylor (Task Force Co-Chair and Director, Wadsworth Center, New York State Department of Health, Albany, NY, USA). "We are also working to improve surveillance and educating the public and medical professionals about it. We must stress that AFM remains a rare disease, but family doctors, paediatricians, emergency departments and urgent care providers, neurologists and other health-care professionals in the USA and overseas currently need to be more aware of it."

Although raising awareness might be accomplished relatively quickly, establishing the cause of, and risk factors for, these cases of AFM is unlikely to be easy; finding a successful treatment could be just as hard. "We know it will be a long road ahead", concludes Tom Clark (Deputy Director, CDC National Center for Immunization and Respiratory Disease [Division of Viral Diseases]), "but we will regularly update health-care professionals and the public as we learn more".

*Adrian Burton*

For more on **AFM, what the CDC is doing, what we know so far, and case numbers** see https://www.cdc.gov/features/acute-flaccid-myelitis/index.html



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**Physicians need to 'think AFM'**