Acute Flaccid Myelitis Surveillance: A Signal Through the Noise

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Ayers et al1, in the current issue of Pediatrics, provide comprehensive surveillance data for the polio-like illness acute flaccid myelitis (AFM) in the United States from January 1, 2015, to December 31, 2017. Importantly, in this study, they found that among the 193 children meeting the confirmed AFM case definition during the 3-year period, 143 instances (74%) occurred in 2016, fitting within the larger epidemiological context of a biennial pattern of AFM outbreaks in the US documented from 2014 to 2018 (Fig 1).2 Additionally, approximately two-thirds of the 2016 cases occurred in August to October, mirroring the summer-to-fall seasonality of the 20143 and 2018 outbreaks.4 Thirty-six percent of respiratory specimens and 19% of stool and rectal specimens tested at the Centers for Disease Control and Prevention (CDC) were positive for an enterovirus or rhinovirus, but viruses were rarely detected in cerebrospinal fluid (CSF) (n = 1) or blood (n = 2). Notably, 69% (22 out of 32) of enteroviruses and rhinoviruses from respiratory specimens were typed as enterovirus-D68; no other picornavirus was detected in more than 3 patients. The authors conclude that the composite nationwide 2015 to 2017 AFM surveillance data suggest a viral etiology but that it is challenging to attribute one specific virus as the cause of AFM.

Although the term AFM was newly coined during the 2014 outbreak, the clinical syndrome of acute flaccid paralysis due to myelitis in the gray matter of the spinal cord has previously been associated with several different infectious and noninfectious causes, including poliovirus, nonpolio enteroviruses, flaviviruses, and autoantibody conditions.5,6 As such, a single etiology to explain all cases of the clinical syndrome of AFM at all times would not be expected. There will continue to be background rates of cases fulfilling the AFM case definition as a result of various etiologies, and even sporadic clusters, such as the geographically isolated enterovirus-A71-associated AFM outbreak in Colorado in 2018.7 The central question remains: what is driving seasonal biennial nationwide outbreaks of AFM since 2014?

Enterovirus-D68 is the only known pathogen whose circulation has temporally correlated with AFM outbreaks in the United States in 2014, 2016, and 2018, both at local sites conducting active surveillance8,9 and in nationwide surveillance from the CDC National Enterovirus Surveillance System10 and New Vaccine Surveillance Network.11 This type of every 2- to 3-year summer-to-fall circulation pattern is common with enteroviruses, driven primarily by serotype-specific immunity12 and dew point temperature.13 Enterovirus-D68 circulation has likewise correlated with AFM outbreaks in Asia,14 Europe,15,16 and South America.17

The epidemiological signal of AFM outbreak periods in the summer to fall of every other year since 2014 in the United States contrasts starkly with the background noise of sporadic cases...
It is already evident in the Ayers et al study and among US AFM cases overall from 2014 to 2018 that enterovirus-D68 has been the predominant pathogen detected. Including the entirety of US AFM epidemiology since 2014 and focusing specifically on the peak August to October periods in even years may further demonstrate a specific association between enterovirus-D68 and AFM during outbreaks. The authors point out that widespread enterovirus circulation can complicate causal attribution to enteroviruses detected from nonsterile sites in AFM cases. However, case control studies, such as the 2014 CDC study in Colorado in which it was shown that the prevalence of enterovirus-D68 detection in AFM cases was not merely reflective of background circulation, can be used to effectively address this challenge. Analyzing the clear signal of AFM outbreaks separately from the background noise of intervening periods of endemic AFM will likely provide additional support for enterovirus-D68 as the driving factor behind recent AFM outbreaks.

Although detection of a pathogen in the CSF would provide definitive proof of causation, in this study and others, no pathogen has been consistently identified in CSF from AFM cases, even with the use of highly sensitive unbiased research technologies for pathogen detection and discovery. Development of intrathecal enterovirus antibody tests for CSF may further facilitate diagnosis of enterovirus-associated AFM, even when the virus is no longer present in CSF, similar to diagnosis of neuroinvasive arboviral infections. Additionally, improving AFM awareness to ensure early diagnosis with prompt and complete specimen collection (including respiratory sampling in addition to CSF and stool) will improve the potential for pathogen detection, as evidenced by increased detection rates from specimens collected within 5 days of prodromal symptom onset.

The study by Ayers et al in this edition of Pediatrics, when placed in the context of the nationwide epidemiology of AFM since 2014, adds an important signal from the 2016 AFM outbreak that further supports enterovirus-D68 as the most likely driver of recent AFM outbreaks in the United States. Enhanced AFM surveillance with focused analysis of distinct signals from outbreak periods is essential to targeting the development of specific therapeutics and preventive vaccines to combat this potentially devastating neurologic condition.

**ABBREVIATIONS**

AFM: acute flaccid myelitis
CDC: Centers for Disease Control and Prevention
CSF: cerebrospinal fluid
REFERENCES


