Acute Flaccid Myelitis in the United States: 2015–2017

Tracy Ayers, PhD,[a] Adriana Lopez, MHS,[b] Adria Lee, MSPH,[c] Anita Kambhampati, MPH,[c] W. Allan Nix, PhD,[b] Elizabeth Henderson, BA,[b] Shannon Rogers, BS,[b] William C. Weldon, PhD,[b] M. Steven Oberste, PhD,[b] James Sejvar, MD,[d] Sarah E. Hopkins, MD, MSPH,[e] Mark A. Pallansch, PhD,[b] Janell A. Routh, MD, MHS,[b] Manisha Patel, MD, MS[b]

abstract

BACKGROUND: Acute flaccid myelitis (AFM) is a neurologic condition characterized by flaccid limb weakness. After a large number of reports of AFM in 2014, the Centers for Disease Control and Prevention began standardized surveillance in the United States to characterize the disease burden and explore potential etiologies and epidemiologic associations.

METHODS: Persons meeting the clinical case criteria of acute flaccid limb weakness from January 1, 2015, through December 31, 2017, were classified as confirmed (spinal cord gray matter lesions on MRI) or probable (white blood cell count >5 cells per mm^3 in cerebrospinal fluid [CSF]). We describe clinical, radiologic, laboratory, and epidemiologic findings of pediatric patients (age ≤21 years) confirmed with AFM.

RESULTS: Of 305 children reported from 43 states, 193 were confirmed and 25 were probable. Of confirmed patients, 61% were male, with a median age of 6 years (range: 3 months to 21 years; interquartile range: 3 to 10 years). An antecedent respiratory or febrile illness was reported in 79% with a median of 5 days (interquartile range: 2 to 7 days) before limb weakness. Among 153 sterile-site specimens (CSF and serum) submitted to the Centers for Disease Control and Prevention, coxsackievirus A16 was detected in CSF and serum of one case patient and enterovirus D68 was detected in serum of another. Of 167 nonsterile site (respiratory and stool) specimens, 28% tested positive for enterovirus or rhinovirus.

CONCLUSIONS: AFM surveillance data suggest a viral etiology, including enteroviruses. Further study is ongoing to better characterize the etiology, pathogenesis, and risk factors of this rare condition.

[c]IHRC Inc. contracting agency to the Division of Viral Diseases, [b]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, [d]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, and [a]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; and [e]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

Drs Ayers, Routh, and Patel conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Lopez, Ms Lee, and Ms Kambhampati designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript; Dr Nix, Ms Henderson, and Ms Rogers conducted laboratory testing and analysis on all samples and reviewed and revised the manuscript; Drs Weldon, Oberste, and Pallansch supervised data collection and laboratory testing and critically reviewed the manuscript for important intellectual content; Drs Sejvar and Hopkins conducted acute flaccid myelitis case classifications and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: Acute flaccid myelitis (AFM) is a severe neurologic condition characterized by flaccid limb weakness. The CDC began tracking AFM in 2014, when an outbreak of 120 cases occurred. Most patients had symptoms of a viral illness shortly before weakness onset.

WHAT THIS STUDY ADDS: This report provides the most comprehensive summary of clinical, laboratory, radiologic, and epidemiologic data of AFM in the United States to date, supporting the every-other-year peak in cases, pediatric predominance, and likely role of viruses, including enteroviruses, in AFM pathogenesis.

To cite: Ayers T, Lopez A, Lee A, et al. Acute Flaccid Myelitis in the United States: 2015–2017. *Pediatrics*. 2019; 144(5):e20191619

Until the late 1950s, poliovirus was a major cause of acute flaccid paralysis (AFP) in the United States, with up to 15 000 paralytic cases annually.[1] Polioviruses can infect anterior horn cells in the gray matter of the spinal cord and cause paralysis in ~0.1% of all infections. After the introduction of effective vaccines in 1955, AFP cases due to poliovirus were eliminated in the United States; the last endemic case was reported in 1979, and the last imported case in 1993.[1] However, nonpolio cases of AFP with similar spinal cord involvement continue to occur, albeit rarely, and have been associated with other enteroviruses (EVs), like coxsackieviruses (CVs), EV-A71, and EV-C105.[2–5]

During late summer of 2014, several cases of AFP among children were identified in Colorado.[6,7] In response to an increase in reports of children presenting similarly in other states, the Centers for Disease Control and Prevention (CDC) developed a case definition for acute flaccid myelitis (AFM), which included persons ≤21 years of age with acute limb weakness and an MRI demonstrating predominantly gray matter lesions of the spinal cord to differentiate this condition from other forms of AFP, such as Guillain-Barré syndrome (GBS).[8] A total of 120 confirmed cases were reported from August through December 2014, with a peak in late summer and early fall. Most cases had predominant anterior horn cell involvement, similar to poliomyelitis lesions. The CDC performed an extensive laboratory evaluation, including testing for poliovirus and other EVs, parechoviruses, arboviruses, and herpesviruses, to identify possible etiologies. Poliovirus was conclusively ruled out as a causative agent, and testing of hundreds of sterile-site specimens, including cerebrospinal fluid (CSF) and serum, provided limited insight into etiology. However, a concurrent nationwide outbreak of severe respiratory disease associated with EV-D68 in 2014 led to focused efforts at the CDC, public health departments, and academic centers to investigate a potential association between AFM and EV-D68.[8,9] Despite these efforts, evidence to support a single etiologic agent as the cause of AFM remained inconclusive.

In 2015, the CDC and the Council of State and Territorial Epidemiologists established standardized surveillance for AFM in the United States to address numerous remaining questions, including the burden of disease, spectrum of clinical presentation, risk factors for paralysis, and etiologies.[10] We describe characteristics of AFM cases reported in the United States from 2015 through 2017.

METHODS

Case Reporting and Classification

From January 1, 2015, to June 30, 2017, a clinical case of AFM was defined as a patient with acute onset of focal limb weakness. In June 2017, the case definition was modified from focal to flaccid to more accurately describe the weakness associated with AFM. After July 1, 2017, a clinical case of AFM was defined as a patient with acute onset of flaccid limb weakness. Health departments and clinicians submitted to the CDC demographic, clinical, epidemiologic, laboratory, and radiographic information on patients meeting the clinical case criteria. An AFM expert panel, consisting of pediatricians and neurologists from CDC and US academic centers, classified patients as confirmed or probable on the basis of a thorough review of all available data for each patient. A confirmed case was a patient who met the clinical case criteria and had an MRI showing a spinal cord lesion largely restricted to gray matter and spanning ≥1 spinal segments. A probable case was a patient who met the clinical case criteria and had CSF pleocytosis (white blood cell [WBC] count >5 cells/mm^3). The primary analysis included confirmed pediatric cases (patients ≤21 years of age); collection of data for adult and probable cases began in August 2015 and is reported in Supplemental Tables 5 and 6. Patients who met the clinical case criteria but could not be classified as confirmed or probable cases were excluded from the primary analysis (Supplemental Table 7).

Laboratory Testing

The CDC requested sterile-site (eg, blood or serum and CSF) and nonsterile-site (eg, nasopharyngeal or oropharyngeal respiratory and stool) specimens from each patient. We tested for poliovirus using virus isolation and molecular methods. During 2015 and 2016, the CDC tested all specimens for EVs and rhinoviruses (EVs/RVs) using a qualitative real-time reverse transcription–polymerase chain reaction (RT-qPCR) pan-EV assay[11] and an EV typing assay (species A–J) by viral protein 1 reverse transcription-seminested PCR and Sanger sequencing.[12] Specimens were also tested for parechoviruses (species A–B) by using RT-qPCR.[13] Respiratory specimens were further tested by using an EV-D68–specific assay.[14] Any respiratory specimens that tested positive for EV-D68 by either viral protein 1 seminested sequencing or by the EV-D68–specific assay were considered EV-D68 positive. Because of wide availability of the pan-EV/RV RT-qPCR assay in the United States and in an effort to preserve CSF specimen volume, the CDC modified its testing algorithm in 2017 to perform only typing of EV/RV-positive specimens submitted by external laboratories. We provide results for the earliest specimen submitted if >1 specimen was submitted per specimen site. Results submitted to the CDC from other laboratories are also summarized in this report; diagnostic testing protocols varied by laboratory.

Data Analysis

Data were entered into a Microsoft Access database. Differences in

categorical variables were assessed by using the binomial test and Mantel-Haenszel χ^2 tests. Annual and state-level incidence rates were calculated by dividing the total number of confirmed pediatric cases by the corresponding estimate of the population ≤21 years of age. Descriptive analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC). Data were collected as part of standardized public health surveillance and determined by the CDC not to be research involving human subjects.

RESULTS

Demographic and Clinical Characteristics of Confirmed Pediatric AFM Cases

From 2015 through 2017, 43 states reported 305 clinical cases. The CDC confirmed 193 pediatric AFM cases from 41 states, with most cases (143, 74%) reported in 2016 (Fig 1). The average annual incidence was 0.71 per million in patients ≤21 years of age (Supplemental Fig 2 A–C). The majority of patients confirmed with AFM were male (118 cases, 61%), white race (102 cases, 53%), and non-Hispanic ethnicity (67 cases, 35%). Median age was 6 years (range: 3 months to 21 years; interquartile range [IQR]: 3–10 years). Onset of limb weakness occurred from August through November for 118 (61%) patients; 104 (88%) occurred in 2016 during the same period. Overall, 161 (83%) patients had fever, cough, rhinorrhea, vomiting, and/or diarrhea for a median of 5 days (range: 0 to 28 days; IQR: 2–7.5 days) before limb weakness onset; 120 (62%) had fever, 127 (66%) had respiratory illness, and 45 (29%) had gastrointestinal illness. In total, 106 patients (55%) had only 1 or 2 limbs affected compared with 87 patients (45%) who had 3 or 4 limbs affected ($P > .05$); 152 (79%) patients had at least 1 upper limb affected. At the time of limb weakness onset, 63 (33%) patients also presented with cranial nerve findings, 69 (36%) had quadriplegia, 51 (28%) had altered mental status, and 59 (33%) required mechanical ventilation (Table 1). Twenty-eight (15%) had underlying medical conditions, of which 15 (8%) reported asthma (Supplemental Table 8). One death was reported in 2017 of a 21-year-old man with cerebral edema and meningoencephalomyelitis. Spinal cord histopathology demonstrated mononuclear inflammatory infiltrates and focal neuronal necrosis; no etiologic agent was identified by using molecular and immunohistochemical techniques.

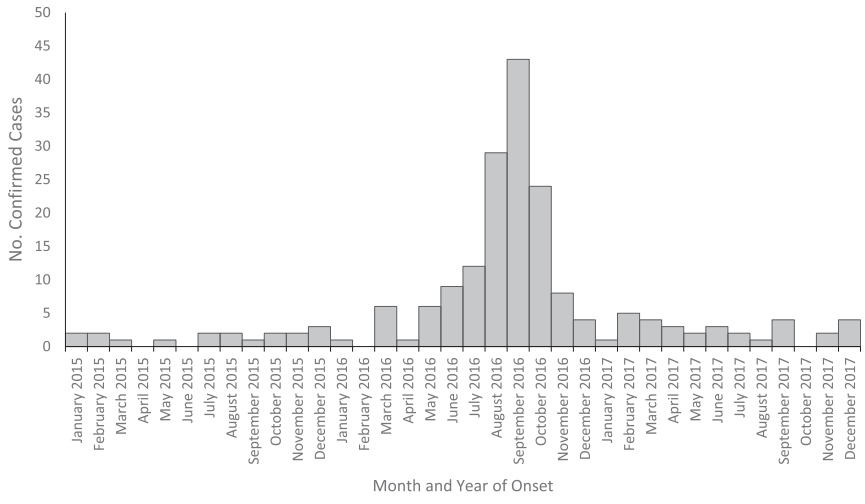

FIGURE 1
Epidemic curve of confirmed pediatric AFM cases by week of illness onset, January 2015 to December 2017 (n = 192). Onset date is based on date of limb weakness onset or date of hospitalization when onset of limb weakness was not reported. One case in 2017 is missing onset and hospitalization date.

MRI Findings

MRI testing protocols varied by hospital, and not all patients meeting the clinical case criteria had total spine imaging performed. Lesions were most commonly identified in the cervical spine in 144 (80%) patients, of which 21 (15%) had all cervical levels affected (Table 2). Among these 144 patients with cervical spine lesions, 122 (85%) also had documented upper limb weakness. Brain MRIs were conducted in 178 (92%) patients, of which 65 (38%) had brainstem lesions, with abnormalities most frequently identified in the pons or medulla (Table 2).

Overall Laboratory Results

A total of 183 (95%) patients had CSF analysis (WBC count, protein, glucose) results available. The median interval between onset of limb weakness and CSF collection was 2 days (range: −4 to 26; IQR: 1–3). CSF pleocytosis was present in 144 patients (81%), with most having a lymphocytic predominance. Median CSF WBC count was 75 cells per microliter (range: 0 to 3261; IQR: 13–158). Median CSF protein and glucose were 47 mg/dL (range: 13 to 915; IQR: 32–66) and 60 mg/dL (range: 4 to 125; IQR: 53–70), respectively (Supplemental Table 9). Overall, at both CDC and non-CDC laboratories, 91 (47%) of 193 patients had a pathogen detected from any site, 20 (10%) had a pathogen detected from a sterile site (CSF and sera), and 82 (42%) had a pathogen detected from a nonsterile site (upper respiratory and stool specimens). Time from limb weakness onset or respiratory or febrile illness onset to specimen collection is available in Supplemental Figs 3 and 4.

TABLE 1 Demographics and Clinical Characteristics of Confirmed Pediatric AFM Cases, United States, 2015–2017

Variable	2015	2016	2017	Total
No. patients at time of acute illness	*n* = 18	*n* = 143	*n* = 32	*N* = 193
Age, y, median (range, IQR)[a]	8.2 (0.4 to 19, 4–13)	5 (0.4 to 21, 3–10)	9 (0.3 to 21, 3–12.5)	6 (0.3 to 21, 3–10)
Sex, *n* (%)				
Male	13 (72)	86 (60)	19 (59)	118 (61)
Female	5 (28)	57 (40)	13 (41)	75 (39)
Race, *n* (%)				
American Indian or Alaskan Native	0 (0)	3 (2)	0 (0)	3 (2)
Asian	2 (11)	8 (6)	0 (0)	10 (5)
Black or African American	6 (33)	24 (17)	7 (22)	37 (19)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
White	8 (44)	77 (54)	17 (53)	102 (53)
Missing	2 (11)	31 (22)	8 (25)	41 (21)
Ethnicity, *n* (%)				
Hispanic or Latino	1 (6)	25 (17)	6 (19)	32 (17)
Not Hispanic or Latino	5 (28)	56 (39)	6 (19)	67 (35)
Missing	12 (67)	62 (43)	20 (63)	94 (49)
Hospitalized, *n* (%)	18 (100)	143 (100)	30 (94)	191 (99)
Respiratory illness preceding limb weakness, *n* (%)	5 (28)	106 (74)	16 (50)	127 (66)
Days to limb weakness, median (range, IQR)	4 (3 to 5, 3–5)	6 (0 to 28, 4–8)	4.5 (0 to 27, 2–14)	6 (0 to 28, 3–8)
Gastrointestinal illness preceding limb weakness[b], *n* (%)	2 (50)	33 (27)	10 (36)	45 (29)
Days to limb weakness, median (range, IQR)	—	2 (0 to 25, 1–6)	3 (0 to 17, 1–8.5)	2 (0 to 25, 1–7)
Febrile illness preceding limb weakness, *n* (%)	6 (33)	93 (65)	21 (66)	120 (62)
Days to limb weakness, median (range, IQR)	1 (0 to 4, 0–3)	2 (0 to 28, 1–5)	6 (0 to 27, 1.5–9)	2 (0 to 28, 1–6)
Respiratory or febrile illness preceding limb weakness, *n* (%)	8 (44)	122 (85)	23 (72)	153 (79)
Days to limb weakness, median (range, IQR)	3 (0 to 5, 2–4)	5 (0 to 28, 2–7)	7 (0 to 27, 2–14)	5 (0 to 28, 2–7)
No. limbs affected, *n* (%)				
1	2 (11)	37 (26)	2 (6)	41 (21)
2	8 (44)	45 (31)	12 (38)	65 (34)
3	1 (6)	16 (11)	1 (3)	18 (9)
4	7 (39)	45 (31)	17 (53)	69 (36)
Site of limb involvement, *n* (%)				
Any upper extremity	10 (56)	118 (83)	24 (75)	152 (79)
Any lower extremity	16 (89)	95 (66)	26 (81)	137 (71)
Cranial nerve findings, *n* (%)				
Any cranial nerve sign	3 (17)	53 (37)	7 (22)	63 (33)
Facial weakness	0 (0)	28 (20)	3 (9)	31 (16)
Dysphagia	1 (6)	17 (12)	2 (6)	20 (10)
Diplopia or / double vision	2 (11)	14 (10)	3 (9)	19 (10)
Dysarthria	1 (6)	13 (9)	1 (3)	15 (8)
Altered mental status, *n* (%)	7 (39)	31 (23)	13 (43)	51 (28)
Seizures, *n* (%)	1 (6)	3 (2)	1 (3)	5 (3)
Mechanical ventilation, *n* (%)	6 (33)	40 (30)	13 (43)	59 (33)
Death, *n* (%)	0 (0)	0 (0)	1 (3)	1 (0)

—, not applicable.

[a] Overall, includes 6 infants aged 0–6 mo and 11 infants aged 7–12 mo.

[b] Gastrointestinal illness data collection began mid-2015. Overall, data were available for 153 patients (2015, *n* = 4; 2016, *n* = 121; 2017, *n* = 28).

CDC Laboratory Results

Only 1 of 81 patients with CSF tested at a CDC laboratory had a positive result (CV-A16 in a 2015 patient). Among 72 patients with serum specimens tested, 2 were positive for EVs: EV-D68 was detected in a patient with onset of limb weakness in 2016, and CV-A16 was detected in the same patient with CV-A16 in the CSF just described. Among 90 patients with upper respiratory specimens tested, 32 (36%) were positive for EV/RV and 2 were positive for parechovirus. Among 77 patients with stool specimens tested, 15 (19%) were positive for EV/RV and 1 was positive for parechovirus; none were positive for poliovirus (Table 3). Respiratory and stool specimens collected within the initial 5 days of respiratory or febrile illness onset were more likely to be RT-PCR positive than those collected after >5 days (67% vs 25%, respectively; $P = .0002$).

Non-CDC Laboratory Results

CSF was tested in 170 patients; 4 were positive for EV. Three of the 4 were sent to the CDC for confirmation and typing; only 1 was positive for EV and subsequently typed as CV-A16 (2015 patient). Adenovirus, Epstein-Barr virus, human herpesvirus 6, and mycoplasma were also detected in CSF from 6 patients. Of the 123 patients with sera tested, 9 were positive for EV, West Nile virus, mycoplasma, and CV-B.

TABLE 2 MRI Findings Among Confirmed Pediatric AFM Cases, United States, 2015–2017

	2015	2016	2017	Total
	No. Patients (%)	No. Patients (%)	No. Patients (%)	No. Patients (%)
MRI of spinal cord performed	*n* = 18	*n* = 143	*n* = 32	*n* = 193
>1 region imaged	16 (89)	125 (87)	28 (88)	169 (88)
Cervical cord imaged	16 (89)	133 (93)	30 (94)	179 (93)
Cervical cord involvement	11 (69)	108 (81)	25 (83)	144 (80)
Thoracic cord imaged	15 (83)	126 (88)	28 (88)	169 (88)
Thoracic cord involvement	10 (67)	77 (61)	18 (64)	105 (62)
Lumbar cord imaged	15 (83)	97 (68)	25 (78)	137 (71)
Conus-cauda equina involvement	8 (53)	41 (42)	6 (24)	55 (40)
Ventral nerve enhancement	3 out of 11 (27)[a]	18 out of 81 (22)[a]	4 out of 11 (36)[a]	25 out of 103 (24)[a]
MRI of brain performed	*n* = 15	*n* = 134	*n* = 29	*n* = 178
Cranial nerve lesions[b]	2 (14)	6 (5)	1 (4)	9 (6)
Cerebral lesions[c]	6 (40)	15 (12)	8 (29)	29 (17)
Cerebellar lesions[d]	2 (14)	12 (10)	2 (8)	16 (10)
Brainstem lesions[e]	7 (47)	46 (36)	12 (43)	65 (38)
Pontine lesions	2 (29)	29 (63)	8 (67)	39 (60)
Medulla lesions	7 (100)	29 (63)	7 (58)	43 (66)
Midbrain lesions	1 (14)	9 (20)	4 (33)	14 (22)

[a] Denominator is the number of patients reported having lumbosacral MRI performed, gadolinium administered, and a result available.
[b] Overall, 163 patients had a result available (2015, *n* = 15; 2016, *n* = 125; 2017, *n* = 24).
[c] Overall, 170 patients had a result available (2015, *n* = 15; 2016, *n* = 127; 2017, *n* = 29).
[d] Overall, 163 patients had a result available (2015, *n* = 14; 2016, *n* = 124; 2017, *n* = 25).
[e] Overall, 171 patients had a result available (2015, *n* = 15; 2016, *n* = 128; 2017, *n* = 28).

Among 151 patients with respiratory specimens tested, 61 (46%) were positive for EV/RV. Among 78 patients with stool tested, 22 (52%) were positive for EV/RV (Table 4).

DISCUSSION

In our summary of national AFM surveillance from 2015 to 2017, we demonstrate that cases were widely distributed across the United States, the majority of cases occurred in late summer or fall, children were predominantly affected, there is a spectrum of clinical severity, and no single pathogen was identified as the primary cause of AFM. We conclude that symptoms of a viral syndrome within the week before limb weakness, detection of viral pathogens from sterile and nonsterile sites from almost half of patients, and seasonality of AFM incidence, particularly during the 2016 peak year, strongly suggest a viral etiology, including EVs.

EVs, such as poliovirus and EV-A71, can cause a wide clinical spectrum ranging from asymptomatic infection

TABLE 3 Laboratory Results of Confirmed Pediatric AFM Cases, CDC Laboratories, United States, 2015–2017

	CSF	Serum or Plasma	Respiratory	Stool or Rectal Swab
	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)
EV/RV	1, 81 (1)	2, 72 (3)	32, 90 (36)	15, 77 (19)
CV-A10	—	—	—	1 (1)
CV-A16	1 (1)	1 (1)	—	1 (1)
CV-B4	—	—	—	1 (1)
Echovirus 18	—	—	—	1 (1)
EV-A71	—	—	—	3 (4)
EV-D68	—	1 (1)	22 (24)	2 (3)
RV-A57	—	—	2 (2)	1 (1)
RV-A58	—	—	1 (1)	—
RV-A59	—	—	1 (1)	—
RV-A66	—	—	1 (1)	1 (1)
RV-A75	—	—	1 (1)	—
RV-A8	—	–	1 (1)	—
RV-B35	—	—	1 (1)	—
RV-B83	—	—	1 (1)	1 (1)
EV/RV untyped	—	—	1 (1)	1 (1)
EV untyped	—	—	—	2 (3)
Parechovirus A	0, 81 (0)	0, 72 (0)	2, 90 (2)	1, 77 (1)

For 2017, no CSF or serum was submitted to the CDC for typing, and 8 respiratory and 10 stool specimens were submitted to the CDC for testing. —, not applicable.

TABLE 4 External (Non-CDC) Laboratory Results for Confirmed Pediatric AFM Cases, United States, 2015–2017

	CSF[a]	Serum or Plasma[a]	Respiratory	Stool or Rectal Swab
	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)	No. Positive, No. Tested (% Positive)
No. patients with specimens tested	170	123	151	78
EV/RV	4, 152 (3)[b]	—	61, 134 (46)	22, 42 (52)
CV-A1	—	—	—	1 (2)
CV-A16	—	—	—	1 (2)
EV-D68	—	—	10 (7)	3 (7)
RV-2 and RV-4	—	—	1 (0)	—
RV untyped	—	—	5 (4)	—
EV/RV untyped	4 (3)[b]	—	45 (34)	17 (40)
EV untyped	—	2[c]	—	—
Adenovirus PCR	—	—	6, 111 (5)	2[d]
Influenza virus PCR	—	—	1, 111 (1)	—
Herpes simplex virus PCR	0, 132 (0)	—	—	—
Varicella zoster virus PCR	0, 65 (0)	—	—	—
Cytomegalovirus PCR	0, 74 (0)	—	—	—
West Nile virus PCR	0, 49 (0)	0, 22 (0)	—	—
West Nile virus IgM	0, 50 (0)	3, 56 (5)	—	—
Other	6[e]	4[f]	9[g]	2[h]

—, not applicable.

[a] No CSF or serum specimens tested positive for EV/RV in 2017.

[b] Three of the 4 specimens were submitted to the CDC for typing. Two were negative for EV/RV, and 1 tested positive for CV-A16 at the CDC.

[c] From other testing, so there was no denominator.

[d] From other testing, so there was no denominator, and 1 specimen tested positive for adenovirus plus astrovirus, sappovirus, enteroaggregative *Escherichia coli*, and *Clostridium difficile*.

[e] One case of adenovirus, 3 cases of Epstein-Barr virus, 1 case of human herpesvirus 6, and 1 case of mycoplasma were detected.

[f] Three cases of mycoplasma and 1 case of CV-B were detected.

[g] One specimen was positive for respiratory syncytial virus and parainfluenza 3, and 2 cases of parainfluenza 2, 1 case of human metapneumovirus, 2 cases of coronavirus, and 3 cases of respiratory syncytial virus were detected.

[h] One specimen was positive for norovirus and *C difficile*, and 1 specimen was positive for enteropathogenic *E coli*.

to much rarer presentations, such as multisystem organ failure and neuroinvasive disease (eg, limb paralysis and meningitis).[15–17] In 2014, multiple reports of AFM cases and concurrent outbreaks of severe respiratory disease caused by EV-D68 nationwide supported a temporal association between EV-D68 and AFM. Similar to other neuroinvasive EVs, EV-D68 can readily induce flaccid paralysis in mouse models and has been detected in CSF specimens of patients with AFM, albeit rarely.[18–26] In 2014, EV-D68 was the most common virus detected, accounting for 20% of respiratory specimens tested. However, multiple testing strategies (including virus-specific PCR or RT-PCR, broad "family-specific" PCR or RT-PCR, and metagenomic sequencing) did not identify a convincing single etiologic signal in sterile-site specimens.[8]

EV testing from 2015 through 2017 demonstrated similar findings to the 2014 investigation. Diagnostic yield from CSF was low (CV-A16 was detected in one patient in 2015, and EV-D68 was detected in one patient in 2014), multiple pathogens were identified from both sterile and nonsterile sites in approximately half of patients, and poliovirus was not detected in any cases. EV-D68 positivity from respiratory specimens of AFM patients with onset in 2015 to 2017 (24%) was similar to 2014; however, EV-D68 was also detected in patients later classified as noncases in this study. After the 2014 investigation, testing for EV-D68 increased because of wider availability of an EV-D68–specific assay, which allowed for more-rapid detection at treating facilities but still limited broader characterization of other type-specific EV circulation that could also be contributing to respiratory and neuroinvasive disease within a community.[27–29] Subnational estimates of EV-D68 circulation in the same regions where AFM cases are occurring have not been well characterized, although studies to evaluate these trends are being implemented. Although a temporal association between EV-D68 and AFM has been reported, additional evidence is still needed to more clearly establish a causal association.

EV circulation is widespread, with a US seasonal peak in the late summer and early fall[21] complicating interpretations correlating EV-positive specimens from nonsterile sites with rare clinical outcomes like paralysis. Seroprevalence estimates of neutralizing antibodies for EVs range from 33% to 99%, depending on serotype.[30] The large burden of EV-D68 respiratory disease detected in 2014 led to hypotheses that EV-D68 was a newly emerging EV also associated with AFM. In a 2012 study of 436 subjects aged 2 to 81 years from Kansas City, Missouri, with sera collected before the 2014 EV-D68 respiratory outbreak, researchers demonstrated detection of neutralizing antibodies against the major 2014 EV-D68 outbreak strain for all

subjects.[31] Serologic evidence of widespread infection with EV-D68, even before the first notable increase of AFM in 2014, suggests that if EV-D68 was the primary cause of AFM in 2014 and 2016, other factors must play a role in the development of this rare outcome.

Because of limited availability of spinal pathology specimens, it remains unknown whether paralysis associated with AFM results from direct pathogen invasion of the central nervous system or a postinfectious process, possibly immune mediated. AFM may be analogous to other diseases that present as AFP, such as transverse myelitis or GBS, which are linked to immune-mediated damage of the spinal cord or peripheral nerves, respectively.[32,33] Alternatively, it may be similar to other EV pathogenesis, like poliovirus, which causes paralysis by direct viral destruction of motor neurons in the anterior horn of the spinal cord. EV-A71 has also been shown to cause brainstem encephalitis and paralysis via direct mechanisms.[2] The short interval between a preceding viral syndrome and onset of limb weakness in these AFM cases could support direct viral invasion as a mechanism. However, given that identification of a pathogen in the CSF is rare, further research into potential immunologic and genetic mechanisms leading to AFM, as well as more sophisticated pathogen evaluations, is warranted. Examinations of soluble and cell-associated markers of immune system activation, particularly in the central nervous system, are underway, as well as investigations of the potential role of other immune-mediated pathogeneses.

Globally, countries vary widely in their surveillance for acute flaccid limb weakness. Many countries conduct AFP surveillance to rule out poliovirus, a critical component of the poliovirus eradication initiative. Some countries, including France, Sweden, and the Netherlands, identify AFM cases through laboratory-based EV surveillance networks, which limits reporting of AFM cases caused by other potential pathogens.[34–38] In our data, viruses other than EVs were identified in 60% of patients with pathogens detected from a sterile site. Important differences in AFM case ascertainment make it challenging to compare the global epidemiology of AFM across countries.

There are several limitations to this analysis, including reliance on voluntary reporting from clinicians and state and local health departments. Although AFM is not a nationally notifiable condition, all states have either made AFM reportable or have reporting requirements for AFP without an alternate diagnosis or for new or emerging conditions of public health importance.. Variability in awareness can lead to underreporting to the health department and affect timely collection of appropriate specimens. Although the case definition was expanded in 2015 to include persons of all ages, adults may also have other reasons for weakness (eg, spinal cord stroke, GBS), making diagnosis of AFM more challenging in this population. AFM likely has a range of clinical severity, and only moderate or severe cases may present for clinical evaluation. Ongoing analysis of the spectrum of illness is necessary to inform surveillance methods and improve specificity and sensitivity of the current case definition. Lastly, EV surveillance to characterize type-specific annual trends and geographic variability is limited, challenging our ability to attribute one specific EV as the etiologic cause of AFM.

CONCLUSIONS

With this report, we provide the most comprehensive summary of clinical, laboratory, radiologic, and epidemiologic data of AFM in the United States to date. The clinical symptoms shortly before weakness onset in most patients and detection of pathogens in sterile and nonsterile sites suggest viruses play a key role in the pathogenesis of AFM. Although EVs should continue to be evaluated as an etiology of AFM, ubiquitous circulation of multiple types of EVs and the rarity of AFM, even during EV season, highlight important knowledge gaps. Additional studies are needed to assess risk factors, establish causality, and develop a more-comprehensive understanding of the mechanisms that lead to AFM.

ACKNOWLEDGMENTS

We thank the Vaccine Preventable Diseases Surveillance Coordinators at the local and state health departments that have contributed to the launch and maintenance of the AFM surveillance program, the Council of State and Territorial Epidemiologists for their continued collaboration on AFM surveillance, Sandra Roush and Holly Vins from the National Center for Immunization and Respiratory Diseases Surveillance Office for their ongoing support to the CDC AFM team, and Drs Wun-Ju Shieh and Sarah Reagan-Steiner from the National Center for Emerging and Zoonotic Infectious Diseases Pathology Branch for their expertise and consultation.

ABBREVIATIONS

AFM: acute flaccid myelitis
AFP: acute flaccid paralysis
CDC: Centers for Disease Control and Prevention
CSF: cerebrospinal fluid
CV: coxsackievirus
EV: enterovirus
EV/RV: enterovirus and rhinovirus
GBS: Guillain-Barré syndrome
IQR: interquartile range
RT-qPCR: qualitative real-time reverse transcription–polymerase chain reaction
WBC: white blood cell

DOI: https://doi.org/10.1542/peds.2019-1619

Accepted for publication Jul 24, 2019

Address correspondence to Manisha Patel, MD, MS, Measles, Mumps, Rubella, Herpesvirus, and Domestic Polio Epidemiology Team Lead, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H24-5, Atlanta, GA 30333. E-mail: dvn4@cdc.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Strebel PM, Sutter RW, Cochi SL, et al. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. *Clin Infect Dis*. 1992; 14(2):568–579
2. Ong KC, Wong KT. Understanding enterovirus 71 neuropathogenesis and its impact on other neurotropic enteroviruses. *Brain Pathol*. 2015;25(5): 614–624
3. Horner LM, Poulter MD, Brenton JN, Turner RB. Acute flaccid paralysis associated with novel enterovirus C105. *Emerg Infect Dis*. 2015;21(10):1858–1860
4. Cho SM, MacDonald S, Frontera JA. Coxsackie B3/B4-related acute flaccid myelitis. *Neurocrit Care*. 2017;27(2): 259–260
5. Kim KT, Cho YW. Coxsackievirus B1 resulting acute flaccid myelitis with entire spinal cord lesion: a case report. *Neurol Sci*. 2019;40(3):627–629
6. Messacar K, Abzug MJ, Dominguez SR. 2014 outbreak of enterovirus D68 in North America. *J Med Virol*. 2016;88(5): 739–745
7. Pastula DM, Aliabadi N, Haynes AK, et al; Centers for Disease Control and Prevention (CDC). Acute neurologic illness of unknown etiology in children - Colorado, August-September 2014. *MMWR Morb Mortal Wkly Rep*. 2014; 63(40):901–902
8. Sejvar JJ, Lopez AS, Cortese MM, et al. Acute flaccid myelitis in the United States, August-December 2014: results of nationwide surveillance. *Clin Infect Dis*. 2016;63(6):737–745
9. Midgley CM, Watson JT, Nix WA, et al; EV-D68 Working Group. Severe respiratory illness associated with a nationwide outbreak of enterovirus D68 in the USA (2014): a descriptive epidemiological investigation. *Lancet Respir Med*. 2015;3(11):879–887
10. Council of State and Territorial Epidemiologists. Revision to the standardized surveillance and case definition for acute flaccid myelitis. 2017. Available at: https://cdn.ymaws.com/www.cste.org/resource/resmgr/2017PS/2017PSFinal/17-ID-01.pdf. Accessed November 8, 2018
11. Kilpatrick DR, Yang CF, Ching K, et al. Rapid group-, serotype-, and vaccine strain-specific identification of poliovirus isolates by real-time reverse transcription-PCR using degenerate primers and probes containing deoxyinosine residues. *J Clin Microbiol*. 2009;47(6):1939–1941
12. Nix WA, Oberste MS, Pallansch MA. Sensitive, seminested PCR amplification of VP1 sequences for direct identification of all enterovirus serotypes from original clinical specimens. *J Clin Microbiol*. 2006;44(8): 2698–2704
13. Nix WA, Maher K, Johansson ES, et al. Detection of all known parechoviruses by real-time PCR. *J Clin Microbiol*. 2008; 46(8):2519–2524
14. US Food and Drug Administration. Medical devices: emergency use authorizations. Available at: https://www.fda.gov/medicaldevices/safety/emergencysituations/ucm161496.htm#enterovirus. Accessed September 12, 2019
15. Huang CC, Liu CC, Chang YC, et al. Neurologic complications in children with enterovirus 71 infection. *N Engl J Med*. 1999;341(13):936–942
16. Pérez-Vélez CM, Anderson MS, Robinson CC, et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. *Clin Infect Dis*. 2007;45(8):950–957
17. Bitnun A, Yeh EA. Acute flaccid paralysis and enteroviral infections. *Curr Infect Dis Rep*. 2018;20(9):34
18. Hixon AM, Yu G, Leser JS, et al. A mouse model of paralytic myelitis caused by enterovirus D68. *PLoS Pathog*. 2017; 13(2):e1006199
19. Wei W, Guo H, Chang J, et al. ICAM-5/Telencephalin is a functional entry receptor for enterovirus D68. *Cell Host Microbe*. 2016;20(5):631–641
20. Brown DM, Hixon AM, Oldfield LM, et al. Contemporary circulating enterovirus D68 strains have acquired the capacity for viral entry and replication in human neuronal cells. *MBio*. 2018;9(5):e01954-18
21. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, Pallansch MA; Centers for Disease Control and Prevention. Enterovirus surveillance–United States, 1970-2005. *MMWR Surveill Summ*. 2006; 55(8):1–20
22. Kreuter JD, Barnes A, McCarthy JE, et al. A fatal central nervous system enterovirus 68 infection. *Arch Pathol Lab Med*. 2011;135(6):793–796
23. Levy A, Roberts J, Lang J, et al. Enterovirus D68 disease and molecular epidemiology in Australia. *J Clin Virol*. 2015;69:117–121

24. Ruggieri V, Paz MI, Peretti MG, et al. Enterovirus D68 infection in a cluster of children with acute flaccid myelitis, Buenos Aires, Argentina, 2016. *Eur J Paediatr Neurol*. 2017;21(6):884–890

25. Pérez G, Rosanova MT, Freire MC, et al. Unusual increase of cases of myelitis in a pediatric hospital in Argentina. *Arch Argent Pediatr*. 2017;115(4):364–369

26. Giombini E, Rueca M, Barberi W, et al. Enterovirus D68-associated acute flaccid myelitis in immunocompromised woman, Italy. *Emerg Infect Dis*. 2017;23(10):1690–1693

27. Huang W, Yin C, Zhuge J, et al. Complete genome sequences of nine enterovirus D68 strains from patients of the lower Hudson Valley, New York, 2016. *Genome Announc*. 2016;4(6):e01394-16

28. Messacar K, Robinson CC, Pretty K, Yuan J, Dominguez SR. Surveillance for enterovirus D68 in Colorado children reveals continued circulation. *J Clin Virol*. 2017;92:39–41

29. Naccache SM, Bender J, Desai J, et al. Acute flaccid myelitis cases presenting during a spike in respiratory enterovirus D68 circulation: case series from a single pediatric referral center. *Open Forum Infect Dis*. 2017;4: S305–S306

30. Zhu R, Cheng T, Yin Z, et al. Serological survey of neutralizing antibodies to eight major enteroviruses among healthy population. *Emerg Microbes Infect*. 2018;7(1):2

31. Harrison CJ, Weldon WC, Pahud BA, et al. Neutralizing antibody against enterovirus D68 in children and adults before 2014 outbreak, Kansas City, Missouri, USA[1]. *Emerg Infect Dis*. 2019; 25(3):585–588

32. Wolf VL, Lupo PJ, Lotze TE. Pediatric acute transverse myelitis overview and differential diagnosis. *J Child Neurol*. 2012;27(11):1426–1436

33. Yuki N, Hartung HP. Guillain-Barré syndrome. *N Engl J Med*. 2012;366(24): 2294–2304

34. Schuffenecker I, Mirand A, Josset L, et al. Epidemiological and clinical characteristics of patients infected with enterovirus D68, France, July to December 2014. *Euro Surveill*. 2016; 21(19):1–12

35. Bal A, Sabatier M, Wirth T, et al. Emergence of enterovirus D68 clade D1, France, August to November 2018. *Euro Surveill*. 2019;24(3):24

36. Dyrdak R, Grabbe M, Hammas B, et al. Outbreak of enterovirus D68 of the new B3 lineage in Stockholm, Sweden, August to September 2016. *Euro Surveill*. 2016;21(46):30403

37. Knoester M, Schölvinck EH, Poelman R, et al. Upsurge of enterovirus D68, the Netherlands, 2016. *Emerg Infect Dis*. 2017;23(1):140–143

38. Knoester M, Helfferich J, Poelman R, et al; 2016 EV-D68 AFM Working Group. Twenty-nine cases of enterovirus-D68-associated acute flaccid myelitis in Europe 2016: a case series and epidemiologic overview. *Pediatr Infect Dis J*. 2019;38(1):16–21

Acute Flaccid Myelitis in the United States: 2015–2017

Tracy Ayers, Adriana Lopez, Adria Lee, Anita Kambhampati, W. Allan Nix, Elizabeth Henderson, Shannon Rogers, William C. Weldon, M. Steven Oberste, James Sejvar, Sarah E. Hopkins, Mark A. Pallansch, Janell A. Routh and Manisha Patel

Pediatrics originally published online October 7, 2019;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Acute Flaccid Myelitis in the United States: 2015–2017

Tracy Ayers, Adriana Lopez, Adria Lee, Anita Kambhampati, W. Allan Nix, Elizabeth Henderson, Shannon Rogers, William C. Weldon, M. Steven Oberste, James Sejvar, Sarah E. Hopkins, Mark A. Pallansch, Janell A. Routh and Manisha Patel

Pediatrics originally published online October 7, 2019;