# Acute Flaccid Myelitis: A New Epidemic Disease?

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# Disclosure

I have no relevant financial relationships to disclose

# Objectives

- Increase awareness of AFM
- Epidemiologic and clinical features
- Current understanding of etiology
- Laboratory and radiologic diagnostic procedures
- Management
- Outcome
- Public health implications for providers

# Acute Flaccid Paralysis

- Immunopathologic disorders
  - Guillain-Barré
  - Transverse myelitis
  - Acute Disseminated Encephalomyelitis (ADEM)
  - Antibody-Associated Disease (MOG-Ab disease)
  - Neuromyelitis Optica Spectrum Disorder (NMOSD)
- Acute Flaccid Myelitis
  - Largely restricted to neural gray matter
  - Poliomyelitis
- Spinal cord compression
  - Tumor
  - Hemorrhage
- Ischemic spinal cord disease
- Post-traumatic myelopathty
- Other:
  - Lupus
  - Sarcoidosis
  - Sjogren's Syndrome

# Poliomyelitis

- Ancient disease (Egypt)
- Lesions first identified in 1870 (Charcot)
  - Polio (Greek = gray)
  - Myelos (Greek = marrow) = poliomyelitis
  - -itis (inflammation)
- Late 19th century to early 20th century
  - Epidemiology changed from predominantly endemic to epidemic form (Sweden and Norway, later in other industrialized countries)
  - Ascribed to increasing numbers of susceptible children due to improvements in hygiene and sanitation, delaying exposure to later in life

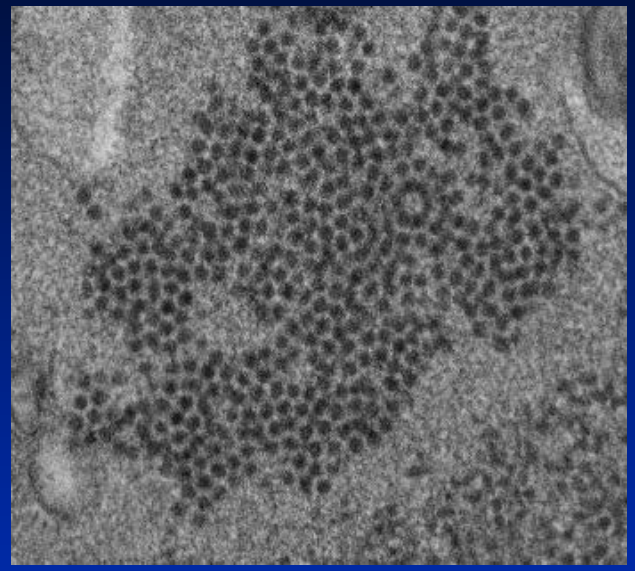
# Poliomyelitis


- Before introduction of vaccine in 1955, over 600,000 children were paralyzed each year
- Since 1988, cases have decreased from an estimated 350,000 to 33 in 2018
  - Type 2 – eradicated in 1999
  - Type 3 – last reported case in 2012
- Pakistan and Afghanistan

# Acute Flaccid Myelitis: Changing epidemiology

- Post-polio
  - Rare, novel condition
  - Single cases
  - Associated with multiple viruses
    - Nonpolio enteroviruses
    - West Nile Virus and other flaviviruses
    - Adenovirus

# Acute Flaccid Myelitis: Changing epidemiology

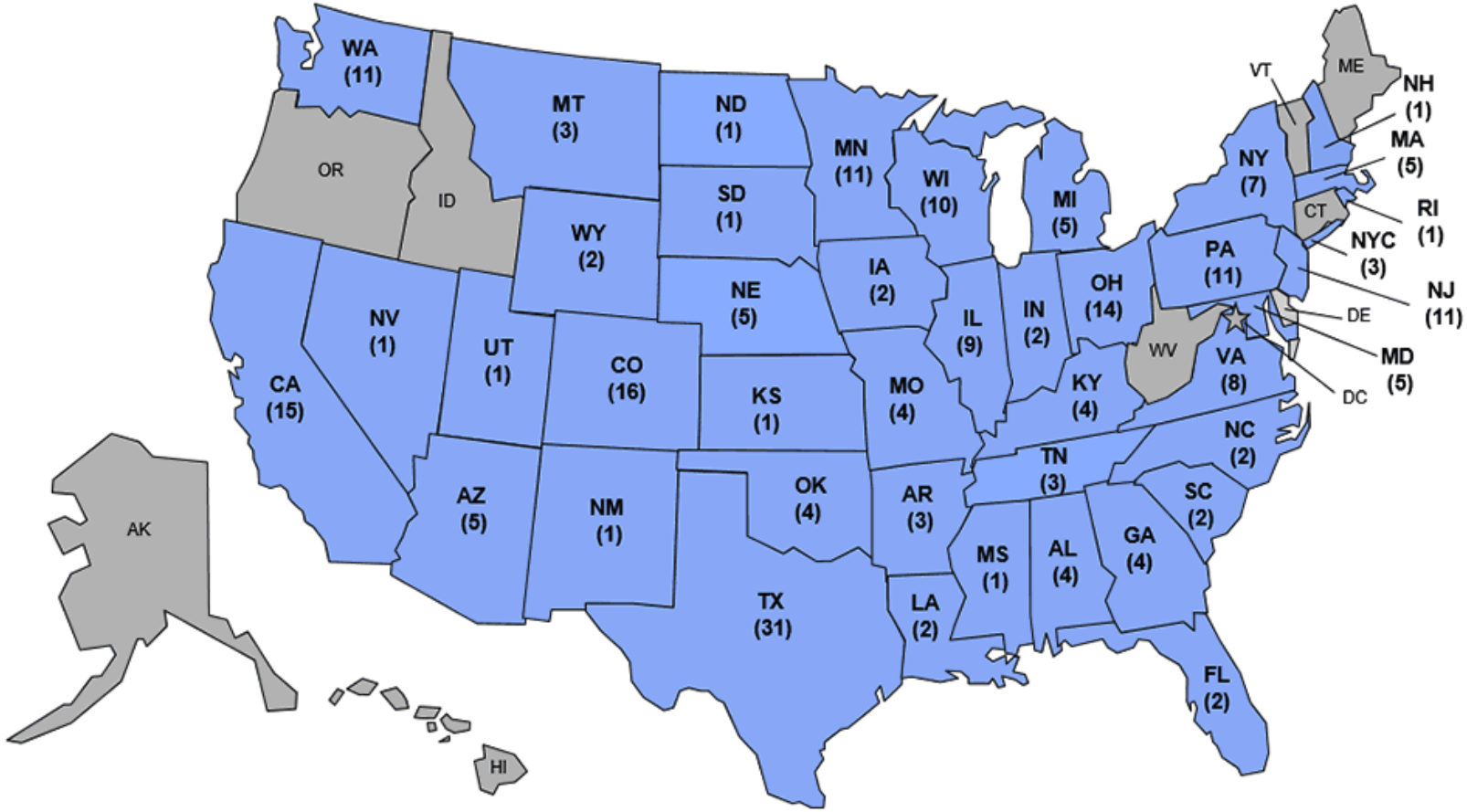


- Emerging globally in epidemic form
  - Recognized in 2010
  - First large outbreak in US – 2014
  - Seasonal waves in US, largest in 2018
  - Temporally associated with emergence of EV-D68 and EV-A71

- **Confirmed case**
  - Acute onset of flaccid limb weakness
  - MRI findings meeting surveillance criteria

## 2018 Cases by State

**2018 confirmed cases of acute flaccid myelitis (AFM) by state (N=235)***




*Confirmed AFM cases as of August 2, 2019. Patients under investigation are still being classified, and the case counts are subject to change. One of the confirmed cases is a foreign resident (based on the country of usual residence) and therefore not included in the state map.

https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

# AFM Cases

- Confirmed since CDC began tracking in 2014: 574
- Biennial seasonal outbreaks with increasing # of cases
- 13 cases confirmed in 2019 as of 6/28 (CA, MD, NE, NC, PA, TX, UT, WV)
  - 63 under investigation

FIGURE 1. Confirmed cases of acute flaccid myelitis reported to CDC (N = 559) — United States, August 1, 2014–December 31, 2018

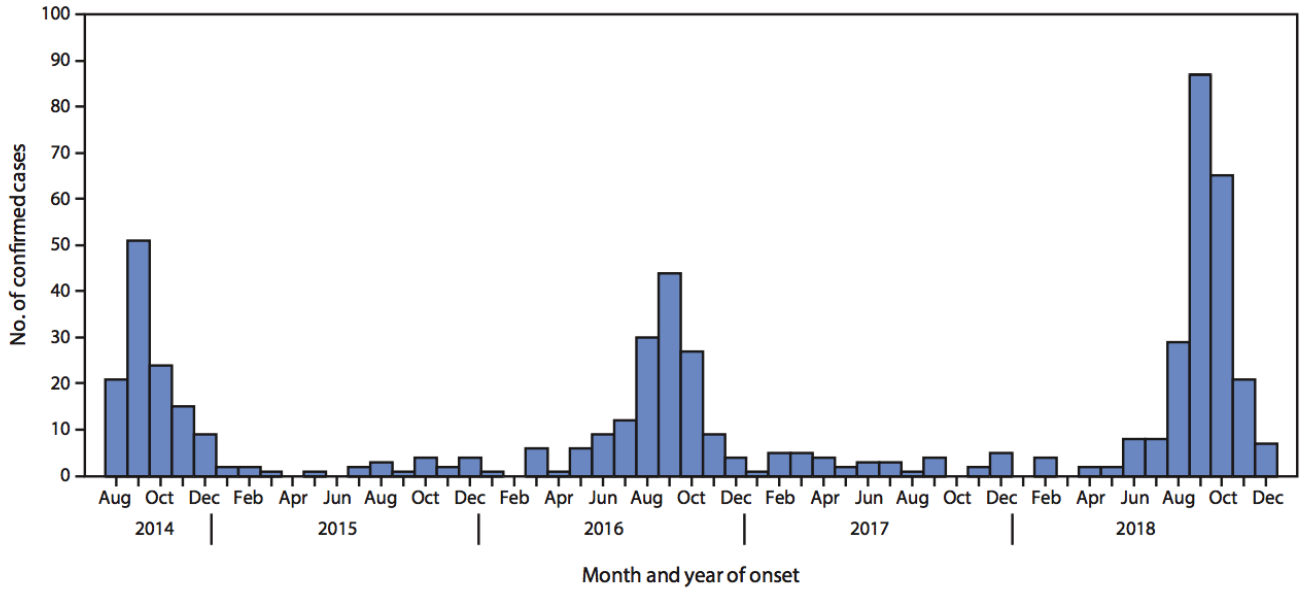
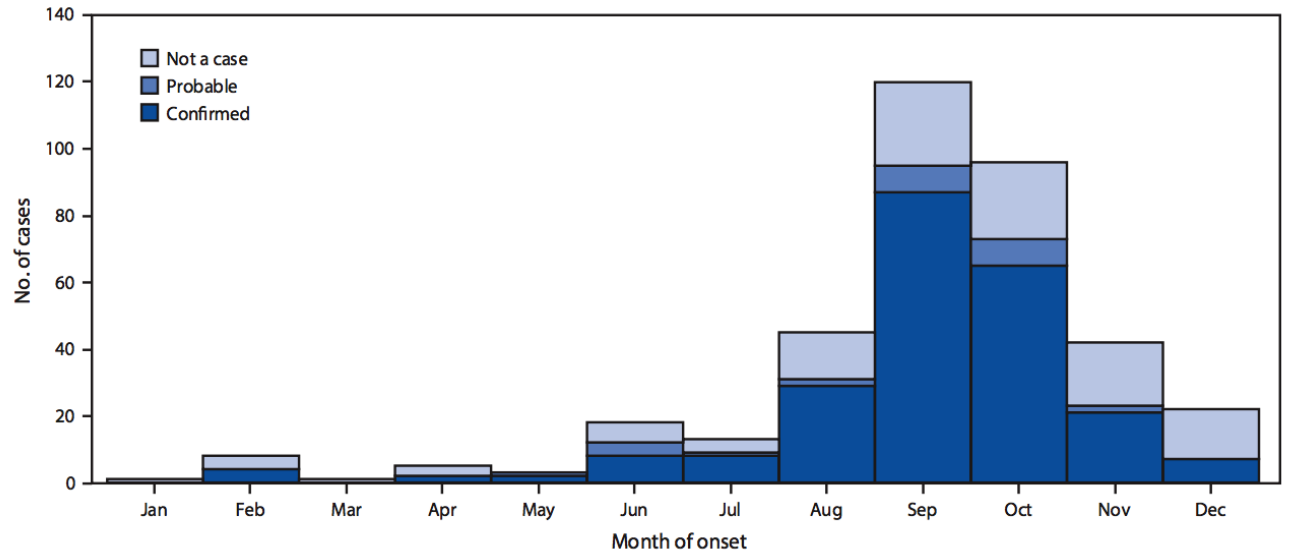



FIGURE 2. Cases of acute flaccid myelitis reported to CDC, by case classification status — United States, 2018




https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.htm; *MMWR* 2019;68(27):608-613

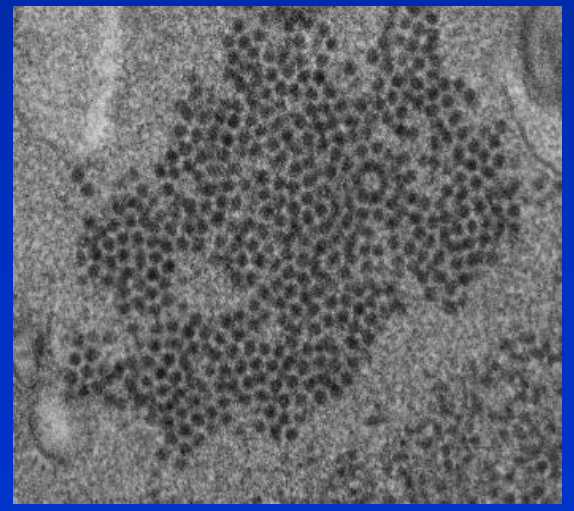
# Nonpolio enteroviruses

- Large family of viruses
- Some are more commonly transmitted by respiratory route
- Endemic and epidemic circulation in late summer/fall
- Wide array of disease syndromes:

| | |
|---|---|
| Respiratory infections | Hand-foot-mouth disease |
| Conjunctivitis | Herpangina |
| Myositis | Meningitis |
| Pleurodynia | Encephalitis |
| Myocarditis | Sporadic AFM |
| Maculopapular rashes | “neonatal viral sepsis” |
| Vesicular rashes | |

# EV-D68 as the cause of epidemic AFM

- Epidemiologic evidence supports EV-D68 as major cause
  - Sudden emergence in 2014 with widespread activity
  - Association with severe respiratory illness
  - Found in nasopharynx of affected patients
- In 2018, EV-A71
  - Known cause of HFM and sporadic AFM
  - Also found in US



NEWS RELEASES

Media Advisory Tuesday, August 13, 2019

# Enterovirus antibodies detected in acute flaccid myelitis patients

*NIH-funded study adds to knowledge about rare condition.*

# EV-D68 as the cause of epidemic AFM

- Mutations and recombination have lead to:
  - Widespread circulation
    - Sporadic respiratory illnesses since discovery in 1962
    - First nationwide outbreak in 2014
  - Increased pathogenicity
    - Unique genome in new clade
    - 2014 strains are neurotropic in mouse model
    - 2014 strains can infect human neuronal cell lines
  - Possibly a new threat for larger epidemics

# Acute Flaccid Myelitis

- Predominantly gray matter injury
  - Anterior horn cell
  - Pathophysiology: unknown
  - Hypotheses:
    - Direct viral invasion with cytopathology
    - Virus-induced autoimmune damage
    - Virus interaction with host microbiome

# Confirmed AFM cases in 2018: Features

- Cases – 233
- Median age – 5.3 years
  - Range: 6 mos – 81 yrs)
- Male – 58%
- Race
  - Asian – 4%
  - Black – 9%
  - White – 63%
  - Multiracial – 2%
  - Unknown – 21%

- Clinical illness
  - Upper limbs only – 42%
  - Lower limbs only – 13%
- In prior 4 weeks (IQR)
  - Any illness – 96% (2-8d)
  - Resp – 83% (3-8d)
  - Fever – 78% (1-5d)
  - Resp or fever – 92% (2-7d)
  - GI tract – 36% (1-7d)
- Mortality – no deaths

*MMWR* 2019;68(27):608-613

# Clinical features

- Sudden denervation-associated muscle weakness
  - Mimics poliomyelitis
  - Sudden onset of asymmetrical limb paralysis
    - Upper > lower
    - Proximal > distal
    - Hyporeflexia
    - Usually no loss of sensation, although can be panful
    - Worsens over hours to days, then stabilizes
  - Accompanying cranial nerve abnormalities
  - Encephalopathy/Seizures – rare
  - Ventilatory failure

# MRI findings

- Spinal cord lesions
  - Largely restricted to gray matter
  - Spanning more than one or more spinal segments
- Pons and medulla lesions
- T2-weighted signal hyperintensity without edema
  - May not develop until >72 hours from onset of weakness

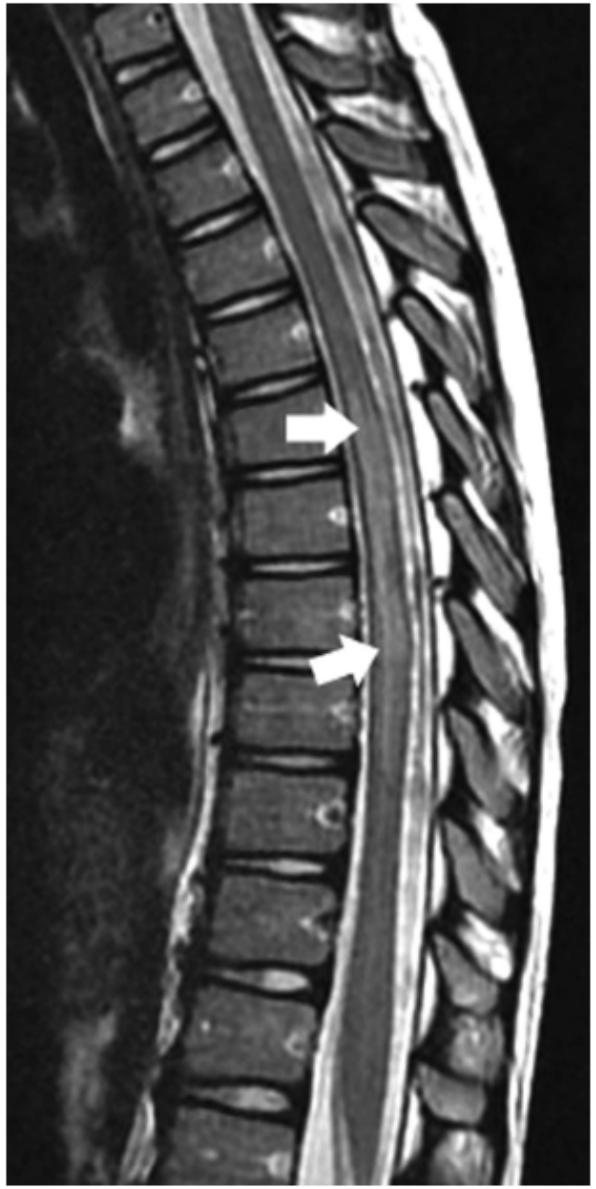


**FIGURE 1.**
Sagittal, T2-weighted magnetic resonance imaging (Patient #8) shows extensive signal hyperintensity involving several levels of the central thoracic spinal cord (arrows).

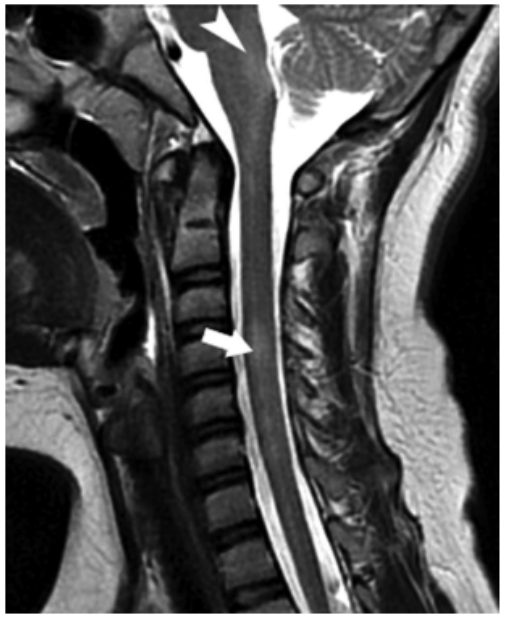


**FIGURE 2.**
Sagittal T2-weighted magnetic resonance imaging (Patient #3) shows signal hyperintensities involving the dorsal pons and medulla (arrowhead). Also note T2 hyperintensity in several levels (C3 to C7) of the cervical spinal cord (arrow). Patient 3 presented with facial paresis only; magnetic resonance imaging clearly demonstrates spinal cord involvement as well.

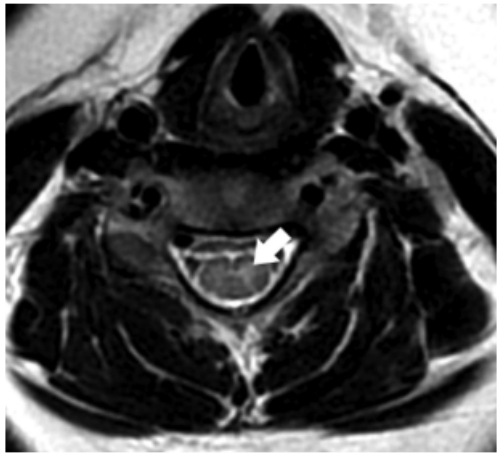


**FIGURE 3.**
Axial T2-weighted magnetic resonance imaging (Patient #3) demonstrates selective involvement of the gray matter of the spinal cord. Note the asymmetric involvement of the left anterior horn (arrow).

*Pediatric Neurology* 2016;55:17-21

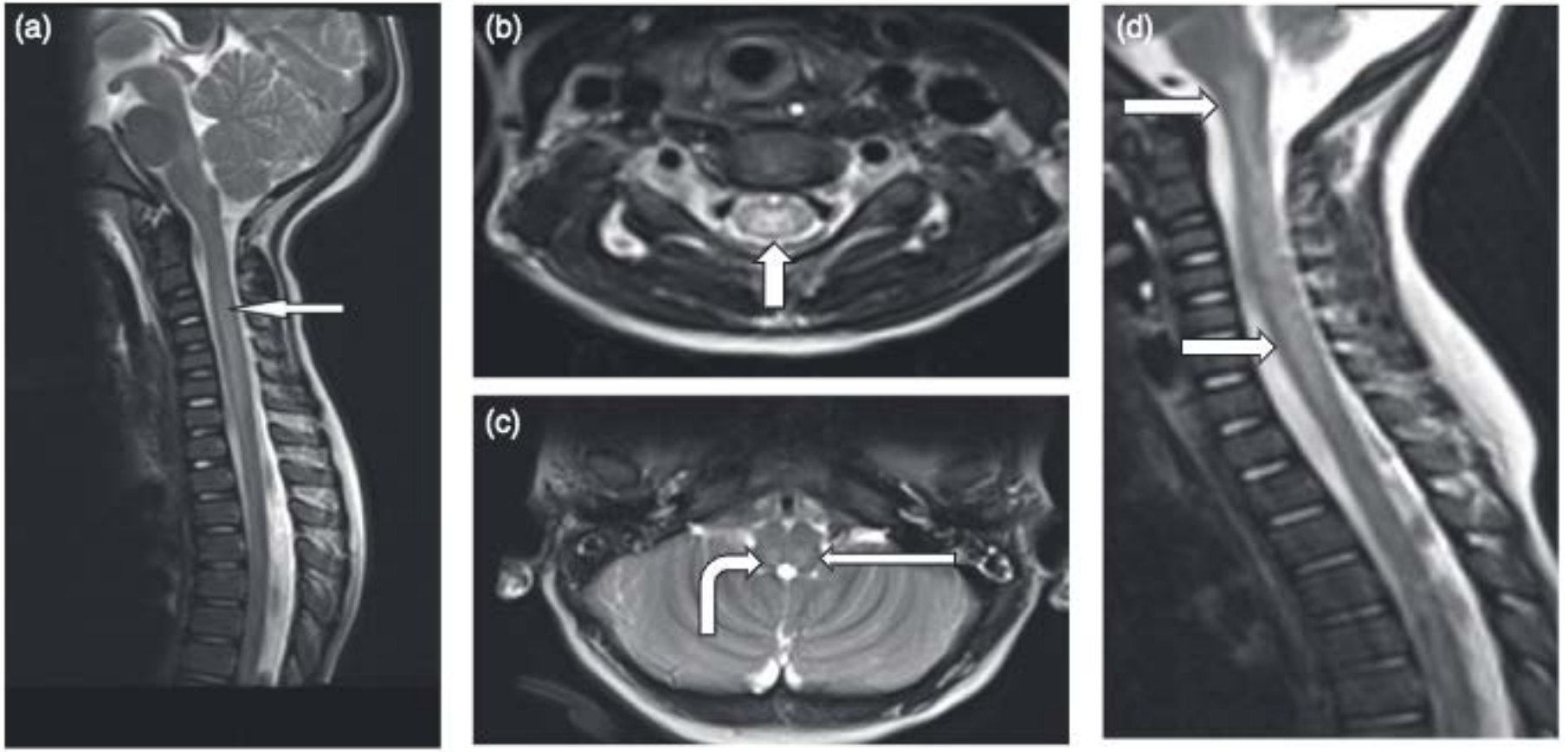



**Figure 2:** Magnetic resonance imaging of the spinal cord and brainstem in acute flaccid myelitis caused by enterovirus D68. The saggital T2-weighted sequences (a,d) showing longitudinal hyperintense signal and the axial T2-weighted sequences (b,c) showing hyperintensity in spinal cord grey matter (b) and dorsal brainstem (c).

Kirolos, et al. *Developmental Med & Child Neuro* 2019;61:376-380

# Confirmed AFM cases in 2018: CSF findings

- Pleocytosis – 96%
- Median cell count – 92
  - Range – 6-814
  - IQR – 42-158

**TABLE 2. Laboratory results from cerebrospinal fluid (CSF), respiratory, and stool specimens collected from patients with confirmed acute flaccid myelitis (N = 233) — United States, 2018**

| Specimen source | No. with specimens available (% of 233) | No. (%) positive | Positive test results (No.) |
|---|---|---|---|
| **CSF** | 74 (32) | 2/74 (3) | EV-A71 (1)<br>EV-D68 (1) |
| **Respiratory** | 123 (53) | 54/123 (44) | EV-D68 (30)<br>EV-A71 (10)<br>Other/Untyped EV/RV (14) |
| **Stool** | 100 (43) | 13/100 (13) | EV-D68 (1)<br>EV-A71 (2)<br>Echovirus 11 (1)<br>Coxsackievirus (3)<br>Parechovirus (4)<br>Other/Untyped EV/RV (2) |

**Abbreviations:** EV = enterovirus; RV = rhinovirus.

*MMWR* 2019;68(27):608-613

# EMG and nerve conduction findings

- May be normal initially
- After 1-2 weeks
  - Low motor amplitudes with normal conduction velocities
  - No sensory nerve conduction abnormalities
- Later stages
  - Spontaneous muscle fiber activity (fibrillation potentials)

*Ann Neurol 2016;80:326-338; Neurology* 2017;89:129-137

# Targeted therapies

- Not enough evidence to endorse or discourage use of:
  - Corticosteroids
    - Mouse model of EV-D68 infection – may be harmful
    - Balance potential risks with degree of cord edema or white matter involvement
  - IVIG
    - No evidence of harm
  - Plasmapheresis
    - Inherent procedural risks, no evidence of harm
  - Antivirals
    - Acyclovir only if HSV is in differential diagnosis

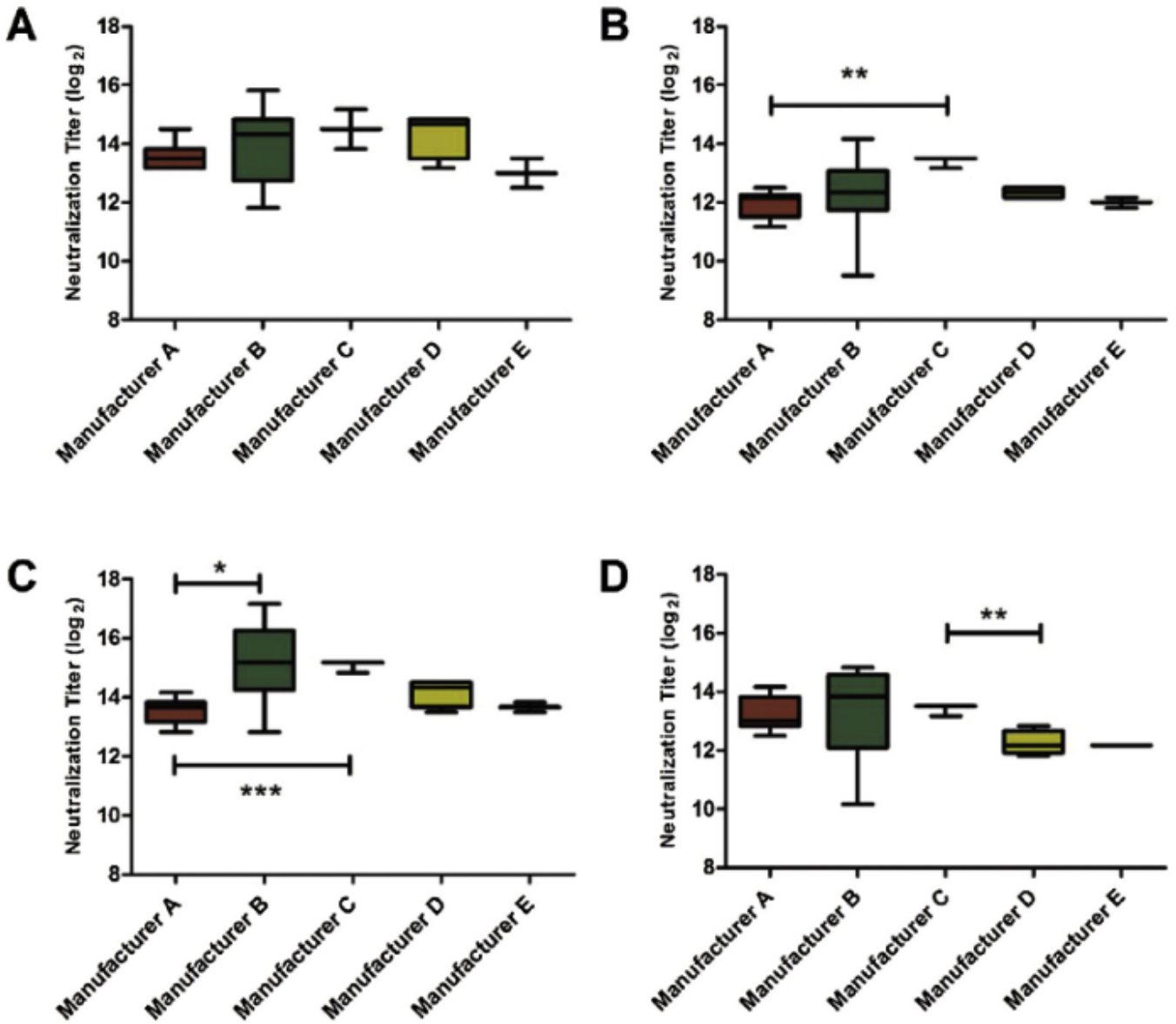


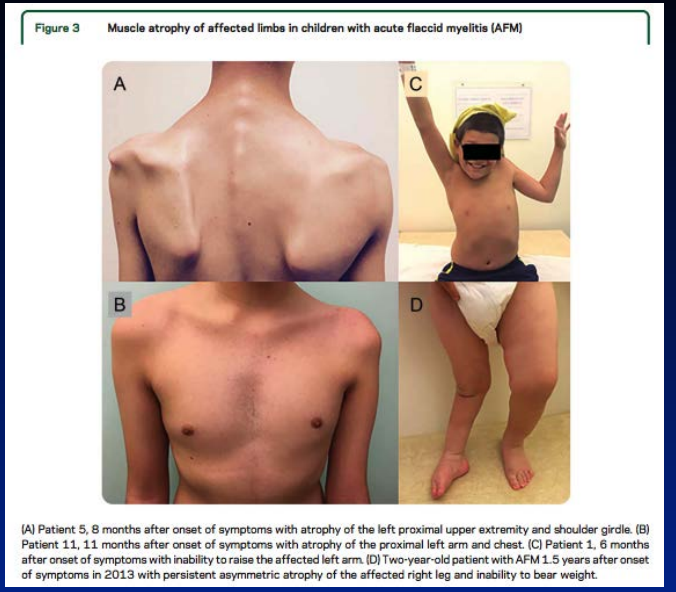

**Fig. 2.** Commercial IVIG lots neutralize EV-D68 strains with equivalent efficiencies. IVIG products were tested for neutralizing antibodies against the EV-D68 strains Fermon (A) and three clinical isolates 14-18949 (B), 14-18952 (C), and 14-18953 (D). For each manufacturer, median neutralization titers are indicated in box plots with horizontal line with 5–95% confidence intervals. (A, $n = 10$; B, $n = 10$; C, $n = 3$; D, $n = 4$, E, $n = 2$). Data represents results from a single assay run. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for difference in median titers.

Zhang, et al *JClinVirol* 2015;69:172-175

# Targeted therapies

- **Not recommended for use (possible harm):**
  - **Fluoxetine (Prozac) – selective serotonin reuptake inhibitor**
    - **In vitro activity against enteroviruses, including EV-D68**
    - **Concentration in brain exceeds serum**
    - **Mouse model of EV-D68 infection – increased mortality**
  - **Interferons**
    - **Failed improvement in West Nile poliomyelitis-like illness and multiple arboviral encephalitis cases**
    - **Concern about potential for harm due to immunomodulatory effects in setting of possible ongoing viral replication**
  - **Biologic modifiers**
    - **Potential interference with T-cell function or humoral response**

# Outcome



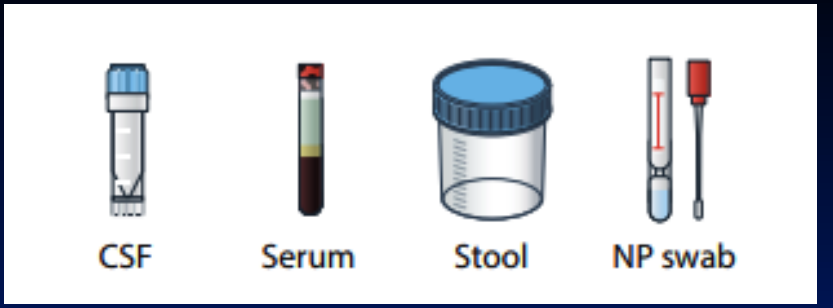

Neurology 2017;89:129-137

- CDC 2018 data: no deaths
- Intensive rehabilitation is associated with continued improvement for over one year
  - Most children have residual weakness and muscle wasting at one year
  - Electrophysiologic studies continue to show defibrillations
- Unknown: will there be a parallel to the post-polio syndrome?

# Recommendations for clinicians

- Report all patients with sudden onset of flaccid limb weakness that meet clinical criteria for AFM to health department regardless of laboratory results or MRI findings

# Data Collection




- For all patients with acute onset of neurologic illness with flaccid limb weakness that meet AFM clinical criteria regardless of laboratory results or MRI findings
  - Collect specimens as close to onset of limb weakness as possible
    - Store and handle as directed
  - Notify and coordinate with State Health Department
    - Additional information will be requested

Louisiana: 800-256-2748

https://www.cdc.gov/acute-flaccid-myelitis/hcp/data-collection.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Facute-flaccid-myelitis%2Fhcp%2Fdata.html

# Specimens to collect and send to CDC for testing for Patients Under Investigation (PUIs) for AFM

## Cerebrospinal fluid (CSF)

CSF

Spun and processed; collect at same time or within 24 hours of serum if feasible

| | |
|---|---|
| **Minimum Amount** | 1 mL |
| **Tube Type** | Cryovial |
| **Storage** | Freeze at -70°C |
| **Shipping** | Ship on dry ice |
| **Results of Testing** | CSF will be used for special studies; EV/RV testing will be batched and results returned as sample amount allows |

## Serum*

Serum

Spun and processed; collect at same time or within 24 hours of CSF if feasible

| | |
|---|---|
| **Minimum Amount** | 0.4 mL |
| **Tube Type** | Tiger/red top |
| **Storage** | Freeze at -70°C |
| **Shipping** | Ship on dry ice |
| **Results of Testing** | Serum will be used for special studies; no individual results will be returned |

# Specimens to collect and send to CDC for testing for Patients Under Investigation (PUIs) for AFM

## Whole stool

Stool

Two samples total, collected at least 24 hours apart, both collected as early in illness as possible and ideally within 14 days of illness onset

| | |
|---|---|
| **Minimum Amount** | ≥1 gram |
| **Tube Type** | Sterile container; Not a rectal swab†. |
| **Storage** | Freeze at -20°C** |
| **Shipping** | Ship on dry ice |
| **Results of Testing** | Results for EV/RV and poliovirus testing will be returned as testing completed (within 14 days) |

## Respiratory - nasopharyngeal (NP) or oropharyngeal (OP) swab

NP swab

Store in viral transport medium

| | |
|---|---|
| **Minimum Amount** | 1 mL |
| **Tube Type** | N/A |
| **Storage** | Freeze at -20°C** |
| **Shipping** | Ship on dry ice |
| **Results of Testing** | EV/RV testing and typing will be performed and results returned within 10 days of sample receipt |

Acute Flaccid Myelitis: Patient Summary Form

**FOR LOCAL USE ONLY**

Name of person completing form: _____ State assigned patient ID: _____

Affiliation_____ Phone: _____ Email: _____

Name of physician who can provide additional clinical/lab information, if needed _____

Affiliation_____ Phone: _____ Email: _____

Name of main hospital that provided patient's care: _____ State: ____ County: _____

*----------DETACH and transmit only lower portion to limbweakness@cdc.gov if sending to CDC----------*

## Acute Flaccid Myelitis: Patient Summary Form

Form Approved
OMB No. 0920-0009
Exp Date: 08/30/2019

***Please send the following information along with the patient summary form (check information included):***
☐ *History and physical (H&P)* ☐ *MRI report* ☐ *MRI images* ☐ *Neurology consult notes* ☐ *EMG report (if done)*
☐ *Infectious disease consult notes (if available)* ☐ *Vaccination record* ☐ *Diagnostic laboratory reports*

**1.** Today's date__ __/__ __/__ __ __ __ *(mm/dd/yyyy)* **2.** State assigned patient ID: _____

**3.** Sex: ☐ M ☐F **4.** Date of birth __ __/__ __/__ __ __ __ Residence: **5.** State_____ **6.** County_____

**7.** Race: ☐American Indian or Alaska Native ☐Asian ☐Black or African American ☐Native Hawaiian or Other Pacific Islander ☐White *(check all that apply)* **8.** Ethnicity: ☐Hispanic or Latino ☐Not Hispanic or Latino

**9.** Date of onset of limb weakness __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

**10.** Was patient admitted to a hospital? ☐yes ☐no ☐unknown **11.**Date of admission to **first** hospital__ __/__ __/__ __ __ __

**12.**Date of discharge from **last** hospital__ __/__ __/__ __ __ __(or ☐ still hospitalized at time of form submission)

**13**. Did the patient die from this illness? ☐yes ☐no ☐unknown **14**. If yes, date of death__ __/__ __/__ __ __ __

**SIGNS/SYMPTOMS/CONDITION:**

| | Right Arm | Left Arm | Right Leg | Left Leg |
|---|---|---|---|---|
| **15**. Weakness? *[indicate yes(y), no (n), unknown (u) **for each limb**]* | Y N U | Y N U | Y N U | Y N U |
| **15a**. Tone in **affected** limb(s) *[flaccid, spastic, normal **for each limb**]* | ☐ flaccid ☐ spastic ☐ normal ☐ unknown | ☐ flaccid ☐ spastic ☐ normal ☐ unknown | ☐ flaccid ☐ spastic ☐ normal ☐ unknown | ☐ flaccid ☐ spastic ☐ normal ☐ unknown |

| | Yes | No | Unk | |
|---|---|---|---|---|
| **16**. Was patient admitted to ICU? | | | | **17**. If yes, admit date: ___/___/_____ |
| In the 4-weeks **BEFORE onset** of **limb weakness**, did patient: | Yes | No | Unk | |
| **18**. Have a respiratory illness? | | | | **19**. If yes, onset date ___/___/___ ___ ___ |
| **20**. Have a gastrointestinal illness (e.g., diarrhea or vomiting)? | | | | **21**. If yes, onset date ___/___/___ ___ ___ |
| **22**. Have a fever, measured by parent or provider ≥38.0°C/100.4°F? | | | | **23**. If yes, onset date ___/___/___ ___ ___ |
| **24**. Travel outside the US? | | | | **25**. If yes, list country: |
| **26**. At onset of limb weakness, does patient have any underlying illnesses? | | | | **27**. If yes, list: |

**Other patient information:**

**28.** Was MRI of spinal cord performed? ☐ yes ☐ no ☐ unknown **29.** If yes, date of spine MRI: ___/___/___ ___ ___

**30.** Was MRI of brain performed? ☐ yes ☐ no ☐ unknown **31.** If yes, date of brain MRI: ___/___/___ ___ ___

**CSF examination: 32**. Was a lumbar puncture performed? ☐ yes ☐ no ☐ unknown
If yes, complete 32 (a,b) *(if more than 2 CSF examinations, list the first 2 performed)*

| | Date of lumbar puncture | WBC/mm³ | % neutrophils | % lymphocytes | % monocytes | % eosinophils | RBC/mm³ | Glucose mg/dl | Protein mg/dl |
|---|---|---|---|---|---|---|---|---|---|
| **32a. CSF** from LP1 | | | | | | | | | |
| **32b. CSF** from LP2 | | | | | | | | | |





**Acute Flaccid Myelitis Outcome – follow-up of confirmed and probable AFM cases (*completed at 60 days, 6 months and 12 months after onset of limb weakness*)**

**33.** Date of follow-up: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

**36.** Impairment: ☐ None ☐ Minor (any minor involvement) ☐ Significant (≤2 extremities, major involvement) ☐ Severe (≥3 extremities and respiratory involvement) ☐ Death ☐ Unknown

**37.** Date of death: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

**38. Physical condition** (includes cardiovascular, gastrointestinal, urologic, endocrine as well as neurologic disorders):

i. Medical problems sufficiently stable that medical or nursing monitoring is not required more often than 3-month intervals
ii. Medical or nurse monitoring is needed more often than 3-month intervals but not each week.
iii. Medical problems are sufficiently unstable as to require medical and/or nursing attention at least weekly.
iv. Medical problems require intensive medical and/or nursing attention at least daily (excluding personal care assistance)

**39. Upper limb functions**: Self-care activities (drink/feed, dress upper/lower, brace/prosthesis, groom, wash, perineal care) dependent mainly upon upper limb function:

i. Age-appropriate independence in self-care without impairment of upper limbs
ii. Age-appropriate independence in self-care with some impairment of upper limbs
iii. Dependent upon assistance in self-care with or without impairment of upper limbs.
iv. Dependent totally in self-care with marked impairment of upper limbs.

**40. Lower limb functions**: Mobility (walk, stairs, wheelchair, transfer chair/toilet/tub or shower) dependent mainly upon lower limb function:

i. Independent in mobility without impairment of lower limbs
ii. Independent of mobility with some impairment of lower limbs, such as needing ambulatory aids, a brace or prosthesis
iii. Dependent upon assistance or supervision in mobility with or without impairment of lower limbs.
iv. Dependant totally in mobility with marked impairment of lower limbs.

**41. Sensory components**: Relating to communication (speech and hearing) and vision:

i. Age-appropriate independence in communication and vision without impairment
ii. Age-appropriate independence in communication and vision with some impairment such as mild dysarthria, mild aphasia or need for eyeglasses or hearing aid.
iii. Dependent upon assistance, an interpreter, or supervision in communication or vision
iv. Dependent totally in communication or vision

**42. Excretory functions** (bladder and bowel control, age-appropriate):

i. Complete voluntary control of bladder and bowel sphincters
ii. Control of sphincters allows normal social activities despite urgency or need for catheter, appliance, suppositories, etc.
iii. Dependent upon assistance in sphincter management
iv. Frequent wetting or soiling from bowel or bladder incontinence

**43. Support factors**:

i. Able to fulfil usual age-appropriate roles and perform customary tasks
ii. Must make some modifications in usual age-appropriate roles and performance of customary tasks
iii. Dependent upon assistance, supervision, and encouragement from an adult due to any of the above considerations
iv. Dependent upon long-term institutional care (chronic hospitalization, residential rehabilitation, etc. Excluding time-limited hospitalization for specific evaluation or treatment)





**Acute Flaccid Myelitis case definition**
(http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/2015PS/2015PSFinal/15-ID-01.pdf)

**Criteria**
An illness with onset of acute focal limb weakness AND
- a magnetic resonance image (MRI) showing spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments, OR
- cerebrospinal fluid (CSF) with pleocytosis (white blood cell count >5 cells/mm³)

**Case Classification**
***Confirmed:***
- An illness with onset of acute focal limb weakness AND
- MRI showing spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments

***Probable:***
- An illness with onset of acute focal limb weakness AND
- CSF showing pleocytosis (white blood cell count >5 cells/mm³).

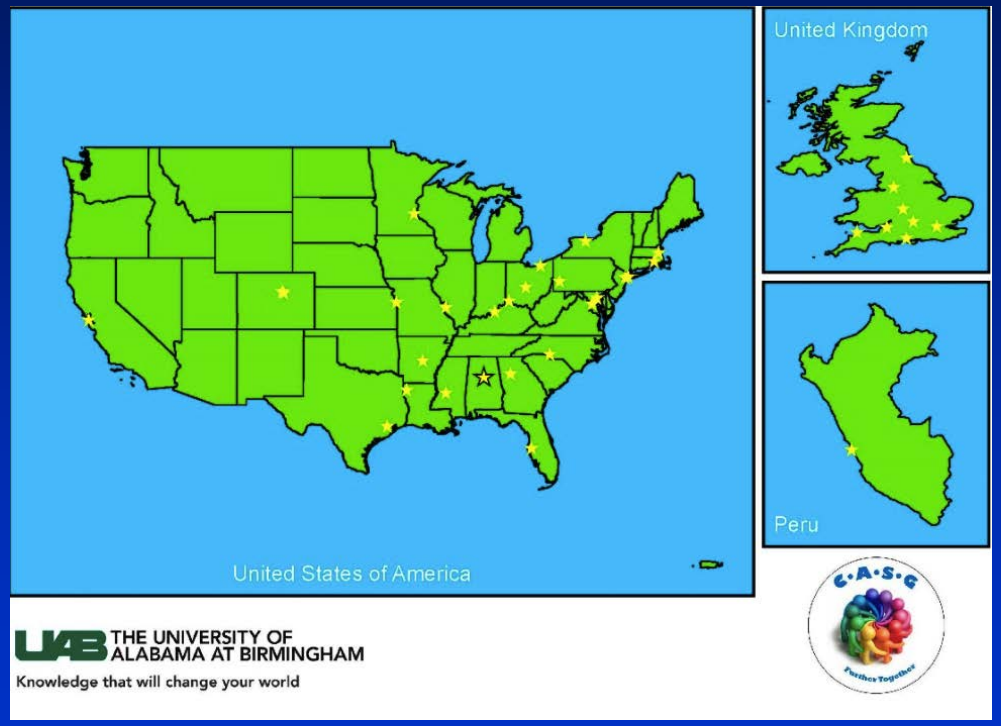
**Acute Flaccid Myelitis specimen collection information**
(https://www.cdc.gov/acute-flaccid-myelitis/hcp/instructions.html)

**Acute Flaccid Myelitis job aid**
(https://www.cdc.gov/acute-flaccid-myelitis/downloads/job-aid-for-clinicians.pdf)

# NIH AFM Initiative

- NIAID Collaborative Antiviral Studies Group
  - 15 million dollar award
  - LSU-Shreveport will be a study site
  - More details when available

  - Contact Dr. Vanchiere or Dr. Bocchini at 318-675-6073



# Key Points

- AFM is an emerging illness and potential threat
- Additional studies are needed to confirm etiology and determine best therapy
- As public health challenge, all pediatricians should
  - Be aware of AFM
  - Apply appropriate diagnostic evaluation
  - Promptly
    - Report cases
    - Obtain recommended specimens