Acute Flaccid Myelitis in the United States

Janell Routh, MD MHS

AFM and Domestic Polio Team Lead

Accessible version: https://www.youtube.com/watch?v=sQzvxhmY9h4

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Acute Flaccid Myelitis Emerged in 2014

Infection with AFM leads to the limb weakness and paralysis.

Health

A mysterious polio-like illness that paralyzes people may be surging this year

McKenzie Anderson, before and after she came down with a mysterious disease called acute flaccid myelitis, which is a lot like polio. (Family photos)

Cover image: https://www.vox.com/2018/10/17/17989694/afm-disease-states-2018

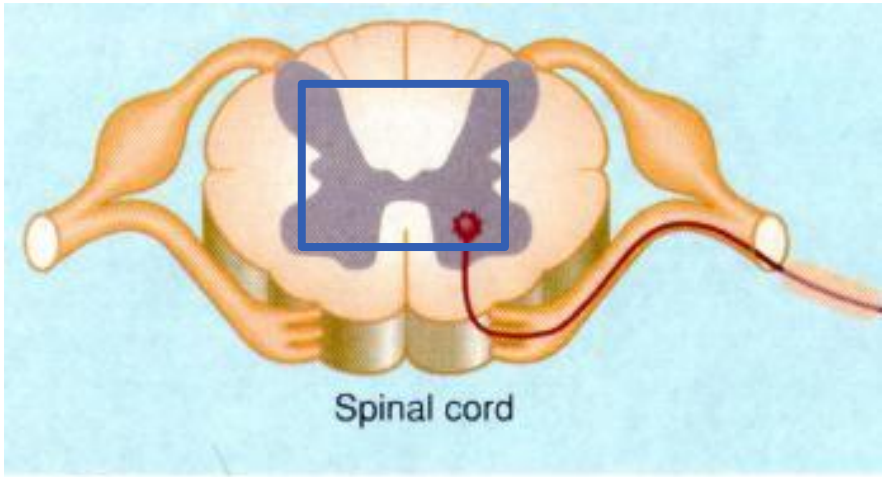
AFM Presents with Rapid Onset of Limb Weakness

Sudden limb weakness

Difficulty with swallowing or speaking

Facial droop or weakness

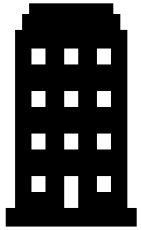
Eyelid Droop (Ptosis)



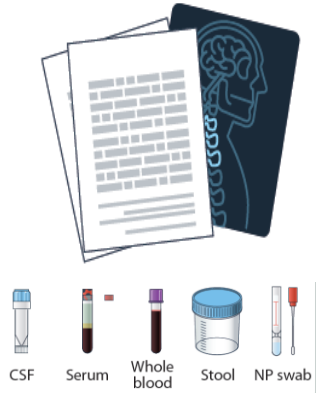
- **Lesions in spinal grey matter, particularly anterior horn cell distribution**
- **Cervical spinal cord most affected**

AFM Surveillance Involves Clinicians and Health Departments

Clinician reports patient under investigation (PUI) for AFM to Health Department (HD)

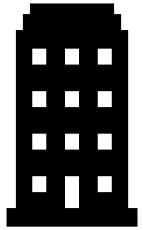


HD verifies PUI meets criteria and reports to CDC



HD collects and coordinates specimens to send to CDC

Neurology panel reviews information and images to classify case for surveillance



Surveillance classification communicated to HD and then HD relays classification to clinician

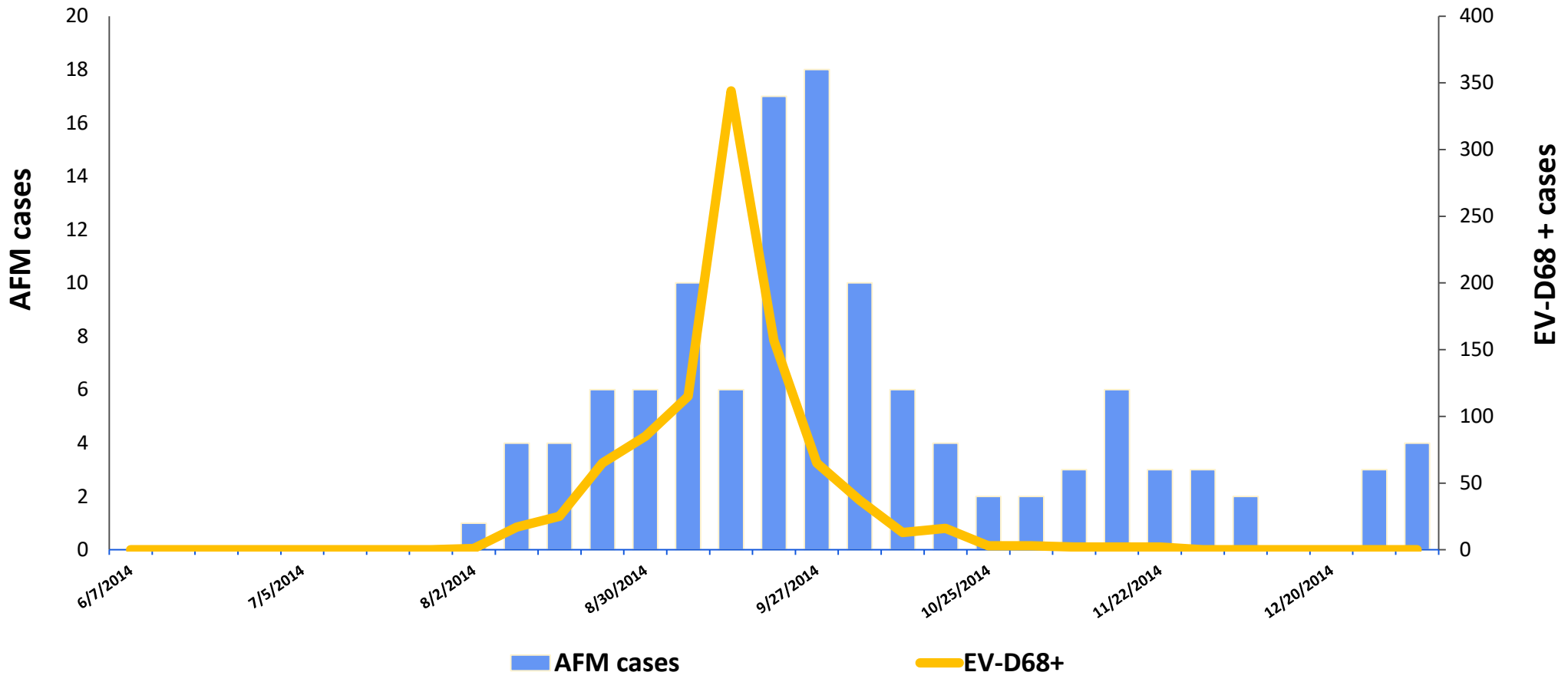
Current Surveillance Case Definitions for AFM

- **Confirmed:** Acute onset of flaccid limb weakness and a spinal cord lesion with predominantly grey matter involvement over 1 or more segments
- **Probable*:** Acute onset of flaccid limb weakness and a spinal cord lesion where grey matter involvement is present but predominance cannot be determined

*only confirmed cases are reported on CDC website

https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definitions.html

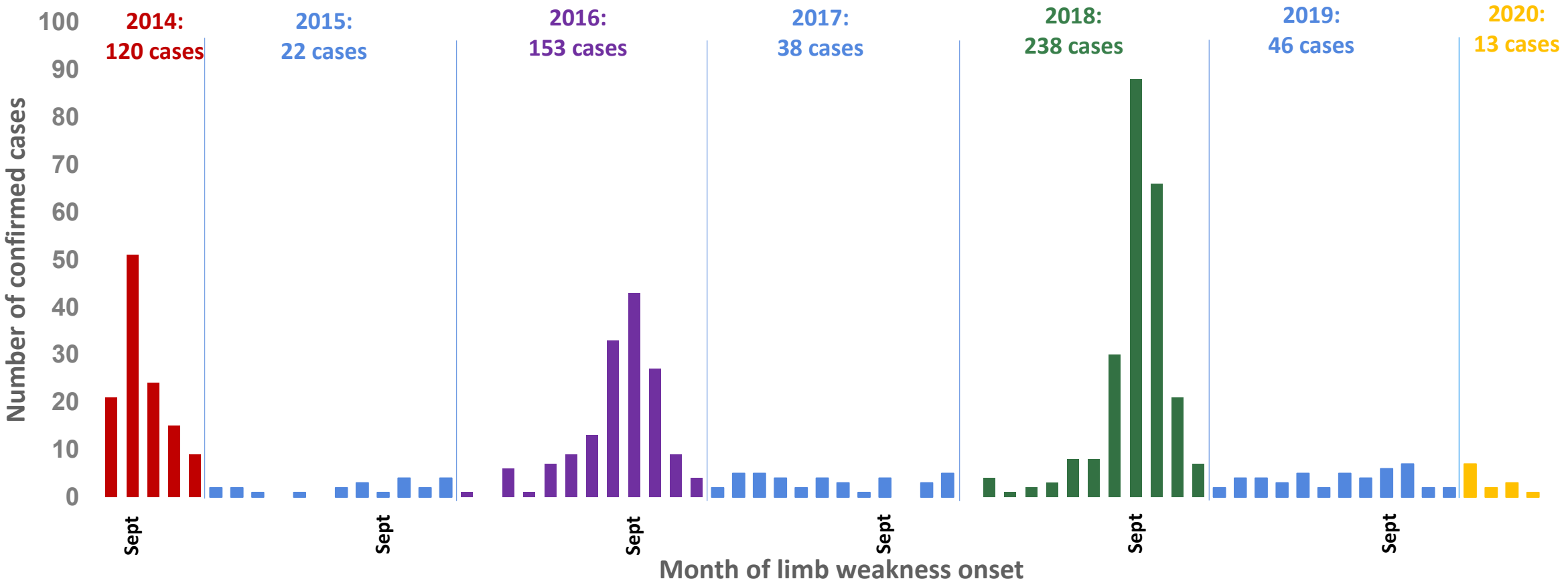
Concurrent Outbreaks of AFM and EV-D68 in 2014



Sejvar J, et al. Acute Flaccid Myelitis in the US, 2014, CID, 2016

EV-D68: enterovirus D-68

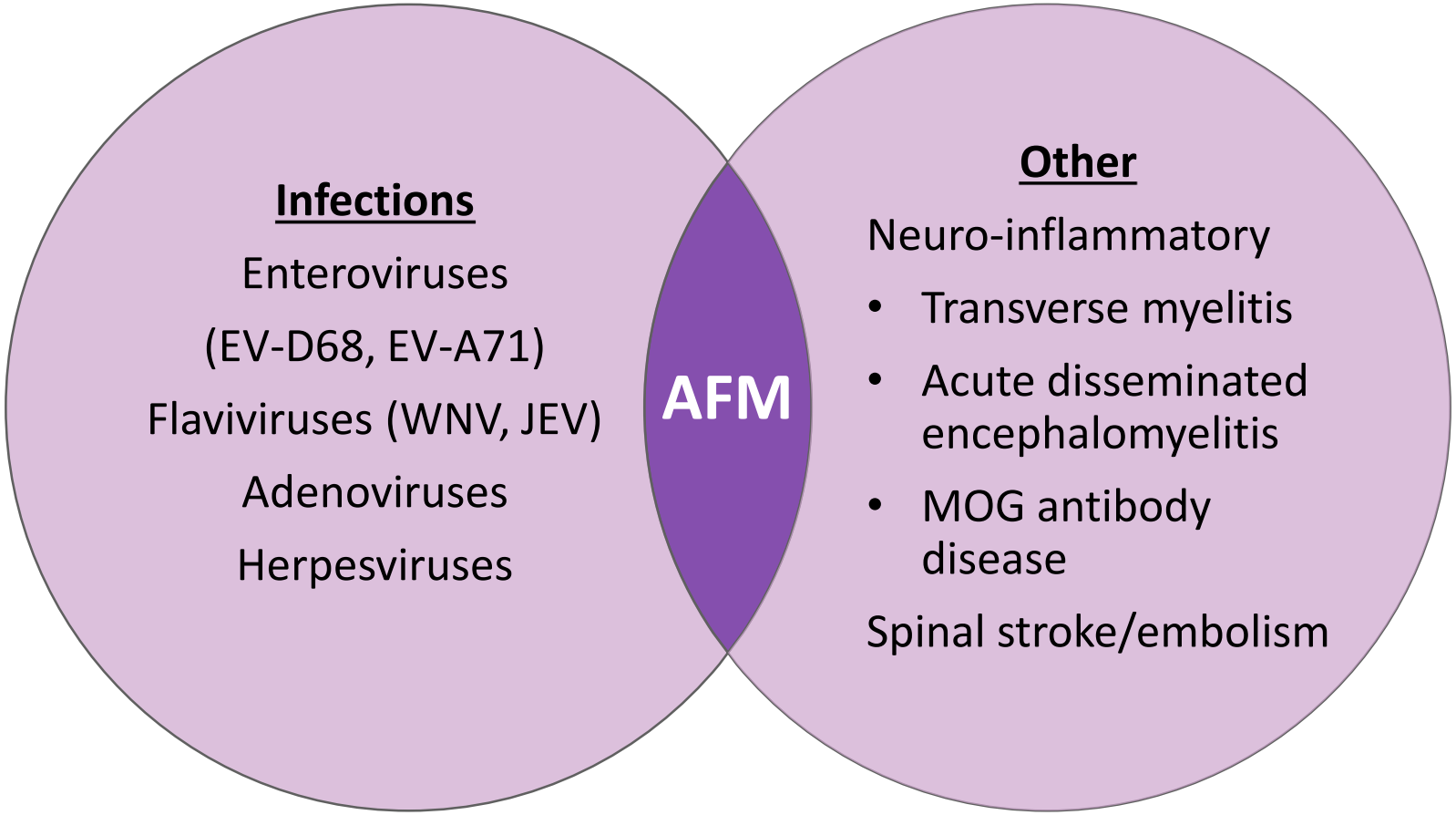
AFM Cases Have Increased Every 2 years Since 2014



Data current as of June 30, 2020

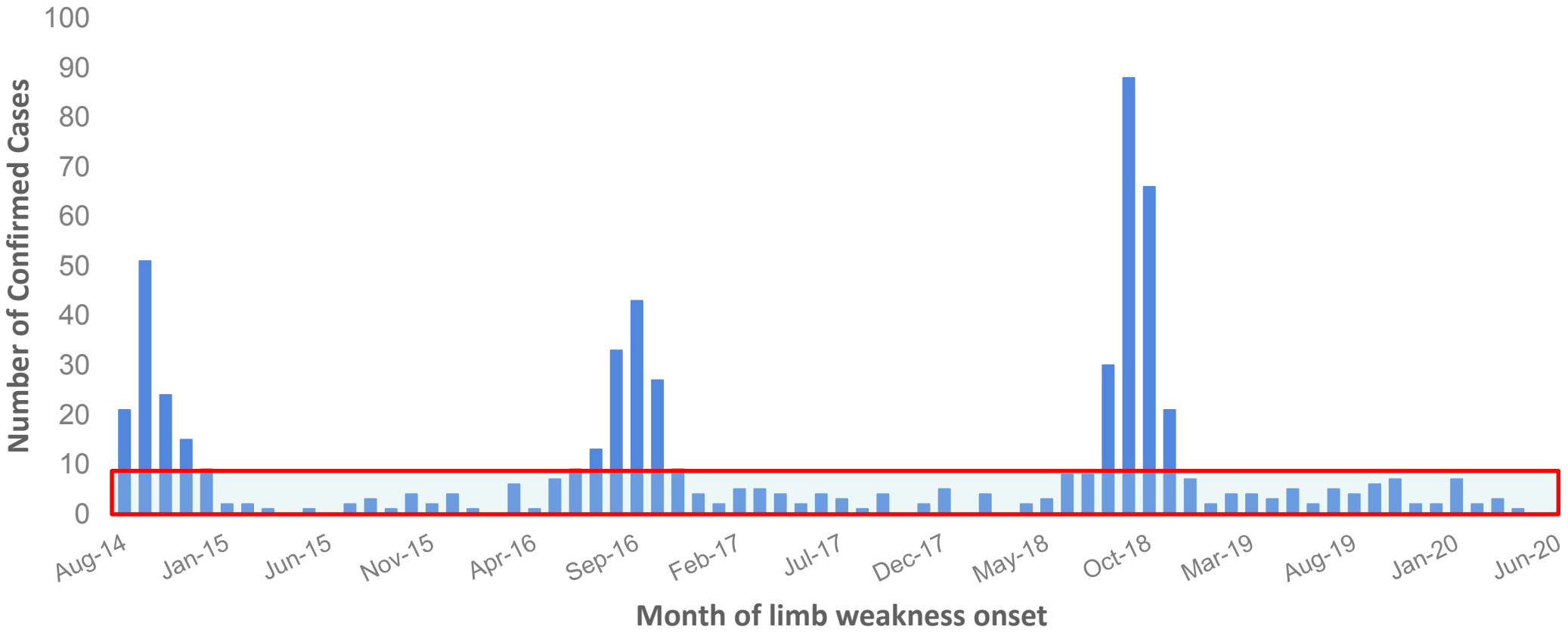
www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

AFM Has Multiple Causes



MOG = myelin oligodendrocyte glycoprotein

U.S. Surveillance Shows a Consistent Baseline Rate of AFM



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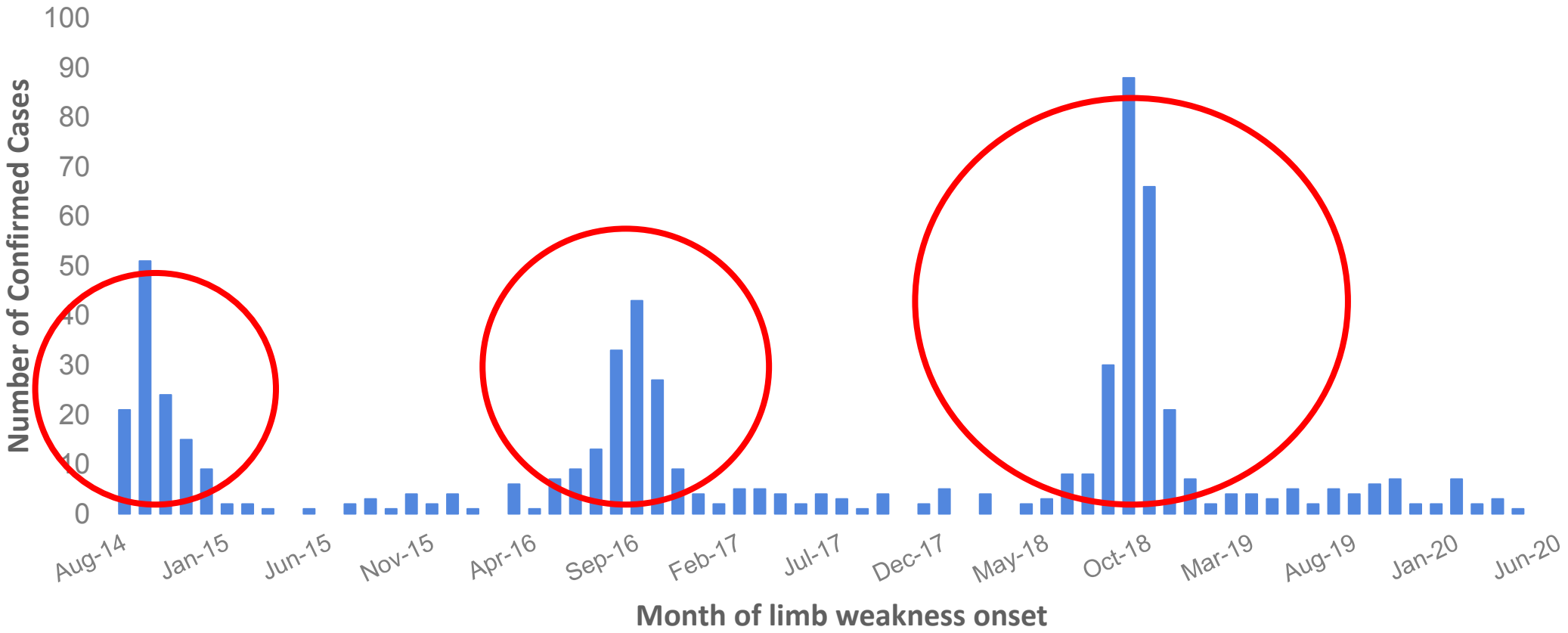
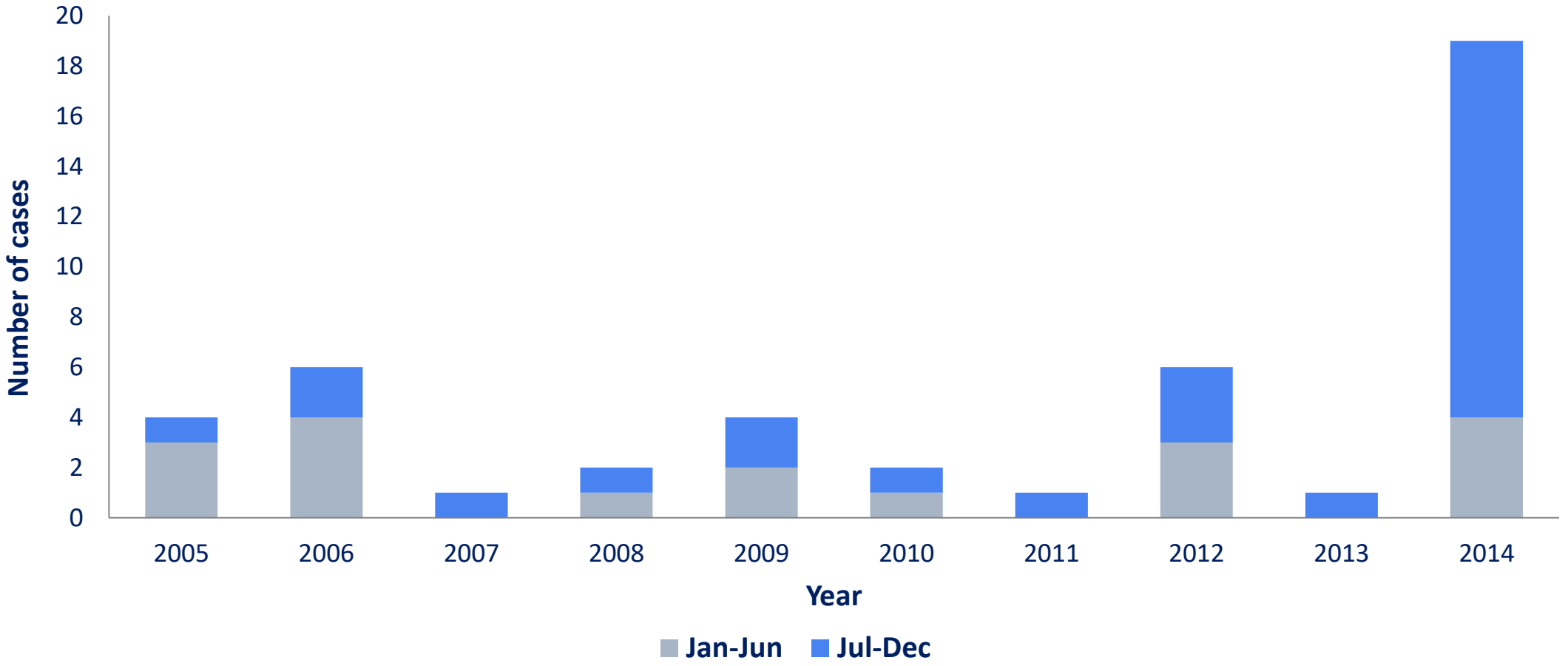
What is Causing the Every Other Year Peaks in AFM?



Data current as of June 30, 2020 www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

2014 Marked a New Epidemiologic Pattern for AFM



Cortese MM, Kambhampati AK, Schuster JE, et.al. PLOS One. January, 2020

Demographic Characteristics of Confirmed AFM cases, 2018

Geography

42 states

Median Age

5.3 years
(IQR: 3.3—8.2)
94% <18 years

Sex

58% male

Race

53% White
20% Hispanic
9% Black
3% Asian

Lopez A, Lee A, Guo A, et.al. MMWR Vol.68; July 9, 2019; data updated 6/1/20

Icon Credits: Juan Pablo Bravo; Marie Van de Broeck; DT Design; MRFA

Clinical Characteristics of Confirmed AFM Cases, 2018

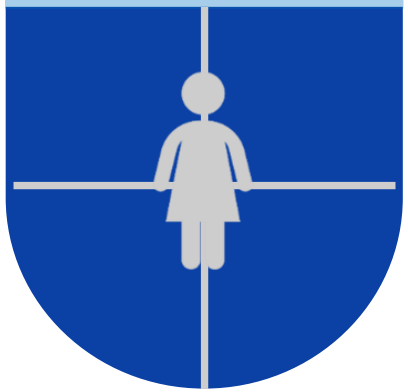
Hospitalization

98%
(54% ICU)

Cells in Cerebrospinal Fluid

87%
WBC count 94 cells/mm^3
(IQR: 43–163)
Lymphocyte predominance

Number of Limbs Affected



1 limb: 37%
2 limbs: 30%
3 limbs: 6%
4 limbs: 27%

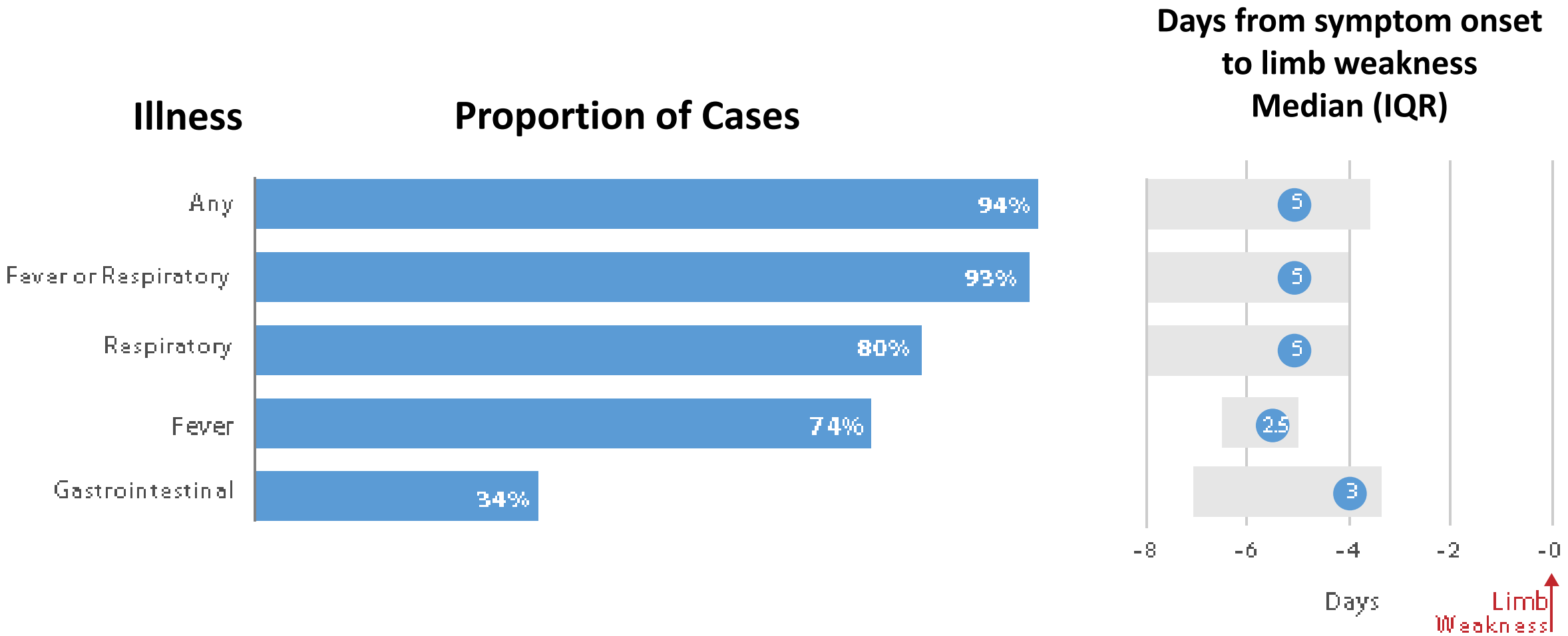
Limb Weakness Distribution

47% **upper** only
16% **lower** only

Lopez A, Lee A, Guo A, et.al. MMWR Vol.68; July 9, 2019; data updated 6/1/20

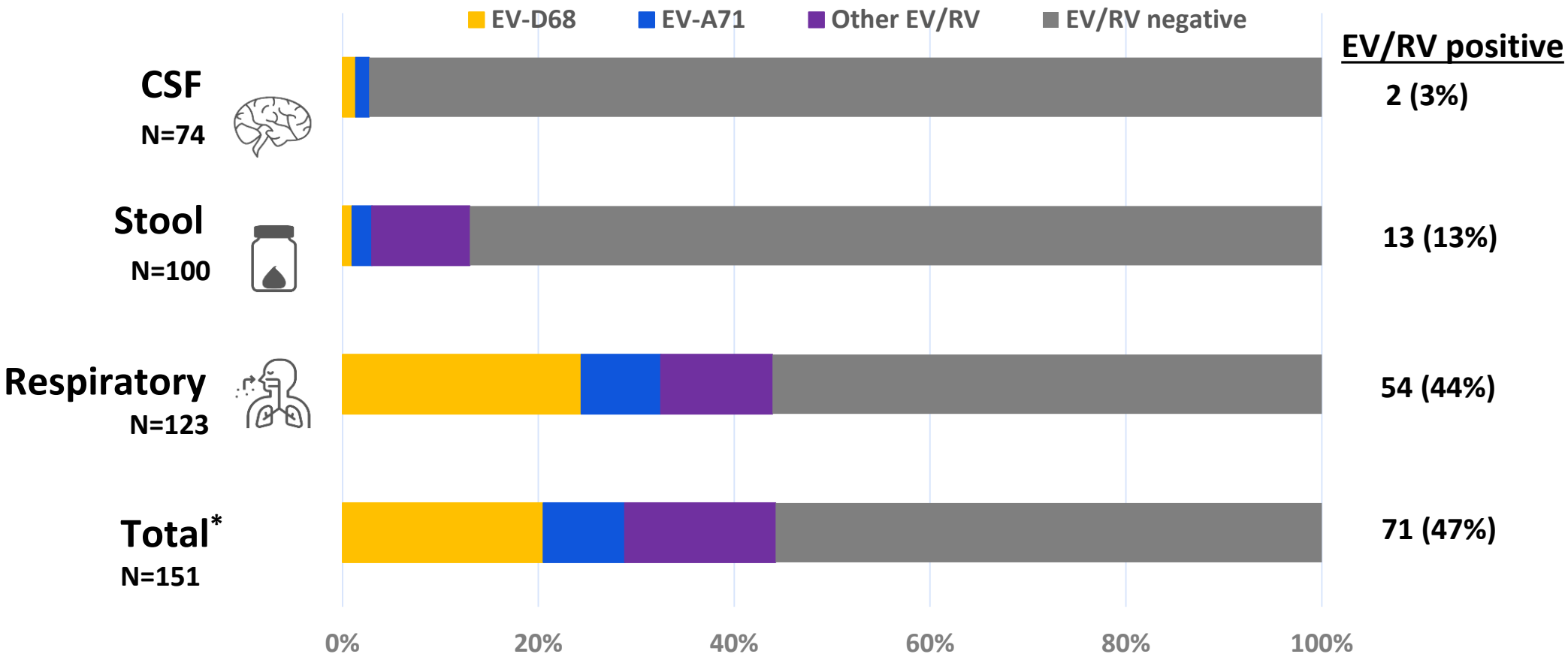
Icon Credits: Juan Pablo Bravo; Marie Van de Broeck; DT Design; MRFA

Symptoms of a Viral Illness Precede Limb Weakness



Lopez, et al. MMWR 2019

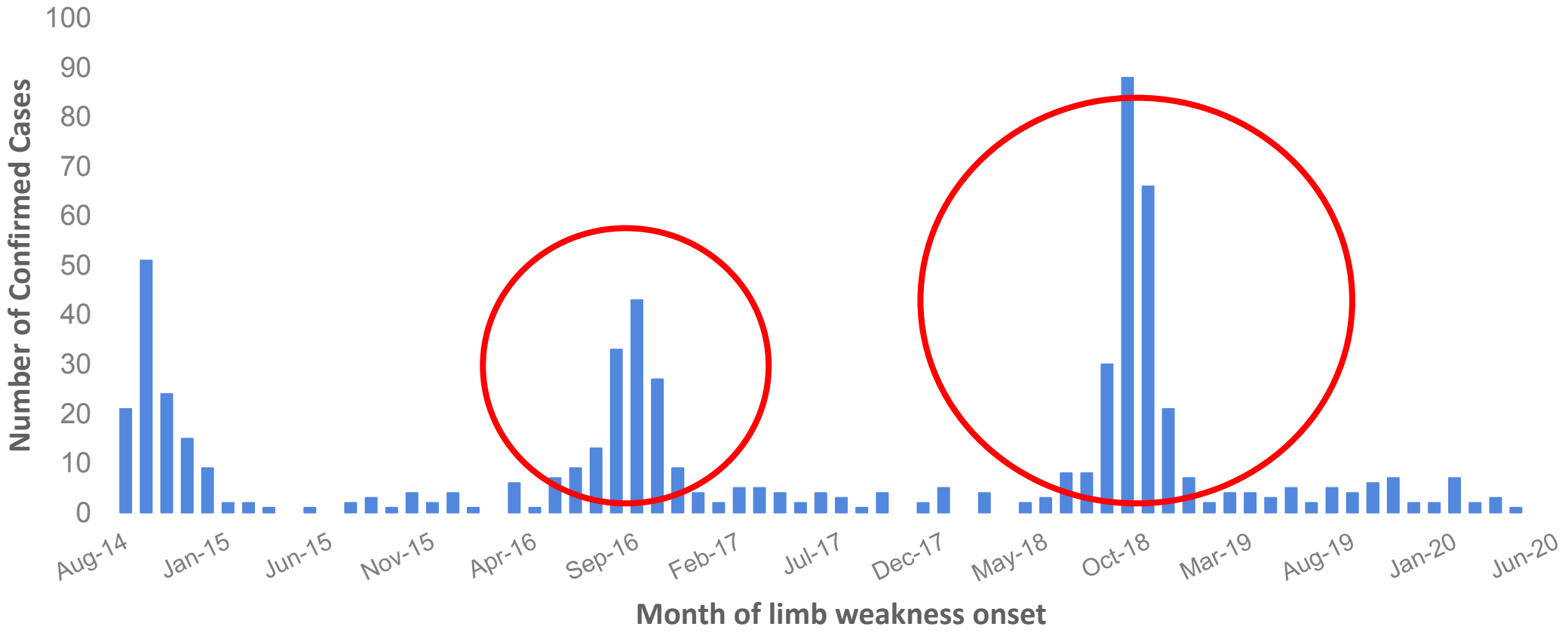
AFM Diagnostic Testing Does Not Often Indicate a Cause



*Some patients had multiple positive specimens

Lopez, et al. MMWR 2019

What is Causing the Every Other Year Peaks in AFM?



Data current as of June 30, 2020 www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

AFM Cases in Peak Years Differ from Those in Non-peak Years

- **Peak year cases (2016, 2018) were more likely to have:**
  - CSF pleocytosis (86% vs 60%)
  - only upper extremity weakness (33% vs 16%)
  - preceding respiratory illness (78% vs 43%)
  - EV/RV isolated from any specimen (38% vs 16%)
- **Only specimens from peak year cases were positive for EV-D68 (54%)**
- **Non-peak year cases (2015, 2017) were more likely to have:**
  - older age (8.3y vs 5.2y)
  - only lower limb weakness (32% vs 13%)
  - more severe disease (18% vs 3%)

McLaren, et.al. Characteristics of Patients with Acute Flaccid Myelitis, United States, 2015 – 2018. EID, Vol 26; February 2020.

AFM Case Characteristics Also Differ Between Peak Years

- **Cases in 2016 were more likely to have:**
  - severe illness (6% vs 0%)
  - cranial nerve involvement (37% vs 19%)
  - a specimen that tested positive for EV-D68 (70% vs 45%)
- **Cases in 2018 were more likely to have:**
  - a respiratory illness prior to limb weakness onset (80% vs 76%)
  - a specimen that tested positive for EV-A71 (17% vs 6%)

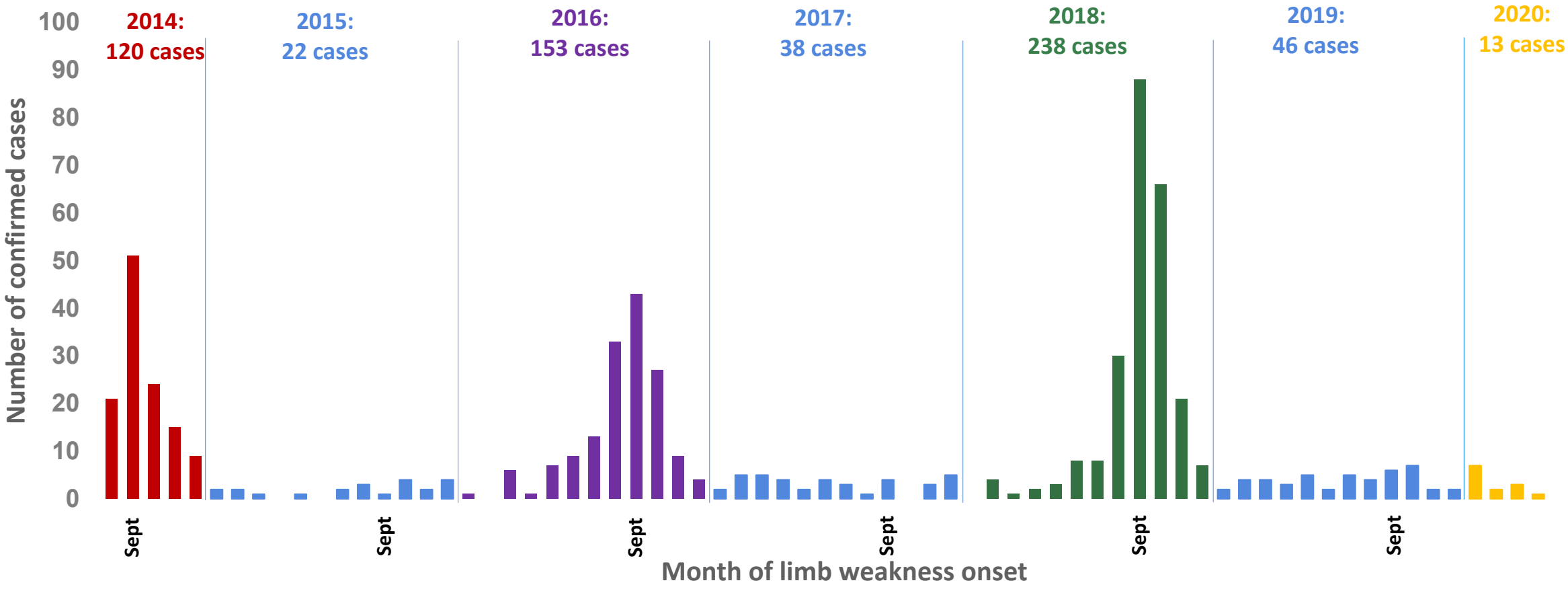
McLaren, et.al. Characteristics of Patients with Acute Flaccid Myelitis, United States, 2015 – 2018. EID, Vol 26; February 2020.

Summary

- **Causal factors of AFM in peak years appear different from those in non-peak years, but even in peak years there may be multiple causes**
- **Differences in EV detection support an association in peak years**
  - Detection of two main EV types in 2018 emphasize need for clinical surveillance plus EV surveillance to understand the full spectrum of AFM
- **Underlying mechanism of disease remains the critical unknown**
  - If EV-D68 is the primary driver in peak years, why does paralysis develop rarely?
  - Do different case characteristics give clues about disease mechanism?
  - Understanding AFM pathogenesis will allow for development of treatment and prevention strategies

McLaren, et.al. Characteristics of Patients with Acute Flaccid Myelitis, United States, 2015 – 2018. EID, Vol 26; February 2020.

What Do We Expect for AFM in 2020?



Data current as of June 30, 2020 www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

AFM from a Parent Perspective: Building an AFM Network in the U.S.

Rachel Scott

AFM Parent and Director of Acute Flaccid Myelitis Association

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Braden's Background

- Braden was five in July 2016
- Had a cold leading up to AFM
- His story bears a strong resemblance to other AFM stories

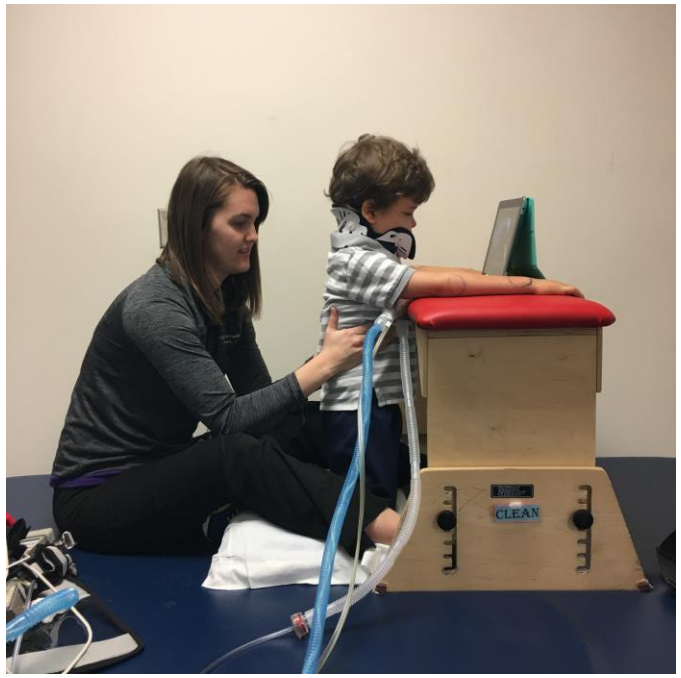
Initial Onset of Acute Flaccid Myelitis

- **July 4, 2016 - Symptoms began**
  - Threw up when he tried to eat
  - No energy
- **July 6, 2016 - Visit to ER**
  - Continued to decline
  - Received fluids, antibiotics and steroids
  - Admitted after no improvement
- **July 9, 2016 - Respiratory failure**
  - Intubated and flown to Houston

Uncertainty about Acute Flaccid Myelitis

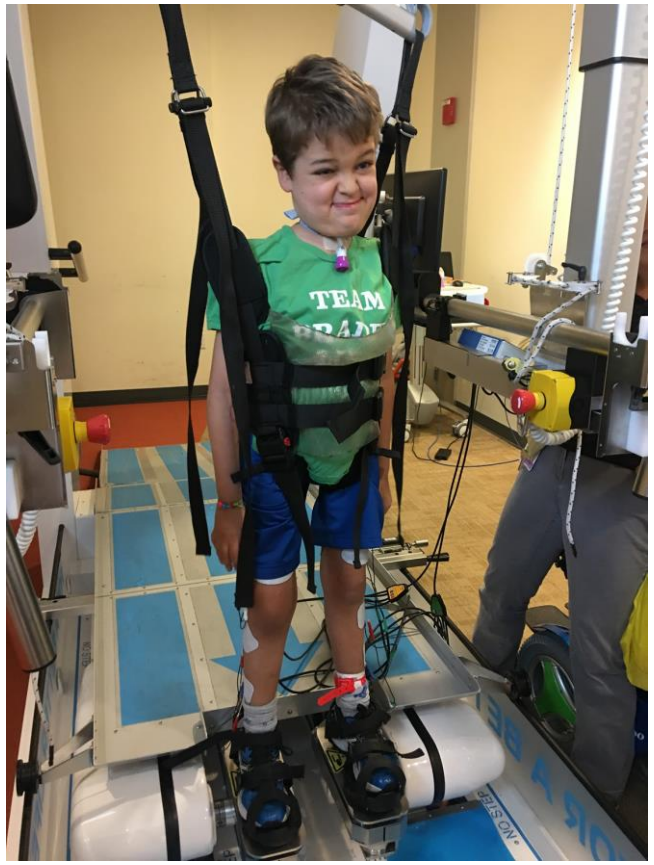
- **July 11, 2016 - MRI**
- **July 12, 2016 - Anterior Horn Cell Disease Diagnosis**
  - Treated with five rounds of IVIg and PLEX
- **July 19, 2016 - second failed extubation**
- **July 29, 2016 - tracheostomy and feeding tube placement**
  - Hospital for almost two months before transfer to rehab
- **Little information available about recovery or treatment**

Inpatient Rehabilitation



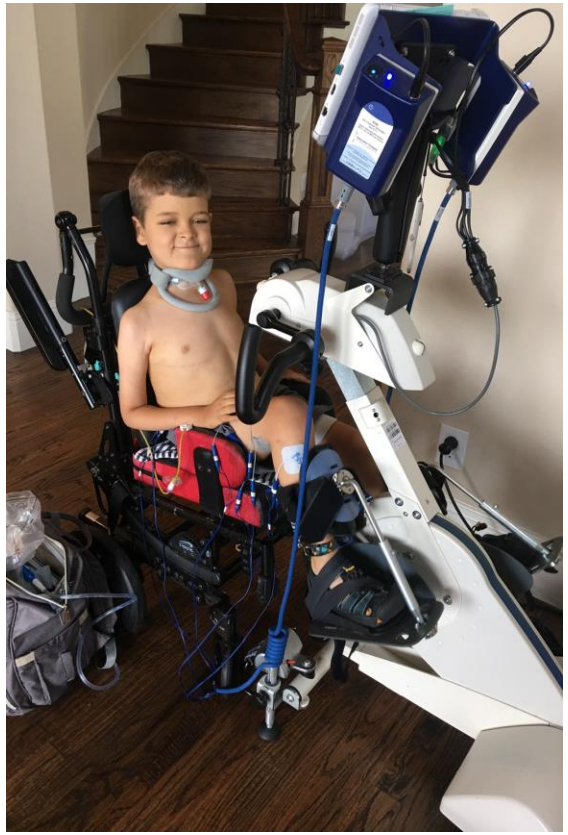
- **August 24, 2016 - Transfer to inpatient pediatric rehab facility in Dallas**
  - Daily physical, occupational, speech therapy
  - In rehab for 5.5 months
- **February 8, 2017 - Discharged to home via ambulance**
  - Take a few steps with maximum assistance
  - Could not manage oral secretions
  - Spent a few hours off vent and tolerated PMV
  - Functional recovery in left arm, none in right arm

Continued Recovery



- **September 21, 2017 - Nerve Transfer in LA**
  - 15 months post-onset
- **January/February 2018 - Intense Rehab at Kennedy Krieger Institute at Johns Hopkins**
  - 5 to 6 hours of daily therapy
- **September 10, 2019 - Nerve decompression in St. Louis**
- **September 19, 2019 - Decannulation**
- **Continuous Home nurses and therapy**

Braden's Current Recovery



- Walks short distances independently
- Decannulated in Sept. 2019
- Regained some swallowing ability
- Still very cute and awesome

Acute Flaccid Myelitis Community

- **Facebook community formed in 2014**
  - Grown to over 800 members
  - Provide emotional support
  - Suggestions for vent weaning, therapy, bracing, supplements, nerve transfers
- **Advocacy Efforts**
  - Met with legislators and members of CDC in DC in November 2018
  - Shared parent perspective on CDC's AFM Task Force in December 2018
- **Formed Acute Flaccid Myelitis Association in January 2019**
  - Provide support and advocate for families

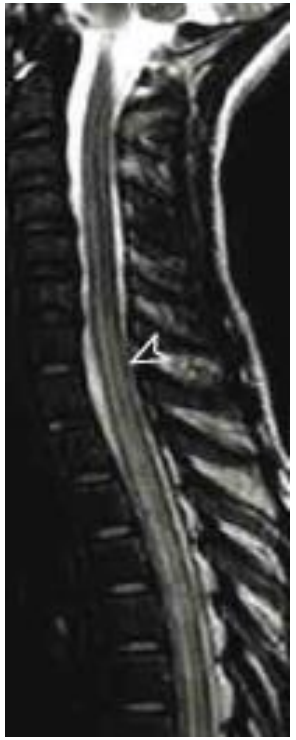
Awareness Saves Lives

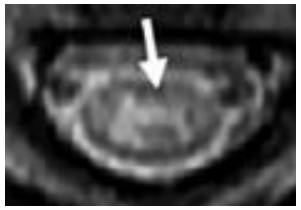
- Corbin was exhibiting symptoms of AFM
- His mother reached out via social media
- She acted quickly and was connected with a knowledgeable neurologist
- Corbin walked out of the hospital

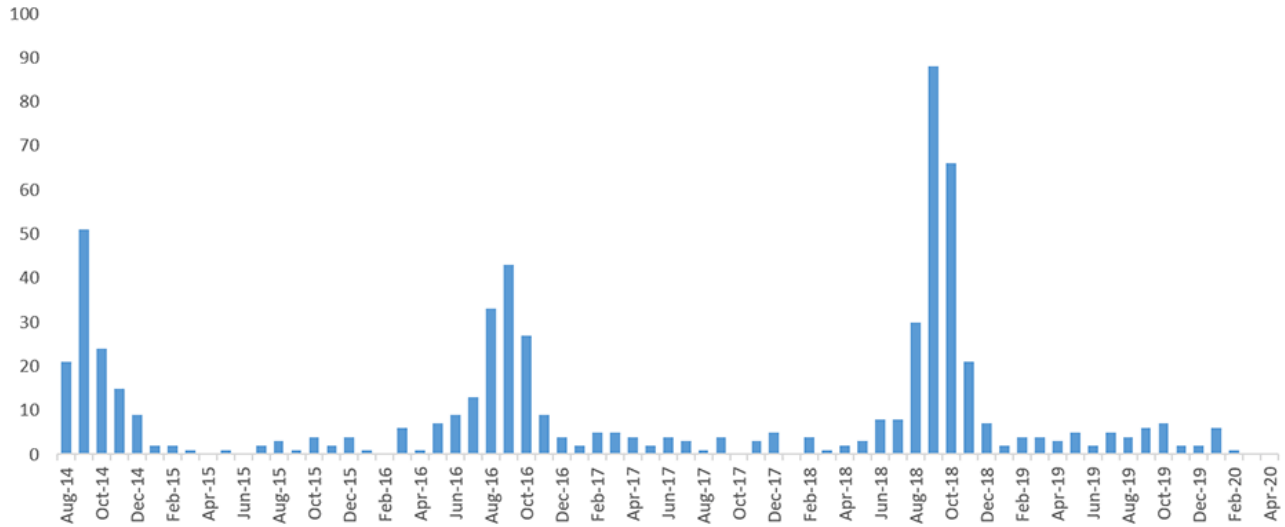
Closing

- **Thank you so much for being here today!**
- **Knowledge about acute flaccid myelitis will lead to improved outcomes for children who will face a life changing diagnosis this summer.**

Clinical Presentation and Diagnosis of Acute Flaccid Myelitis





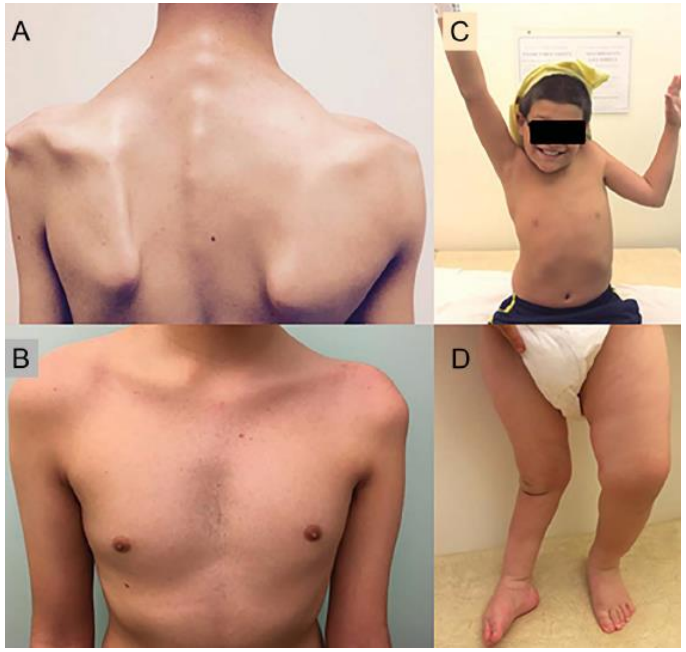


Kevin Messacar, MD

Associate Professor

University of Colorado

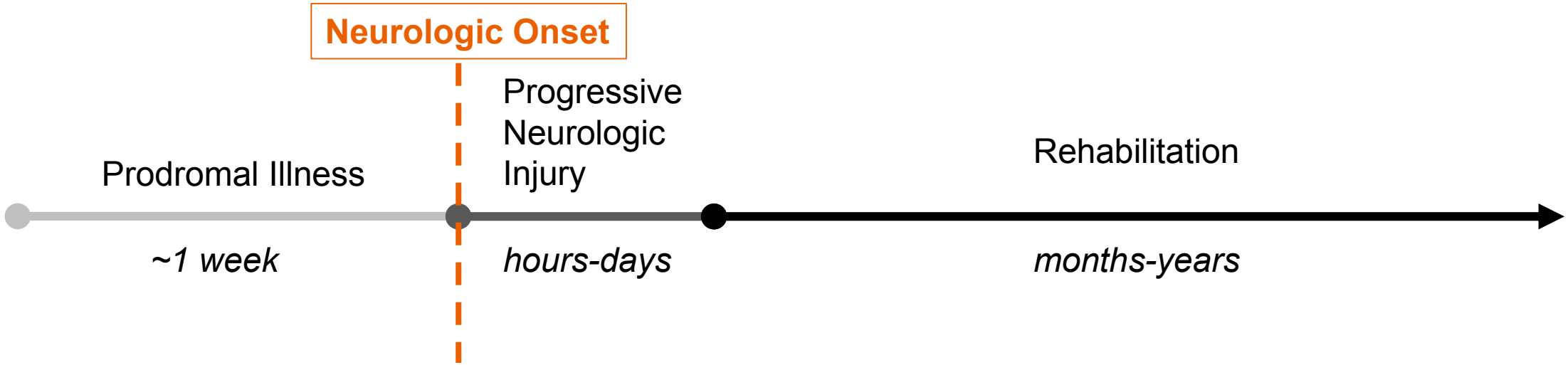
Children's Hospital Colorado



Objectives

- Recognize presenting signs of acute flaccid myelitis
- Order and interpret diagnostic tests to diagnose acute flaccid myelitis
- Identify resources to help manage cases of acute flaccid myelitis
- Report to public health and submit specimens for suspected cases of acute flaccid myelitis

Overview: Clinical Presentation of Acute Flaccid Myelitis



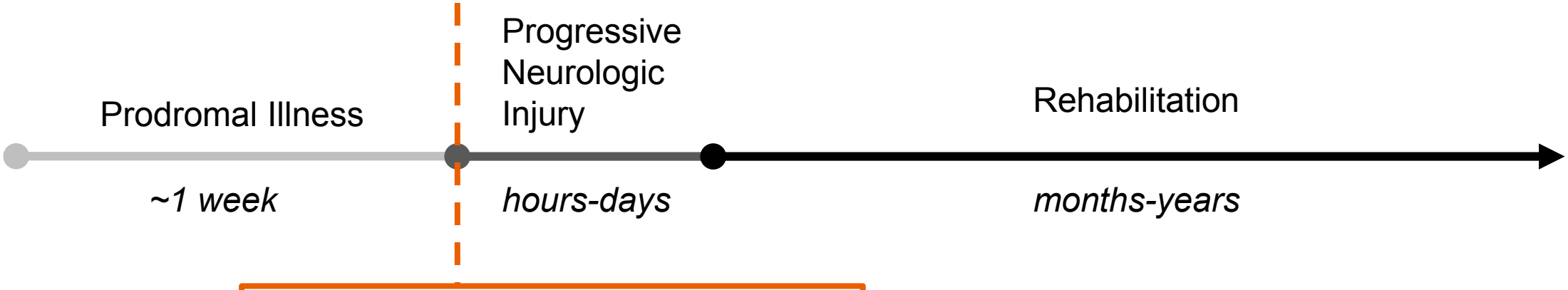
Messacar K, Schreiner TL, Van Haren K, et al. *Annals of neurology*. 2016;80(3):326-338

Acute Flaccid Myelitis: Prodromal Illness

- **Most children have an acute illness preceding AFM**
  - Fever and respiratory symptoms (cough, congestion, sore throat, asthma-like symptoms) in >90%
  - Gastrointestinal symptoms (vomiting, diarrhea) in >30%
  - Hand-foot-mouth lesions in cases associated with some enteroviruses (e.g. EV-A71)
- **Precedes neurologic onset by average of 5-7 days**
- **Prodromal symptoms may improve or resolve prior to neurologic onset**

Messacar K, Schreiner TL, Van Haren K, et al. *Annals of neurology*. 2016;80(3):326-338
McLaren N, Lopez A, Kidd S, et al. *Emerging infectious diseases*. 2020;26(2).

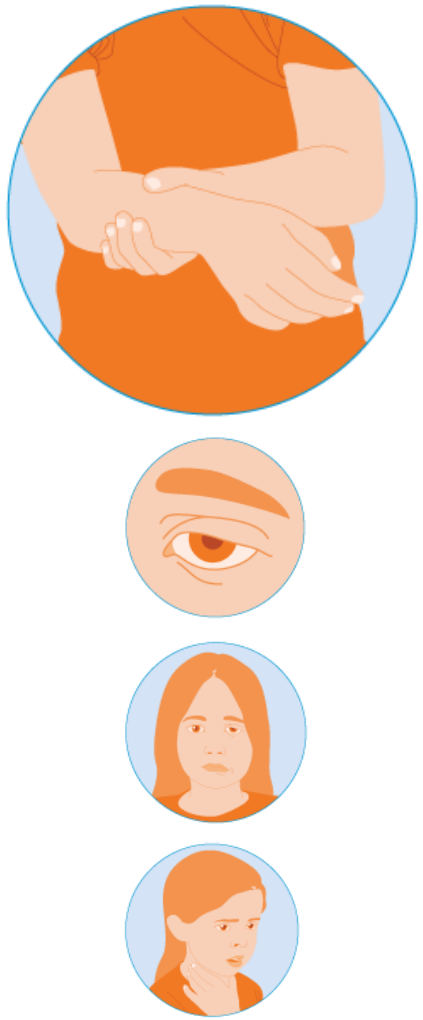
Acute Flaccid Myelitis: Neurologic Onset



- Fever recurrence
- Meningeal signs
  - Headaches, vomiting
  - Stiff neck
  - Back pain
- Pain in limb

Messacar K, Schreiner TL, Van Haren K, et al. *Annals of neurology.* 2016;80(3):326-338

Acute Flaccid Myelitis: Progressive Neurologic Injury



- **Acute onset of flaccid limb weakness**
  - Hypotonic, hyporeflexic
  - Asymmetric
  - Upper extremities more than lower extremities
  - Proximal more than distal
  - Wide spectrum of severity (1→4 limbs, 0/5→4/5 strength)
- **Cranial nerve dysfunction (> 30%)**
  - Eye muscle weakness
  - Facial weakness
  - Bulbar weakness (e.g., difficulty swallowing, drooling, soft voice)
- **Less common: sensory changes, seizures, encephalopathy**

Messacar K, Schreiner TL, Van Haren K, et al. *Annals of neurology*. 2016;80(3):326-338
McLaren N, Lopez A, Kidd S, et al. *Emerging infectious diseases*. 2020;26(2).

Differential Diagnosis: Acute Limb Weakness

- **AFM has been mistaken for:**
  - Musculoskeletal injury (trauma, brachial plexus injury, elbow dislocation)
  - Generalized fatigue, malaise, weakness
  - Psychiatric disorder (conversion, malingering)

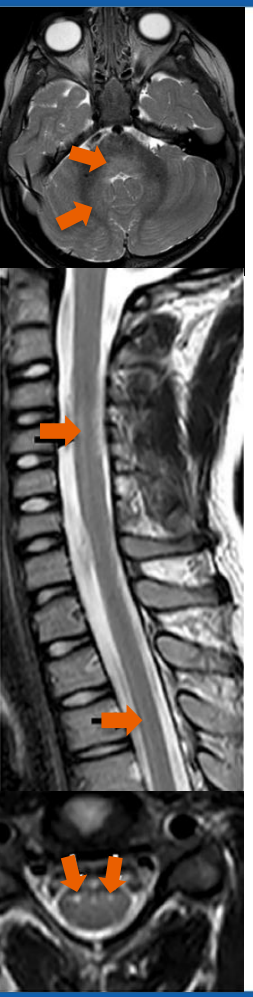
- **Conditions to differentiate from AFM:**
  - Autoantibody myelitis (MOG, NMO)
  - Transverse myelitis
  - Guillain Barré syndrome
  - Acute demyelinating encephalomyelitis
  - Spinal stroke

Careful history (fever) and complete neurologic exam helps differentiate

Clinical, laboratory, and neuroimaging helps differentiate

Hopkins SE. *Curr Treat Options Neurol*. 2017;19(12):48. Hopkins SE, Elrick MJ, Messacar K. *JAMA pediatrics*. 2018.
Elrick MJ, Gordon-Lipkin E, Crawford TO, et al. *JAMA pediatrics*. 2018.

Acute Flaccid Myelitis: Diagnostic Evaluation



AFM Diagnosis

- **Neurologic exam:** flaccid limb weakness
- **Brain/spinal cord MRI:** longitudinal gray matter involvement with/without brainstem lesions
- **Lumbar puncture:** CSF pleocytosis

AFM Etiologic Evaluation

- **Early biological specimen collection**

Maloney JA, Mirsky DM, Messacar K, et al. *American journal of Neuroradiology.* 2015;36(2):245-250.
www.cdc.gov/acute-flaccid-myelitis/downloads/job-aid-for-clinicians-508.pdf

Think AFM? Report AFM!

Report all suspected cases to state health department and submit requested biological specimens

Job Aid for Clinicians

How to send information to the health department about a patient under investigation (PUI) for AFM

1. **Identify PUI for AFM: patient with onset of acute flaccid limb weakness**

2. **Contact your health department when you identify a PUI for AFM. For health department contact information, call the CDC Emergency Operations Center at 770-488-7100.**

https://www.cdc.gov/acute-flaccid-myelitis/downloads/job-aid-for-clinicians-508.pdf

Acute Flaccid Myelitis: Management

Management: Supportive Care

- **Hospitalization during acute phase**
- **Monitor and support respiratory status**
  - Assess gag/ability to protect airway, negative inspiratory force
  - Intubation and mechanical ventilation if respiratory failure
- **Monitor constipation, urinary retention**
  - Bowel regimen, catheterization
- **Support hydration and nutrition**
  - Enteral (tube) feeding
- **Neurology, infectious disease consults**

Murphy O and Pardo CA on behalf of the Acute Flaccid Myelitis Working Group. "Clinical guidance for evaluation, management and rehabilitation of acute flaccid myelitis & establishment of diagnostic criteria" (unpublished), 2020.

Acute Flaccid Myelitis: Treatment and Prevention

Therapeutics

- **No controlled studies of treatment**
  - Immunomodulatory therapies given most commonly: IVIG, steroids, PLEX
  - No approved anti-enteroviral therapies
    - Fluoxetine showed no signal of efficacy
  - AFM Physician Consult and Support Portal

Vaccines

- **Poliovirus vaccine preventable**
  - No EV-A71 or EV-D68 vaccines currently available in US

AFM Physician Consult and Support Portal

The goal of the AFM Physician Support Portal is to **connect medical professionals and offer 24/7 consultation**. If you suspect a case of Acute Flaccid Myelitis (AFM) and would like to **schedule a consult with neurologists specializing in AFM** and other rare neuroimmune disorders, please complete the form below. We will help set up a **peer to peer consult** for clinical support from physicians at the University of Texas Southwestern's Transverse Myelitis Center or Johns Hopkins Myelopathy and Myelitis Center.

www.cdc.gov/acute-flaccid-myelitis/hcp/clinical-management.html#summary-of-interim
Siegel Rare Neuroimmune Association AFM Physician Consult and Support Portal <wearesrna.org/living-with-myelitis/resources/afm-physician-support-portal>
IVIG = Intravenous Immune Globuline; PLEX = plasma exchange

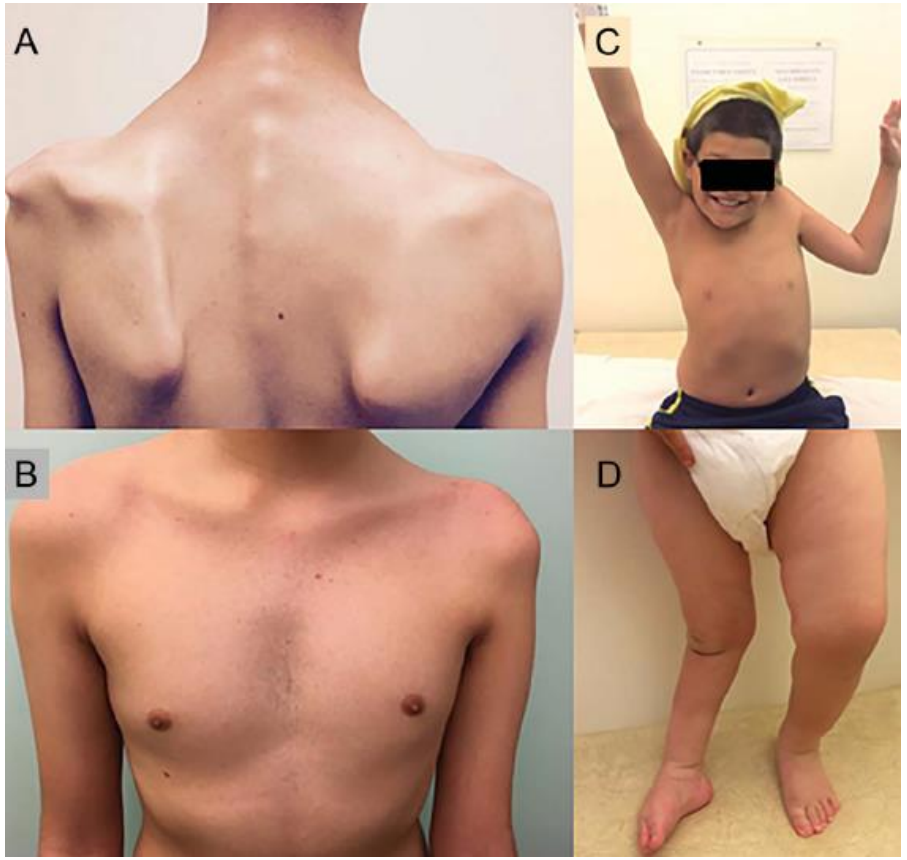
Acute Flaccid Myelitis: Rehabilitation

- **Early, aggressive and continued rehabilitation therapies (physical, occupational, speech, respiratory, psychological therapies)**
- **Nerve and tendon transfer can lead to functional improvements in selected cases**

Martin JA, Messacar K, Yang ML, et al. *Neurology.* 2017;89(2):129-137.
Gordon-Lipkin E, Munoz LS, Klein JL, et al. *Dev Med Child Neurol.* 2018.
Saltzman EB, Rancy SK, Sneag DB, et al. *Pediatric Neurology.* 2018;88:25-30.

Acute Flaccid Myelitis: Outcomes

- **Most show functional improvements**
  - Distal, less-affected muscles more than proximal, more-affected muscles more than completely denervated muscles
- **Most recovery occurs early**
  - Improvements may continue past 12 months
- **Motor deficits persist in ~75%**
  - Few with complete recovery



Polio-like muscle atrophy in affected limbs

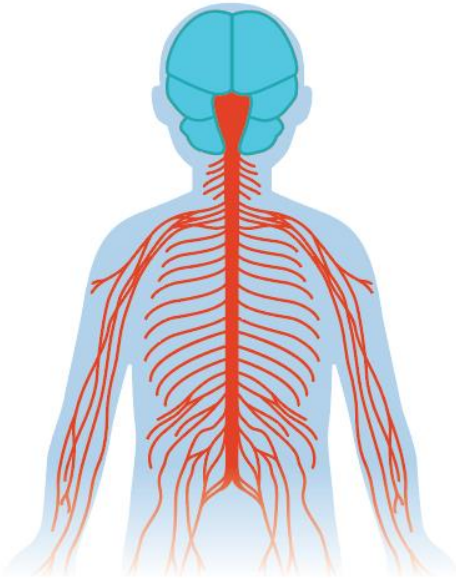
Martin JA, Messacar K, Yang ML, et al. *Neurology*. 2017;89(2):129-137.
Gordon-Lipkin E, Munoz LS, Klein JL, et al. *Dev Med Child Neurol*. 2018.

All Healthcare Providers Need to Recognize AFM

- **THINK AFM** in any patient with new onset weakness, particularly:
  - Children with asymmetric, flaccid weakness
  - Following a febrile illness
  - Summer-fall season during enterovirus outbreaks
- **DIAGNOSE AFM** by careful neurologic exam, neuroimaging, lumbar puncture
  - **Look for cause** by collecting early biologic specimens (CSF, blood, stool, NP/OP)
- **MANAGE AFM** with respiratory and neurological supportive care, rehabilitation
  - **Get help** from neurology and infectious disease consultants, physician support portal
- **REPORT AFM** to your state health department as soon as you suspect it
  - **Submit requested biological specimens** using CDC Job Aid

www.cdc.gov/acute-flaccid-myelitis/hcp/clinicians-health-departments.html NP/OP: nasopharyngeal/oropharyngeal

Building Research Partnerships for Acute Flaccid Myelitis



Emily Erbelding, M.D., M.P.H.

Director

Division of Microbiology and Infectious Diseases (DMID)

NIAID, NIH, HHS

AFM: Pathogenesis

- Enterovirus D68 infection is most likely candidate
- Other enteroviruses (A71) may contribute
- Direct viral effect on motor neurons?
- Or is neuronal damage mediated by the host immune response?
- Is there genetic susceptibility to AFM after EVD68 infection?

More Evidence for a Causal Role of Non-Polio Enteroviruses in AFM

nature medicine

Letter | Published: 21 October 2019

Pan-viral serology implicates enteroviruses in acute flaccid myelitis

Ryan D. Schubert, Isobel A. Hawes, [...] Michael R. Wilson

Nature Medicine **25**, 1748–1752(2019) | Cite this article

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio AN OPEN ACCESS JOURNAL PUBLISHED BY THE AMERICAN SOCIETY FOR MICROBIOLOGY

Research Article | Clinical Science and Epidemiol

Antibodies to Enteroviruses in Cerebrospinal Fluid of Patients with Acute Flaccid Myelitis

Nischay Mishra, Terry Fei Fan Ng, Rachel L. Marine, Komal Jain, James Ng, Riddhi Thakkar, Adrian Caciula, Adam Price, Joel A. Garcia, Jane C. Burns, Kiran T. Thakur, Kimbell L. Hetzler, Janell A. Routh, Jennifer L. Konopka-Anstadt, W. Allan Nix, Rafal Tokarz, Thomas Briese, M. Steven Oberste, W. Ian Lipkin

Christine A. Biron, Editor

DOI: 10.1128/mBio.01903-19 Check for updates

More Evidence for a Causal Role of Non-Polio Enteroviruses in AFM

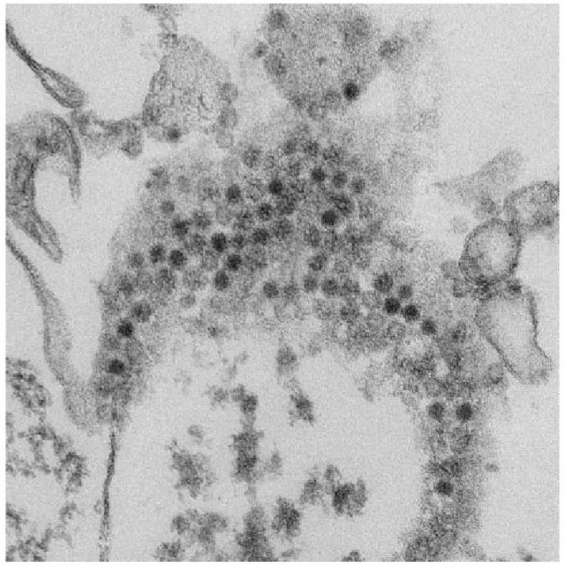
National Institute of Allergy and Infectious Diseases

July 23, 2019

News Release

NIH Awards Contract for Acute Flaccid Myelitis Natural History Study

- $10 million over 5 years to University of Alabama at Birmingham (UAB) to organize and implement an international, multi-site study
- UAB's David Kimberlin, MD is PI; Carlos Pardo-Villamizar, MD of Johns Hopkins is co-PI

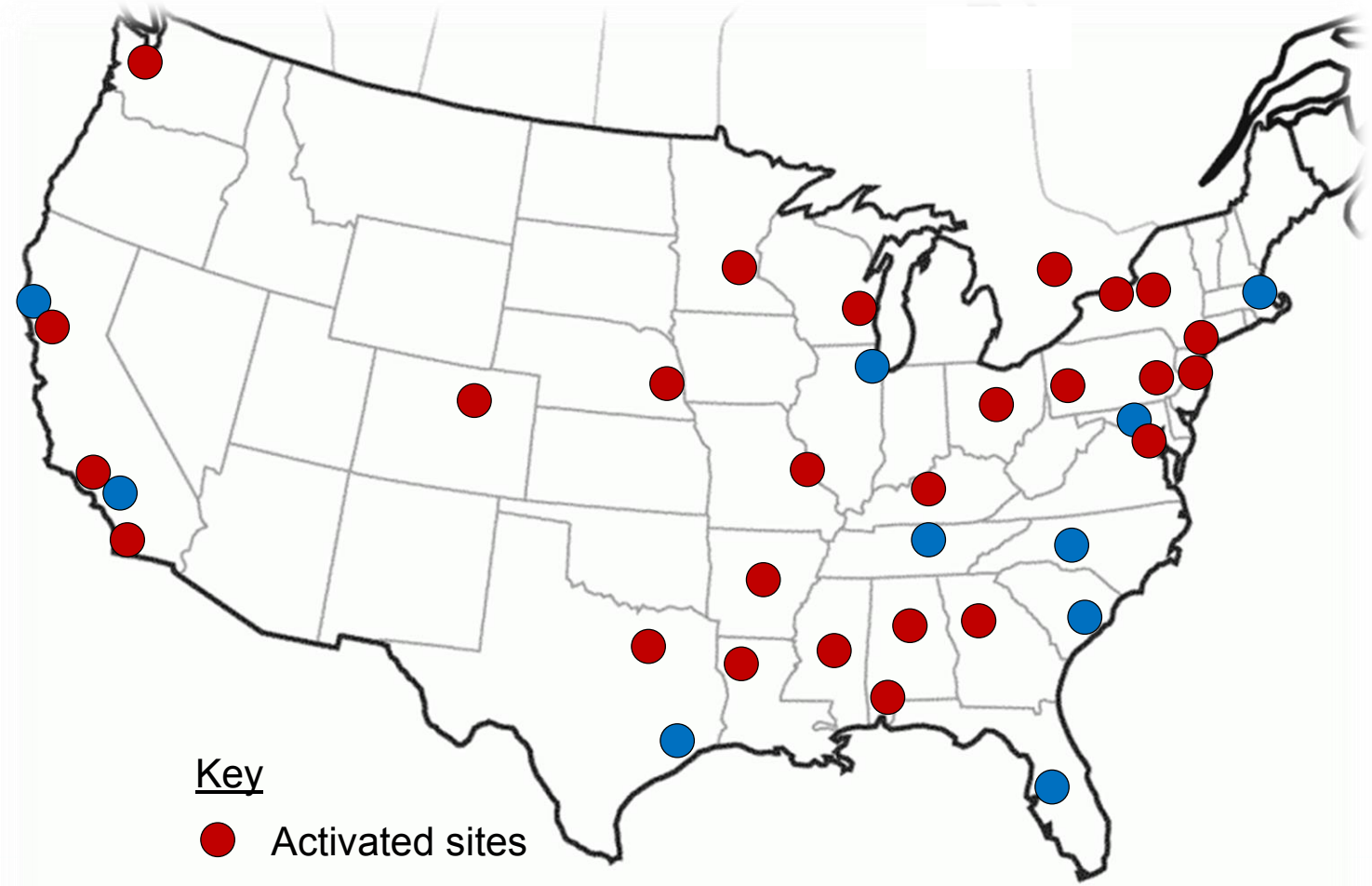


AS Fauci/NIAID

Natural History Study: Objectives

- To characterize the natural history of AFM in the first 12 months following enrollment.
- To describe the clinical diagnostic evaluations and therapeutic interventions for suspected AFM cases.
- To identify risk factors for development of AFM.
- To identify determinants of outcome of AFM.
- To describe the clinical characteristics of household contacts of patients being evaluated for AFM.
- To establish a biorepository of samples to support further investigation

AFM Study Sites



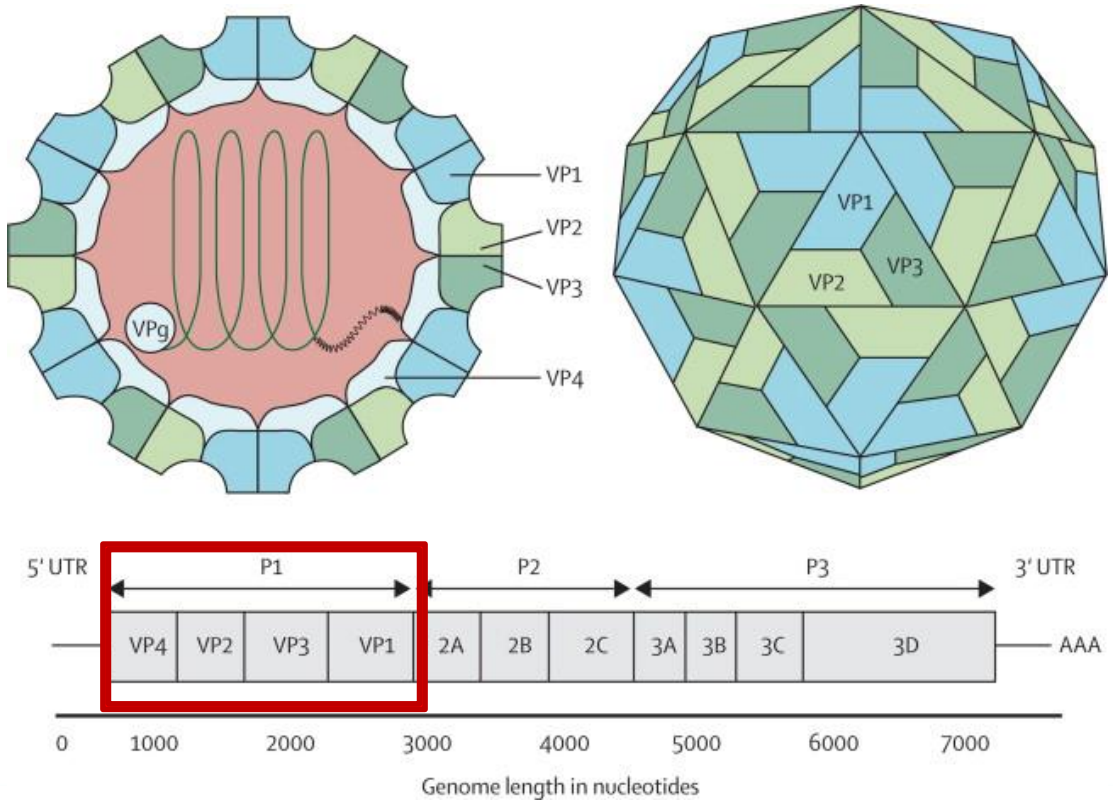
Updated May 26, 2020

Vaccine Development

- **Whole inactivated EV-D68 vaccine:**
  - Currently utilizing preclinical services to obtain new isolates from CDC, and identify cell line for manufacturing
  - BAA issued to support vaccine manufacturing
- **Virus-like particle (VLP) vaccine prototype:**
  - VRC scientists are currently refining and characterizing VLPs expressed and self-assembled from EV-D68 structural protein sequences.

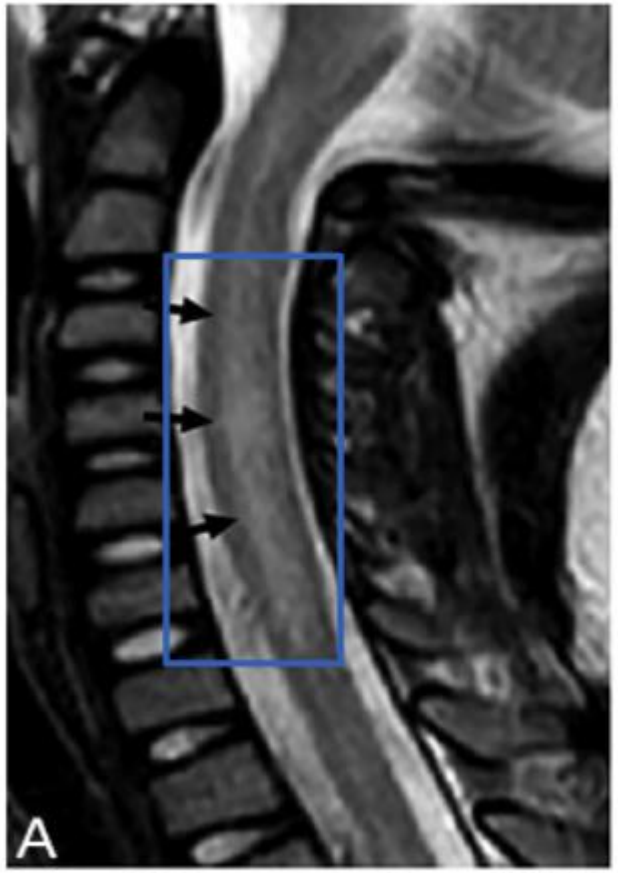
Vaccine Development

- Orderly antigen arrays are immunogenic
- Quaternary epitopes preserved
- Licensed VLP products
  - Insect, yeast, and bacterial cells
- Structures available
- Protein engineering may provide basis for generalizable design



NIAID Workshop on AFM Preparedness

- **February 19, 2020; Rockville, MD**
- **Objectives**
  - Determine research priorities
  - Catalyze development of countermeasures
  - Generate discussion regarding use of countermeasures



JA Maloney et al., *Am J Neuroradiol* (2015).

AS Fauci/NIAID

Remaining Research Questions - I

- What changed in 2014 for a rise in cases of AFM? Will every-other-year periodicity continue?
- What is different about a host that gets AFM from a host that does not get AFM after EV infection?
- What are the B and T cell responses/epitopes in EV-mediated AFM?

Remaining Research Questions - II

- What is the fundamental pathophysiology of non-polio enterovirus mediated AFM? What is the role of direct viral infection of cells vs. immune mediated damage?
- What is the mechanism of viral spread to the CNS?
- Why are anterior horn cells targeted by EV-D68? Could other cells (interneurons, myocytes) also be infected?
- Are mutations in EV-D68 over time antigenically significant?
- How narrow is timing of therapeutic window for treating AFM?

Summary

- Collaborations among government, academic and parent partners have strengthened AFM research efforts
- Ongoing efforts:
  - Develop large and small (e.g., mouse) animal models
  - Improve diagnostic testing
  - Develop and test monoclonal antibodies and other enteroviral therapeutics
  - Vaccine development
  - Test new approaches to rehabilitation