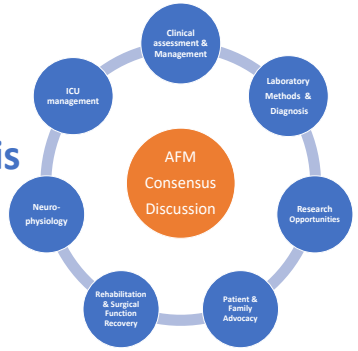
Acute Flaccid Myelitis Working Group




JOHNS HOPKINS MEDICINE

Johns Hopkins Myelitis & Myelopathy Center

# Acute Flaccid Myelitis:

## AFM Preparedness for 2020 and Beyond

**Carlos A. Pardo, MD**

Division of Neuroimmunology and Neuroinfectious Disorders

Johns Hopkins Myelitis and Myelopathy Center

# Educational objectives

- An update on preparedness for AFM outbreaks
  - Our response
  - Diagnosis and management
  - Public health effort and research
  - The future on management

# Disclosures

**Comercial Disclosures:**

- None

**Research Support Disclosures unrelated with this lecture:**

- National Institutes of Health, NINDS/Fogarty

## FUNDING

Johns Hopkins Myelitis & Myelopathy Center

The Johns Hopkins PROJECT RESTORE
*Restoring hope, function, and lives to MS & TM patients*

**Bart McLean Fund for Neuroimmunology Research**

THE TRANSVERSE MYELITIS ASSOCIATION

SRNA connect. care. cure. | Siegel Rare Neuroimmune Association

# Acute Flaccid Myelitis

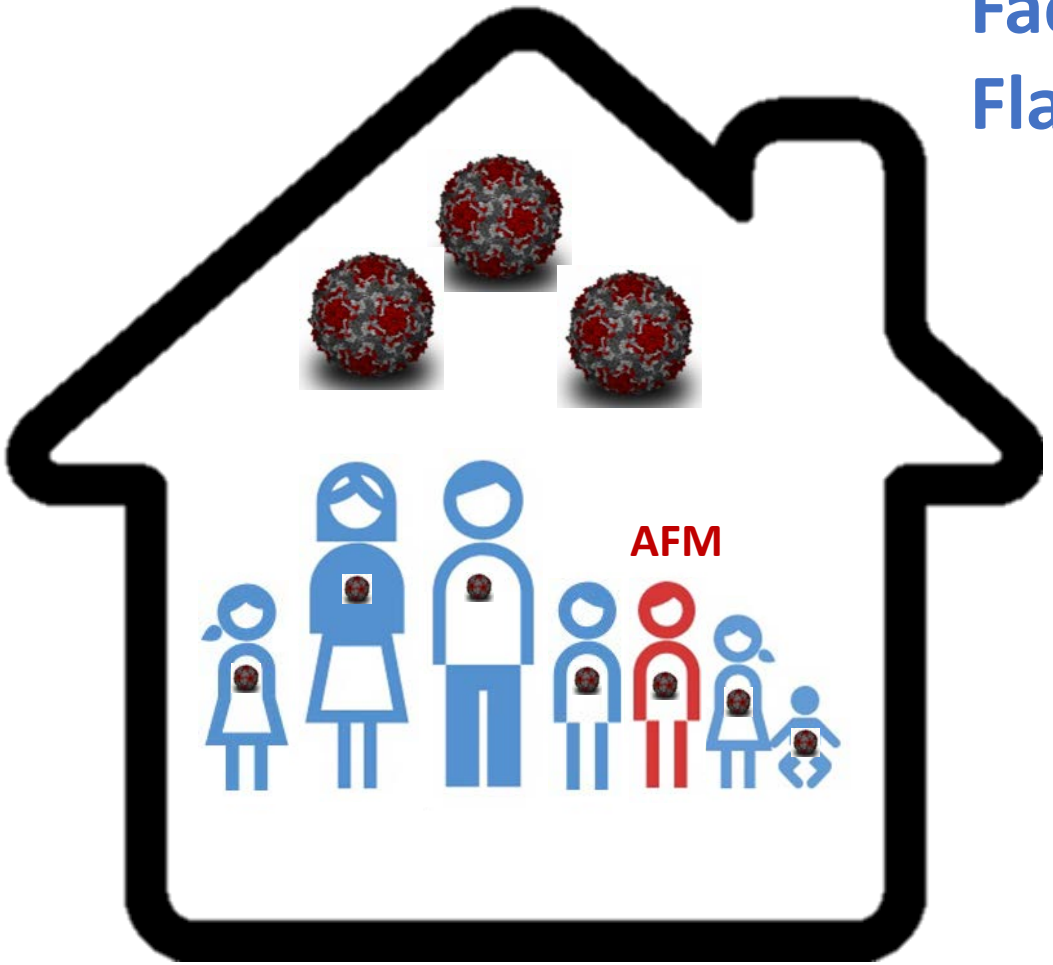
In most of the cases of AFM there is preceding history of upper respiratory Infection in almost all member of the Household

- **Age 1-12 ys in average**
- **No sex predilection ; Male:Female**

Environmental factors associated

- **Seasonality**

# Factors in Acute Flaccid Myelitis



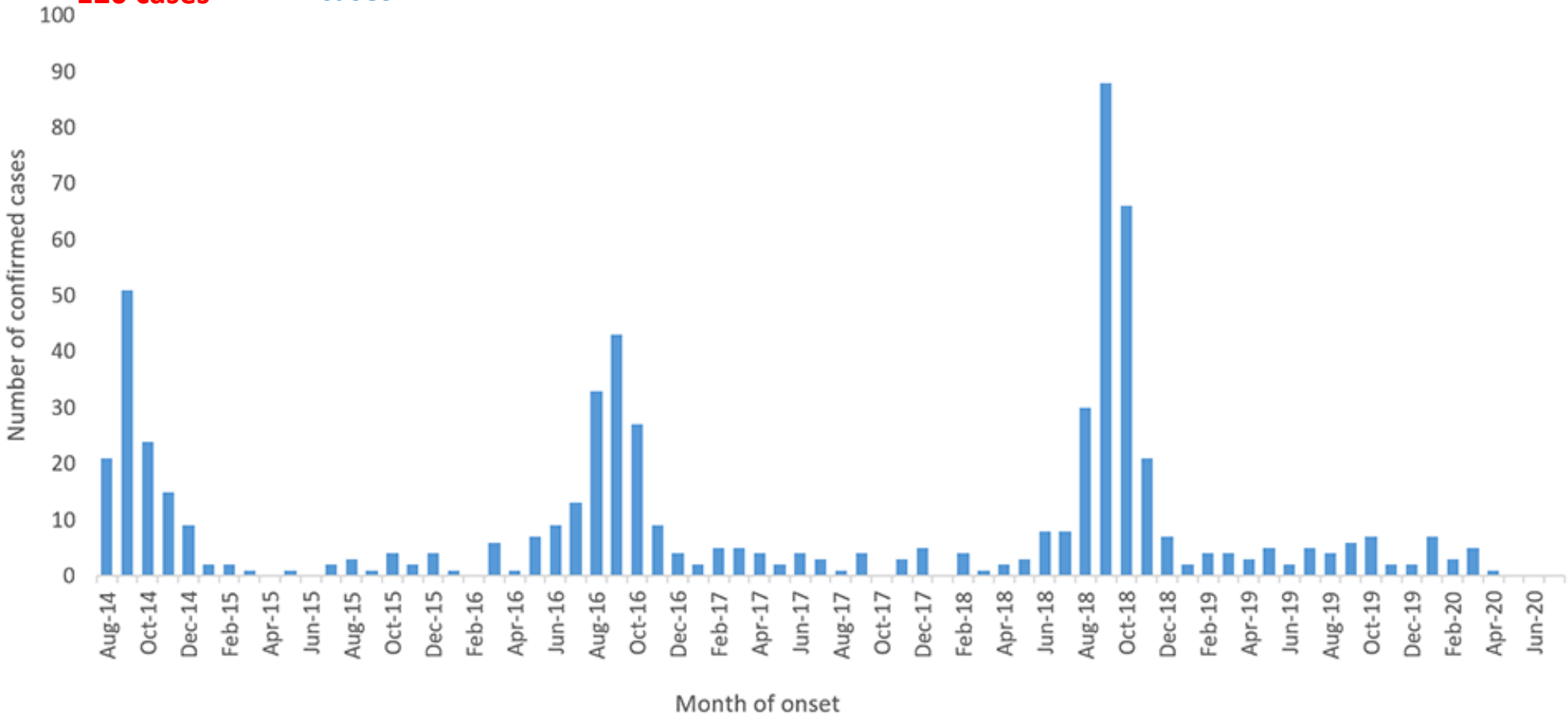

After many members of a household are affected by infectious symptoms only one subject is affected by AFM

# Epidemiology of AFM in the USA: 2014-present

## Aug 2014 – July 2020 (n > 630)

https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html
Data current as of July 31, 2020

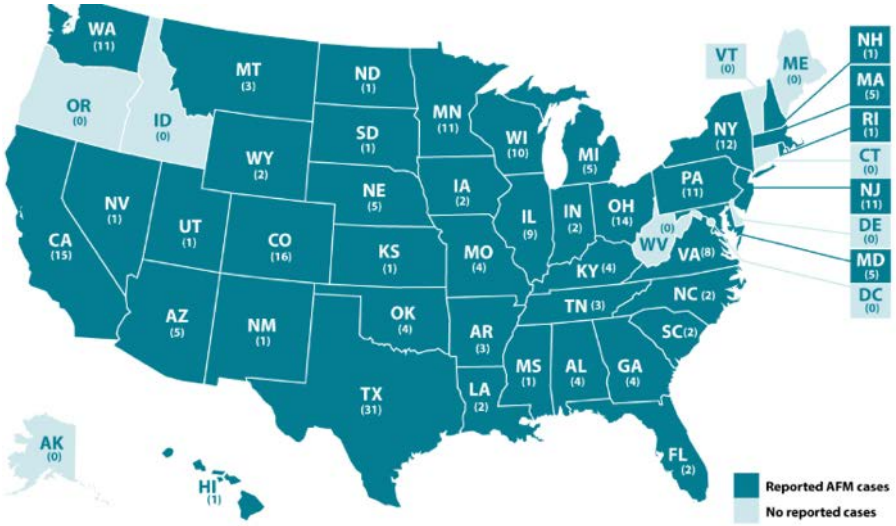
**2014:** **120 cases** | **2015:** 22 cases | **2016:** 153 cases | **2017:** 38 cases | **2018:** 238 cases | **2019:** 46 cases | **2020:** 16 cases..?



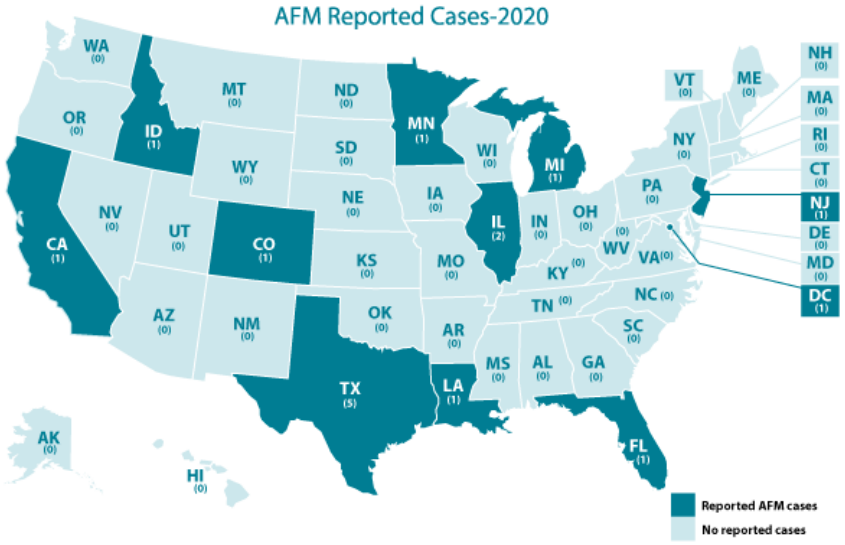
# Epidemiology of AFM in 2028 (n=238) and 2020 (n=16)

## Widespread distribution in 42 states in 2018

**2018**

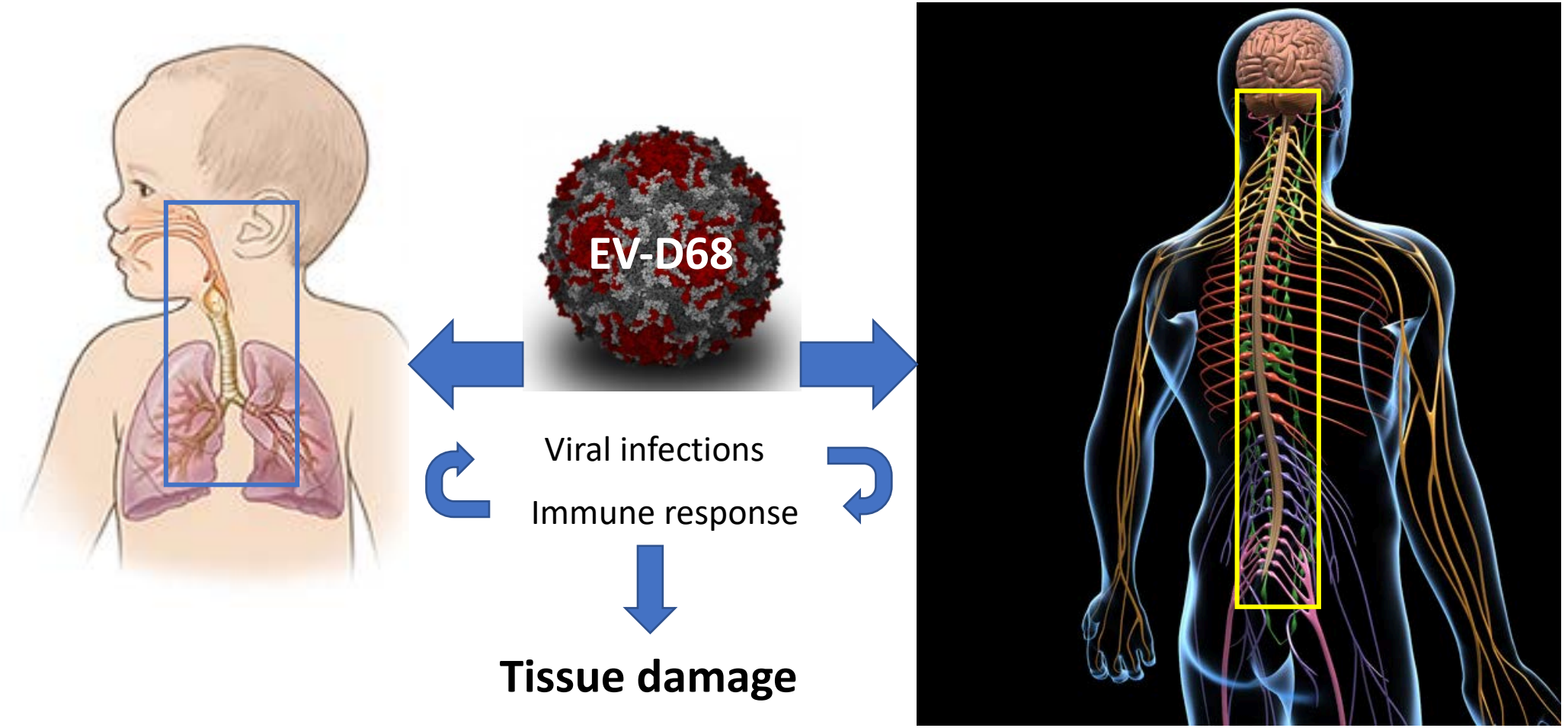



**2020**

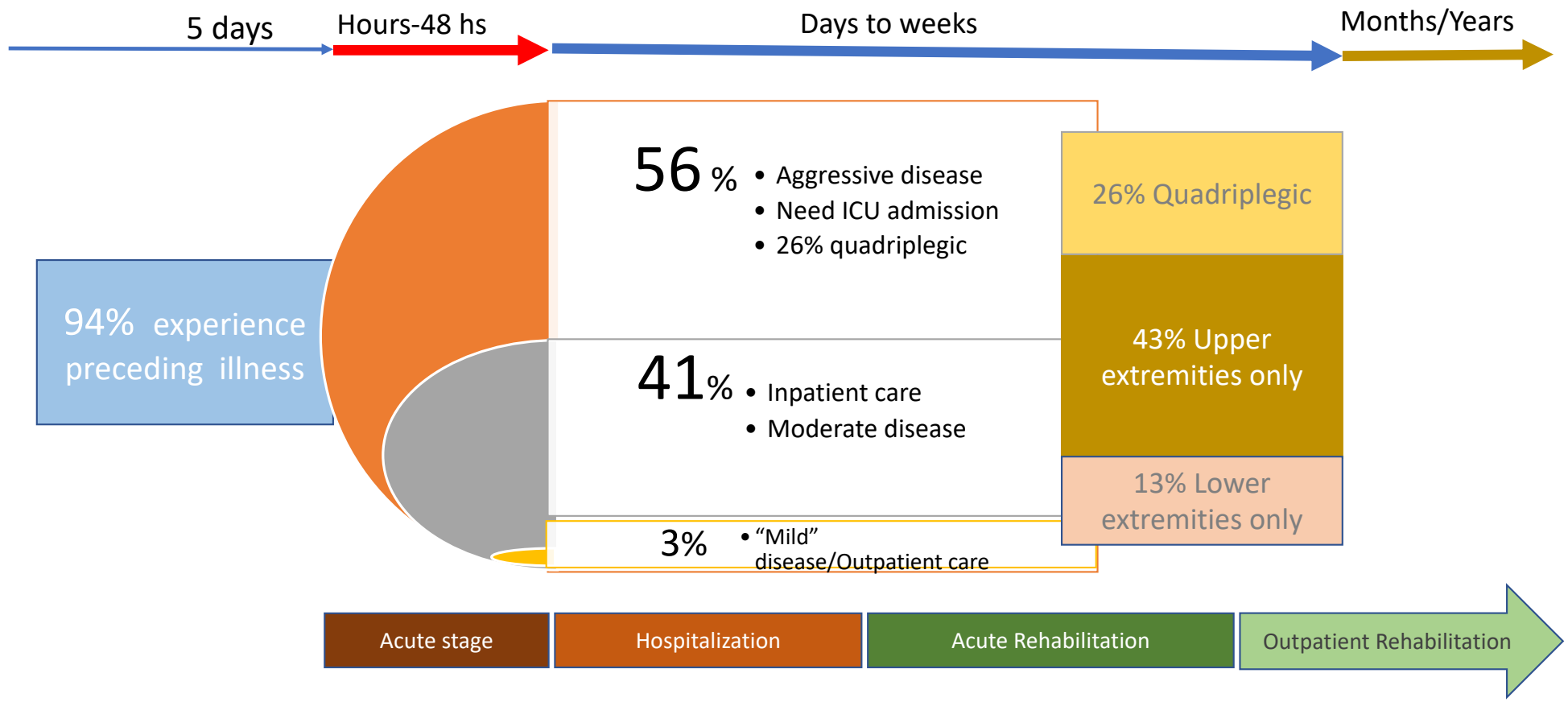



https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html
Data current as of June 1, 2020

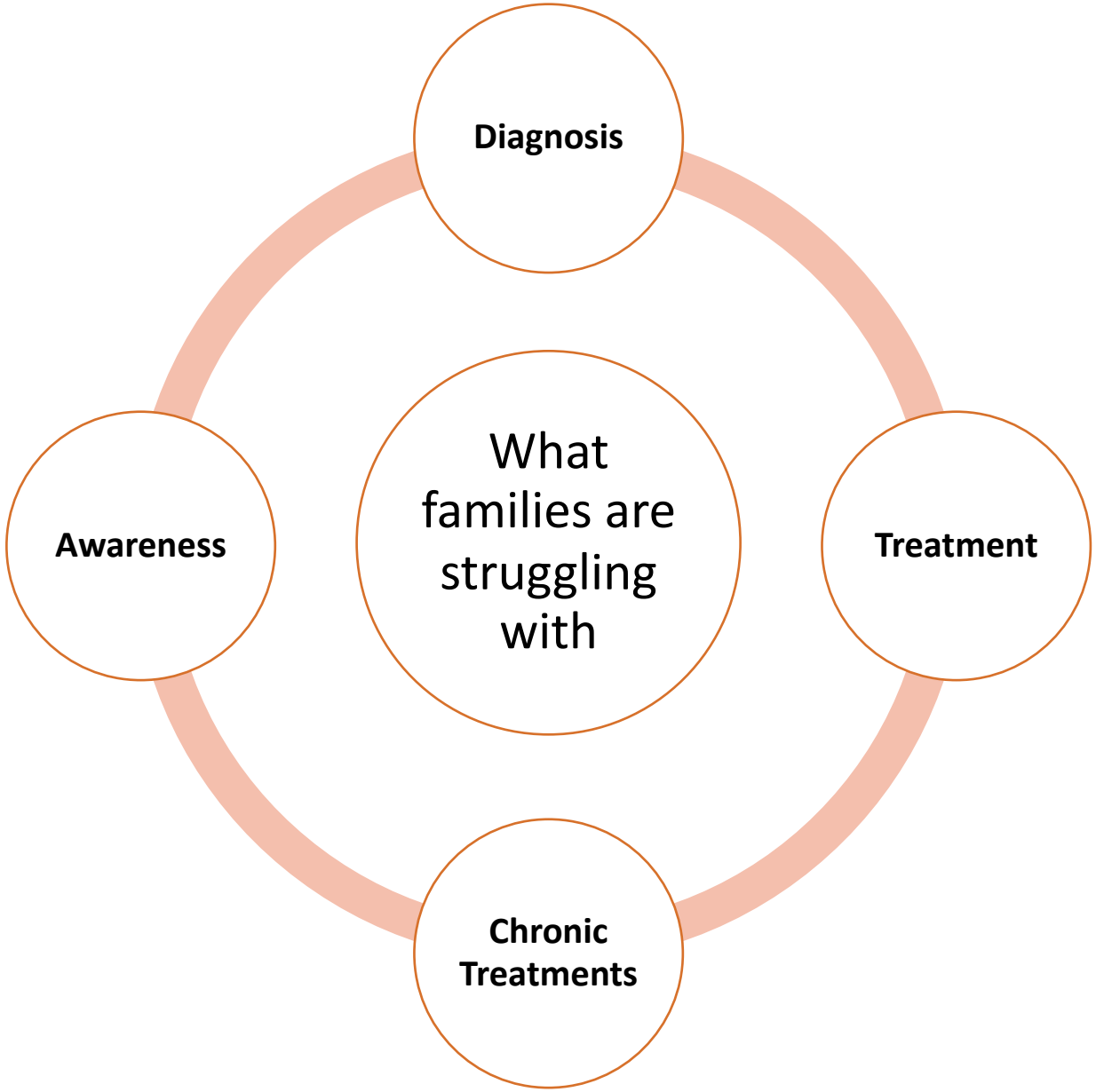
# Tissue susceptibility to Enterovirus-D68 Infection

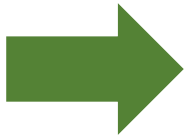


# The Clinical Profile of Acute Flaccid Myelitis 2018

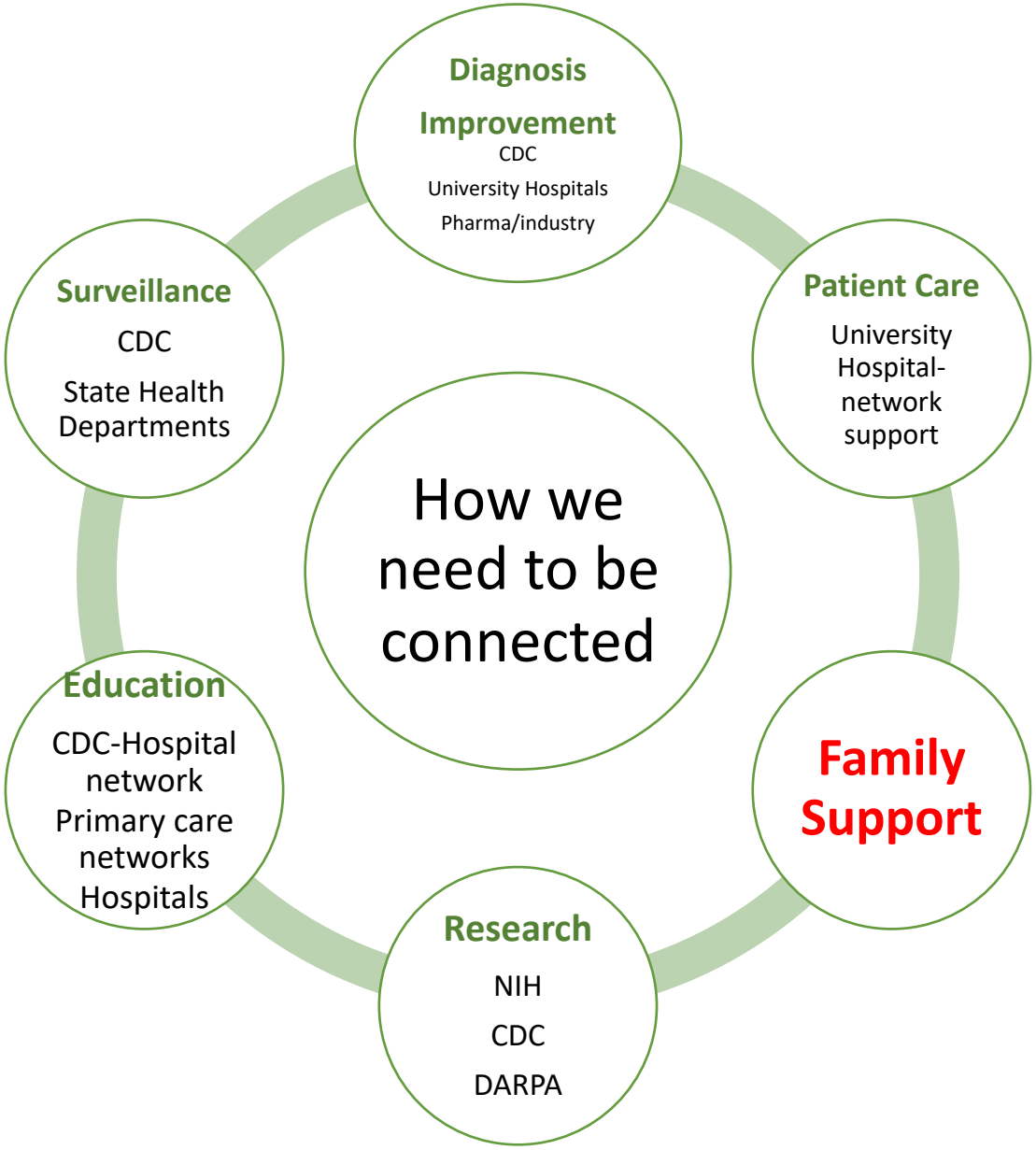


# What do we need?



# What do we need?



# Acute Flaccid Myelitis Working Group


## A model of horizontal collaboration to achieve consensus on the clinical diagnosis, management and research focused on acute flaccid myelitis (AFM)

**Objectives:**

- To establish a consensus for diagnosis and management of AFM during the acute and chronic stages of disease
- Conceive, develop, and conduct collaborative clinical studies to understand the natural history of AFM
- To facilitate clinical and basic science research to accelerate the discovery of treatment approaches in AFM

# AFM Working group Network

- Mayo Clinic (Rochester, MN)
- Children's Hospital of Wisconsin (Milwaukee)
- The Hospital for Sick Children (SickKids), U. of Toronto (Canada)

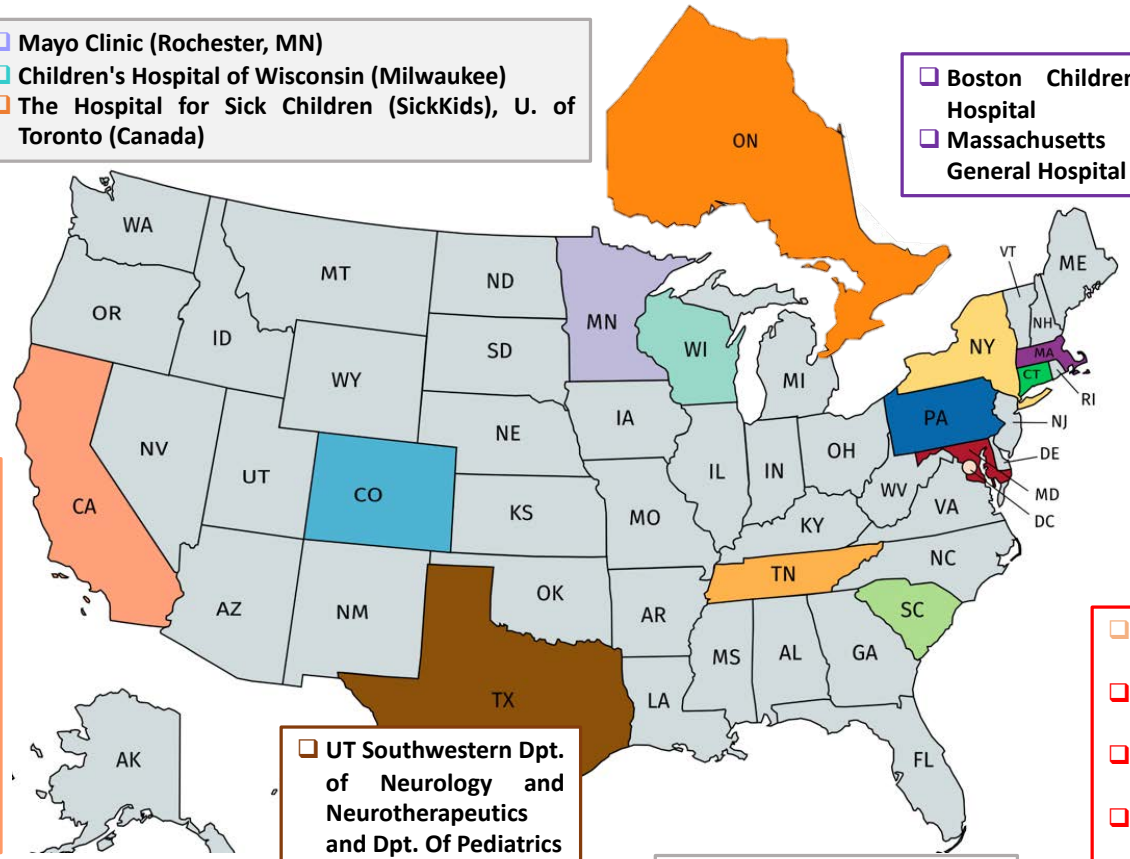
- Children's Hospital Colorado (Aurora)
- University of Colorado, Dept. of Neurology (Aurora)

- Boston Children's Hospital
- Massachusetts General Hospital

- Columbia University, Dept. of Neurology
- Columbia University Vagelos College of P &S
- Weill Cornell School of Medicine
- Mt. Sinai Hospital

- Yale School of Medicine, Dept. of Pediatrics and Neurology
- Children's Hospital of Philadelphia
- University of Pennsylvania, Dept. of Neurology

- UCSF Benioff Children Hospital
- Kaiser Permanente San Francisco Medical Center
- Stanford University, Dept. of Neurology and Pediatrics
- Children's Hospital Los Angeles
- J. Craig Venter Institute, La Jolla




- UT Southwestern Dpt. of Neurology and Neurotherapeutics and Dpt. Of Pediatrics

- Vanderbilt University Medical Center (Nashville)
- Medical University of South Carolina (Charleston)

- Children's National Medical Center (Washington, DC)
- Johns Hopkins University School of Medicine (Baltimore)
- Johns Hopkins Bloomberg School of Public Health (Baltimore)
- Kennedy-Krieger Institute (Baltimore)
- Sinai Hospital, Dept. of Pediatric Neurology (Baltimore)
- National Institutes of Health (Bethesda)

# A Consensus on Clinical Diagnosis of Acute Flaccid Myelitis 2020

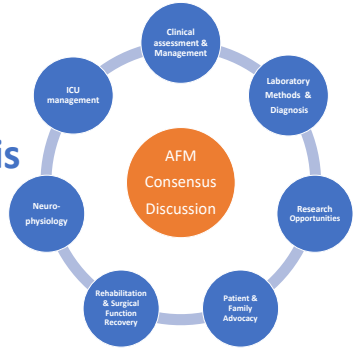
Acute Flaccid Myelitis Working Group


| Diagnostic Items | Level of Diagnostic Certainty | | | |
|---|---|---|---|---|
| | **Definite** | **Probable** | **Possible** | **Uncertain** |
| **H1:** Acute onset of limb(s) weakness (Period from onset to nadir: Hours to ten days) | P | P | P[a] | P |
| **H2:** Prodromal fever or illness[b] | P/A | P/A | P/A | P |
| **E1:** Weakness involving one or more limbs, neck, face, and/or cranial nerves | P | P | P[a] | P |
| **E2:** Decreased muscle tone in at least one weak limb | P | P | P/A | P |
| **E3:** Decreased or absent deep tendon reflexes in at least one weak limb[c] | P | P | P/A | P |
| **MRI:** Spinal cord lesion with predominant gray matter involvement, with or without nerve root enhancement[d] | P | P | P | ND |
| **CSF:** Pleocytosis (white cell count > 5 cell/L)[e] | P | A or ND | P/A or ND | P/A or ND |
| **Abbreviations:**<br>**H:** History, **E:** Examination, **CSF:** cerebrospinal fluid<br>**P:** Diagnostic element is present, **A:** Diagnostic item is absent<br>**P/A:** Presence of this diagnostic element is supportive but not required, **ND:** Test was not done | | | | |
| **Factors that may suggest an alternative diagnosis** | | | | |
| **1:** Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities, or medications. | | | | |
| **2:** Presence of sensory deficits on exam.[f] | | | | |
| **3:** Lesions in supratentorial white matter or cortex should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others. | | | | |
| **4:** Lack of CSF pleocytosis should prompt consideration of Guillain-Barré syndrome, botulism, ischemic cord lesions, and others. | | | | |
| **5:** Positive serum aquaporin-4 (AQP-4) antibody will exclude AFM. | | | | |
| **6:** Positive serum myelin oligodendrocyte glycoprotein (MOG) antibody suggests MOG-antibody associated disease.[f] | | | | |

Murphy O. et. al. Under review, 2020

# A Consensus on Management of Acute Flaccid Myelitis 2020

Acute Flaccid Myelitis Working Group

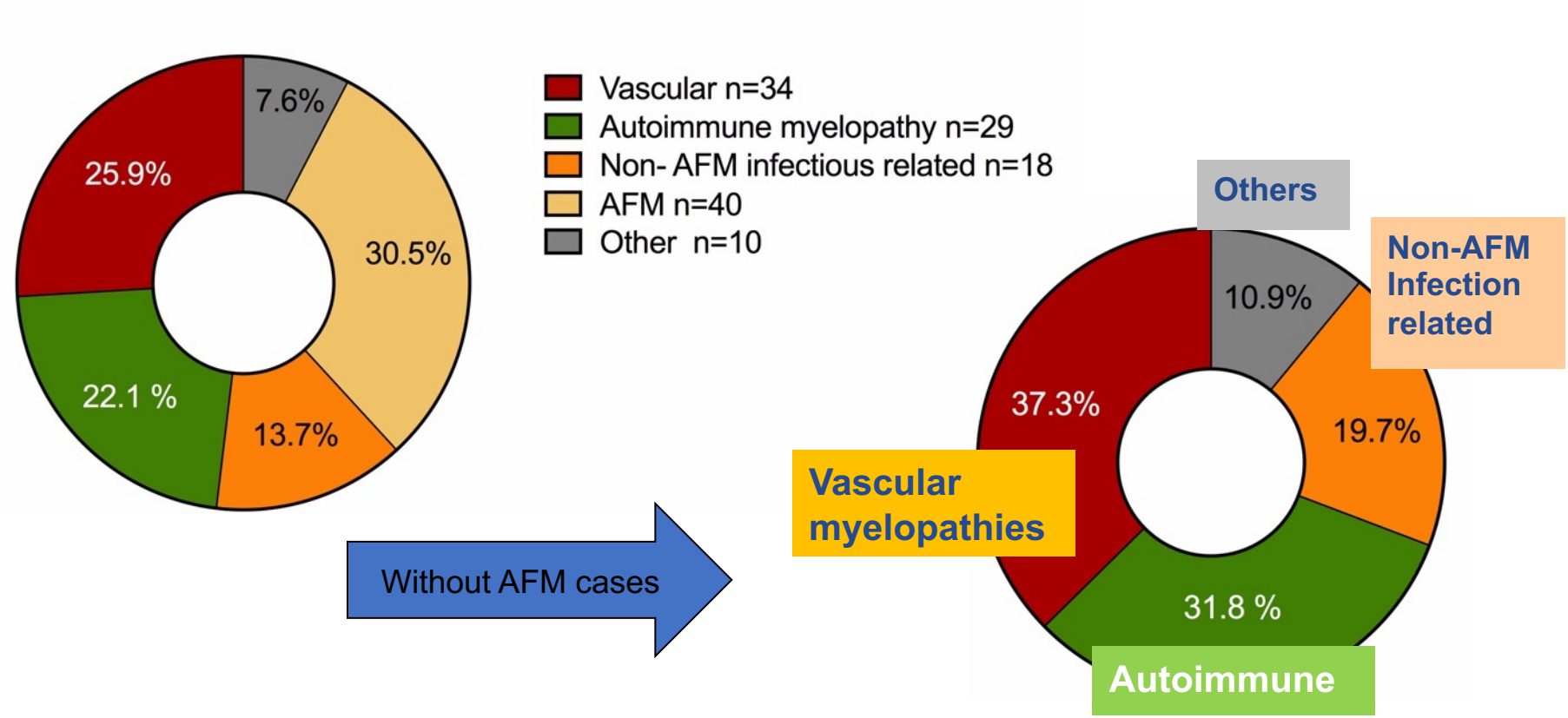



Murphy O. et. al. Under review, 2020

- Acute Management
  - Respiratory status
  - Sedation
  - Pain and autonomic dysfunction
  - Immunomodulatory and antiviral therapies
  - Early rehabilitation
- Inpatient rehabilitation
- Nerve and tendon transfer surgeries
- Medium and long-term rehabilitation
- Long-term medical management

# AFM has changed the spectrum of pediatric myelopathies:

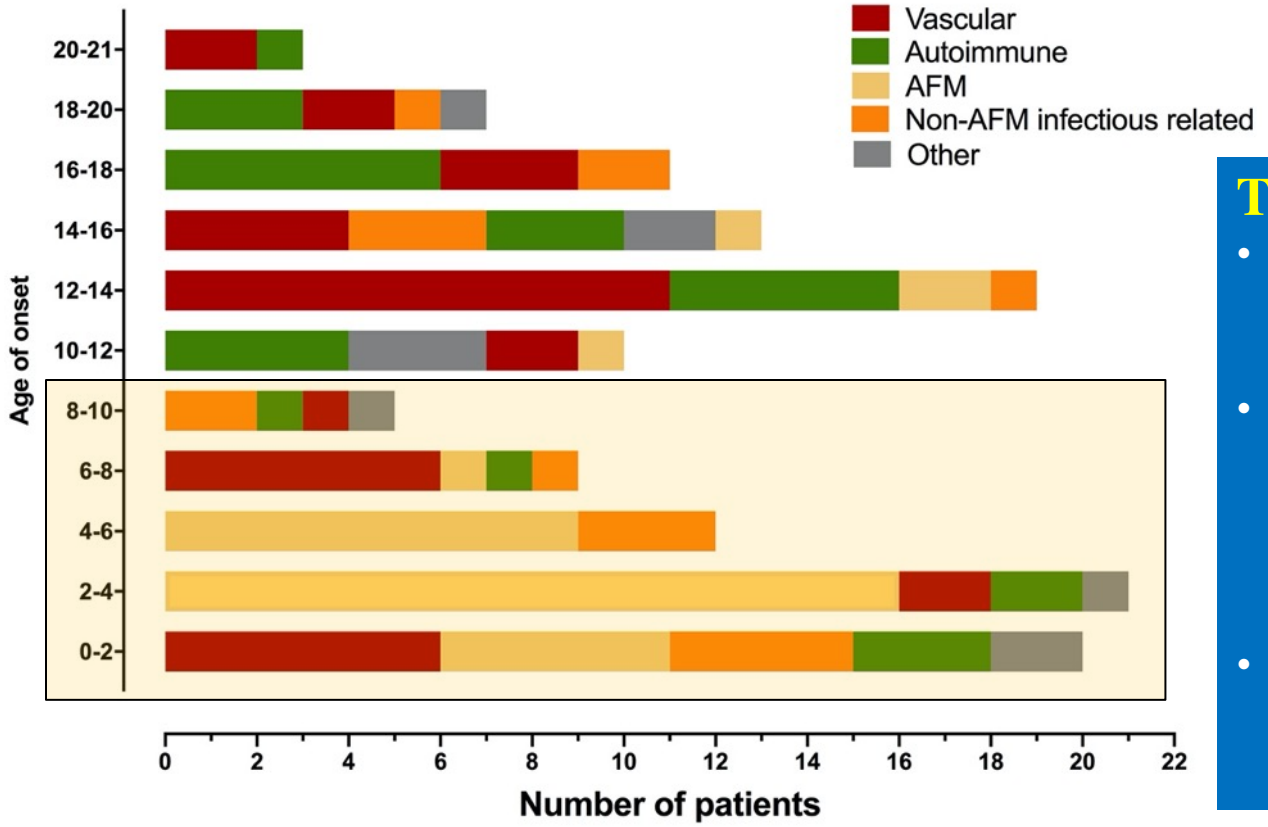
## Age-profile in patients at JHMMC 2010-2018




Garcia-Dominguez, M, Gordon-Lipkin E, Murphy O, Pardo CA et al. JHM&M Center 2019, unpublished

# Pediatric Myelopathies:

## Age-profile in patients at JHMMC 2010-2018
## n=131 patients

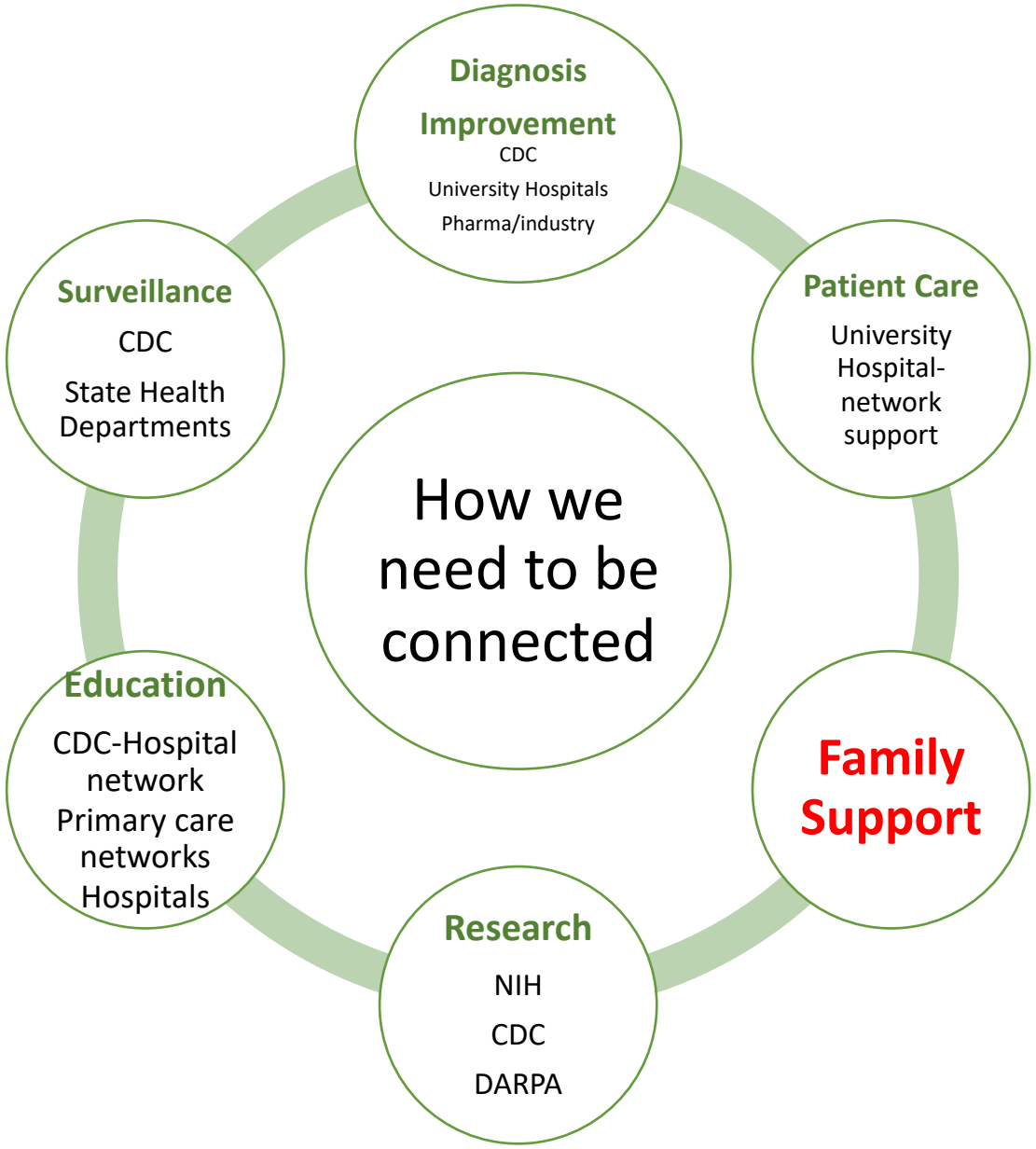



**Take-home message:**

- Vascular and inflammatory myelopathies occur at all spectrum of ages in children
- Since 2014, AFM has changed the epidemiology of myelitis in the USA. AFM occurs mostly in very young children.
- Vascular and autoimmune myelopathies are frequent in older children and teenagers.

Garcia-Dominguez, M, Gordon-Lipkin E, Murphy O, Pardo CA et al. JHM&M Center 2019, unpublished

# ….there is a long road in front of us for understanding AFM




**What do we need to learn about AFM?**

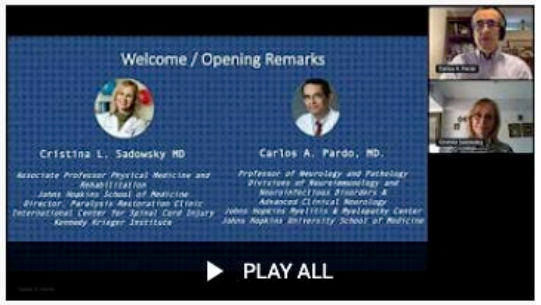
- What is the role of viruses in pathogenesis?
- How the immune system is involved in AFM?
- How to improve diagnosis?
- Factors associated with prognosis and outcomes
- Strategies to improve diagnosis
- Strategies to improve treatments and outcomes
- Development of preventive measures and possible vaccines

# Acute Flaccid Myelitis:

## What we have learned in order to be prepared

Google: AFM Virtual Symposium Youtube

SRNA connect. care. cure. | Siegel Rare Neuroimmune Association




2020 AFM Virtual Symposium – Part I

14 videos • 164 views • Last updated on Jun 14, 2020


2020 AFM Virtual Symposium – Part II

10 videos • 47 views • Last updated on Jun 15, 2020


2020 AFM Virtual Symposium – Part III

12 videos • 105 views • Last updated on Jun 20, 2020


2020 AFM Virtual Symposium – Part IV

14 videos • 46 views • Updated 7 days ago

**Acute Flaccid Myelitis Working Group**

# Acute Flaccid Myelitis:
## What we have learned in order to be prepared

SRNA connect. care. cure. | Siegel Rare Neuroimmune Association

Google: AFM Virtual Symposium Youtube

Part I https://www.youtube.com/playlist?list=PLXi60bECkjnWc16yfgMVN1u7qOuRM8d14

Part II https://www.youtube.com/playlist?list=PLXi60bECkjnVje4VHjzW5pzkeYtSJBdqt

Part III https://www.youtube.com/playlist?list=PLXi60bECkjnV2Iqm1SxKm_V2QvDHfg3yR

Part IV https://www.youtube.com/playlist?list=PLXi60bECkjnVwvAk3_fPWS700NR6JeBaS

Part V https://www.youtube.com/playlist?list=PLXi60bECkjnVSYQ3C8lte69RmWbaguX_I

# NIH Natural History Study of AFM
# DMID #19-0005

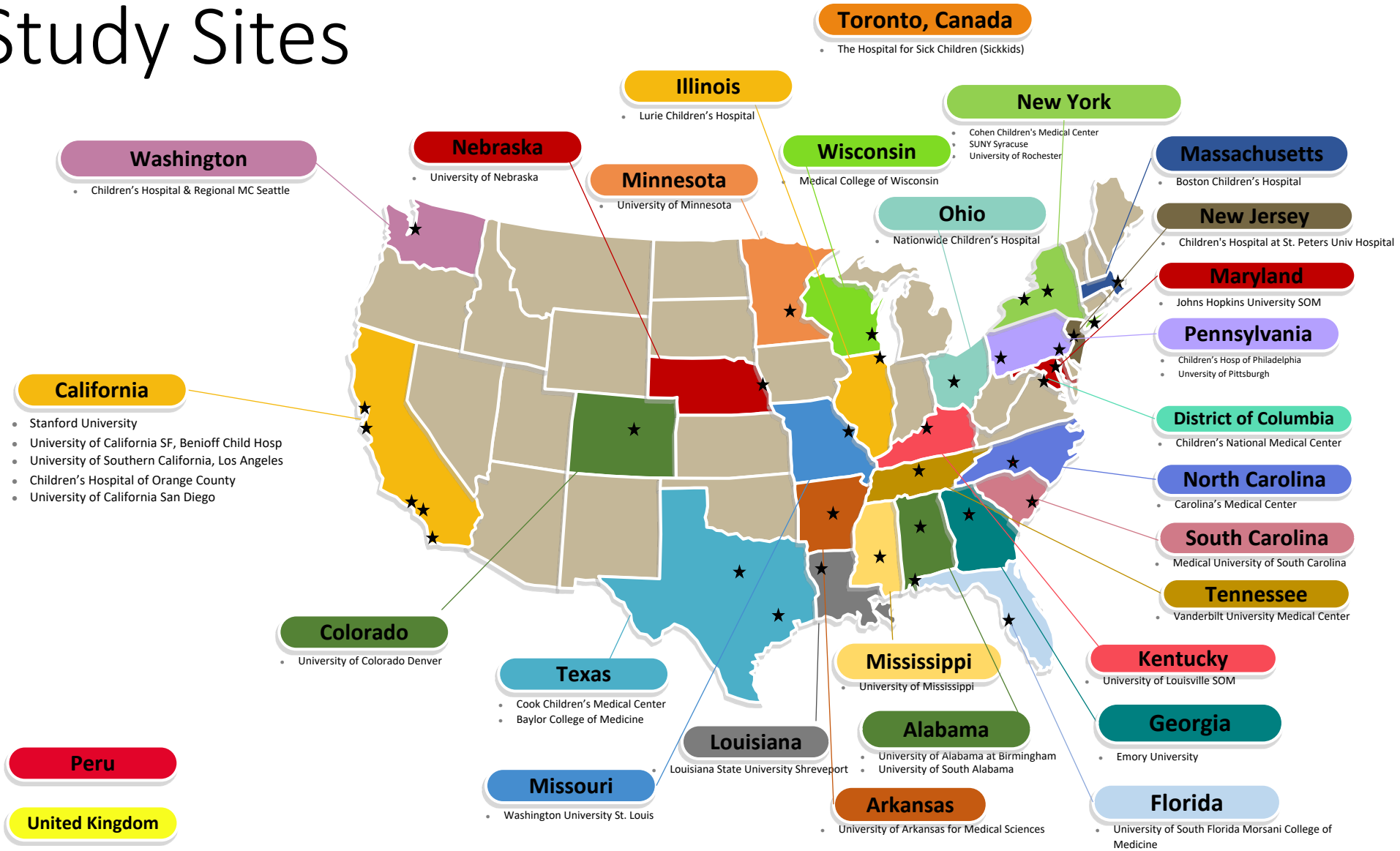
**A PROSPECTIVE STUDY OF ACUTE FLACCID MYELITIS (AFM) TO DEFINE NATURAL HISTORY, RISK FACTORS, AND PATHOGENETIC MECHANISMS**

UAB MEDICINE
PEDIATRICS

NIH National Institute of Allergy and Infectious Diseases

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

# NIAID Acute Flaccid Myelitis Natural History Study Sites



# Group 1 (AFM Cases)
# Inclusion and Exclusion Criteria

Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Onset of flaccid limb weakness involving one or more extremities suggestive of possible, probable, or confirmed AFM within previous 30 days
- MRI of spinal cord that has been or will be obtained clinically
- Age < 18 years
- Weight ≥ 7.8 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:

- Known condition other than AFM causing the flaccid limb weakness
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

*Note: Subjects enrolling in Group 1 may subsequently be determined by the Protocol Adjudication Committee to not have AFM. This assessment will not occur in real time. If a subject is deemed to have AFM, they will be classified as Group 1A cases (possible, probable, or confirmed AFM cases). If a subject is deemed to not have AFM, they will be classified as Group 1B cases (non-AFM cases) and analyzed accordingly.*

| | Study Day (window)[a] | | | | Study Month (window)[a] | | |
|---|---|---|---|---|---|---|---|
| | 1[b] | 3 (± 1 day) | 7 (± 2 days) | 28 (-18 to +3 days) | 3 (± 2 months) | 7 (± 2 months) | 12 (± 3 months) |
| Screening and informed consent | X | | | | | | |
| Baseline demographics[c] | X | | | | | | |
| Detailed patient history | X[d] | | | | X[e] | | |
| Assessment of neurologic illness in household members | X | | | | | | X |
| Neurologic examination[f] | X | X | X | X | X | X | X |
| Neuroimaging by MRI[g] | X[h] | | | | | | |
| Nasopharyngeal specimen for biorepository[i] | X | X | | | | | |
| Oropharyngeal specimen for biorepository[i] | X | X | | | | | |
| Serum for biorepository[j] | X | | X | X | | X | |
| Whole blood for biorepository[k] | X | | X | X | | X | |
| PBMCs and plasma for biorepository[l] | X | | X | X | | X | |
| Stool for biorepository[m] | X | | | | | | |
| Cerebrospinal fluid for biorepository[g] | X[n] | | | | | | |
| Record cerebrospinal fluid indices | X[o] | | | | | | |
| Record subsequent hospitalizations[p] and medical diagnoses following study enrollment | | X | X | X | X | X | X |
| Record results of clinical virologic workup | | | | X[q] | | | |
| Record results of clinical immunologic workup | | | | X[r] | | | |
| Record targeted concomitant medications administered as treatment of AFM | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] |
| Record therapeutic procedure(s) attempted | | | | X[t] | X[t] | X[t] | X[t] |
| Record electromyography (EMG) and nerve conduction study (NCS) results[g] | X[u] | | | | | | |
| Assessments of degree of neurologic sequelae | X[v] | | | | X[v] | X[v] | X[v] |

# Group 2 (controls)
## Inclusion and Exclusion Criteria

**Inclusion Criteria:**

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Residing household contact of a child enrolled in Group 1 of this study within previous 30 days
- Weight ≥ 6.0 kg
- Agrees to Future Use of Specimens

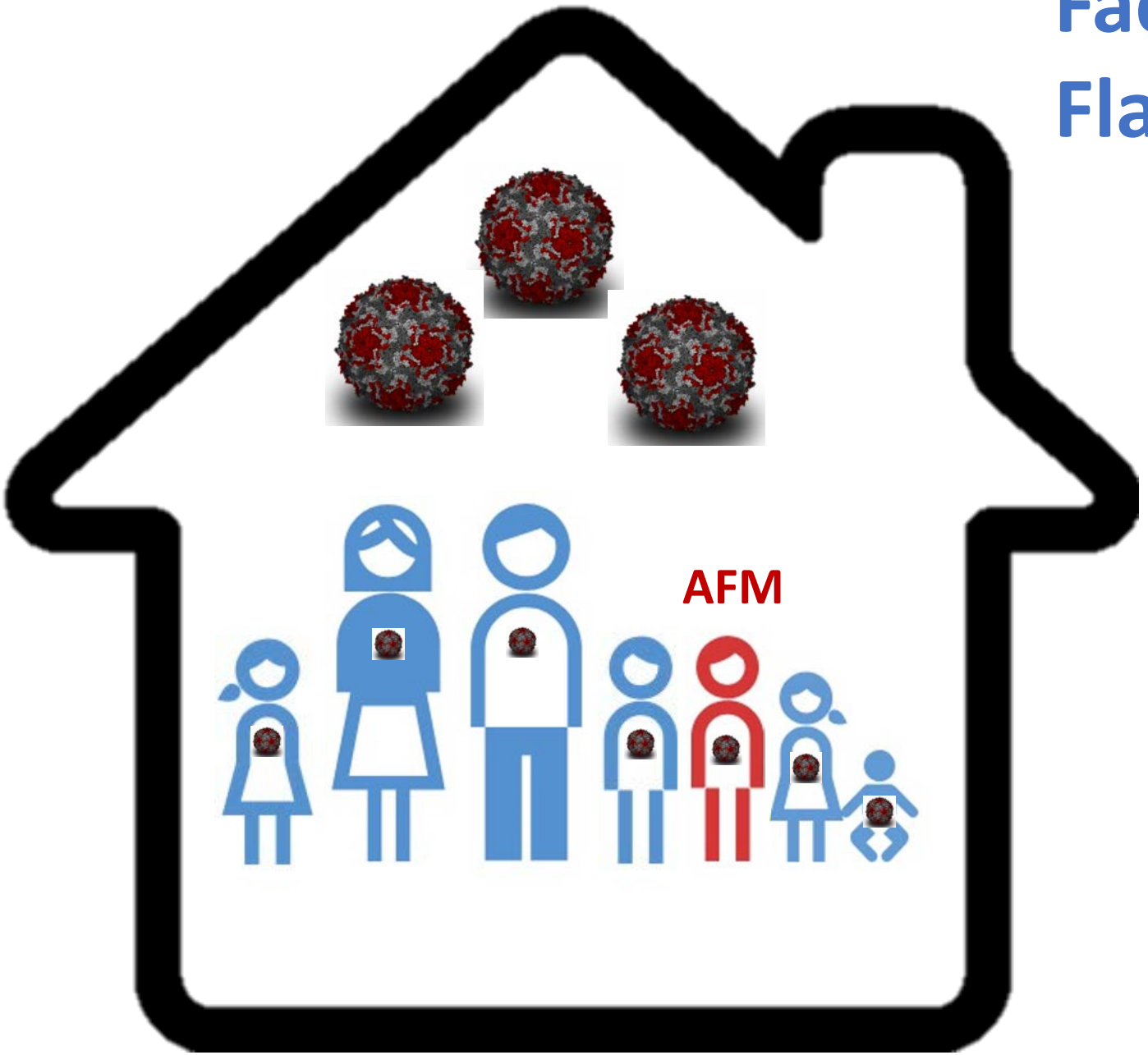
**Exclusion Criteria:**

- Flaccid limb weakness involving one or more extremities
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

*Note: If a subject enrolled in Group 2 subsequently develops findings suggestive of AFM, they may be asked if they would like to enroll into Group 1 of the study and be followed and analyzed accordingly.*

| | Study Day (window) | | | Unscheduled Sick Visit[b] |
|---|---|---|---|---|
| | 1 (+ 1 day)[a] | 7 (± 4 days) | 28 (± 9 days) | |
| **Screening and informed consent** | X | | | |
| **Baseline demographics[c]** | X | | | |
| **Detailed patient history[d]** | X | | | |
| **Neurologic examination[e]** | X | | | X[b] |
| **Nasopharyngeal specimen for biorepository[f]** | X | X | X | X |
| **Oropharyngeal specimen for biorepository[f]** | X | X | X | X |
| **Serum for biorepository[g]** | X | | X | |
| **Whole blood for biorepository[h]** | X | | X | |
| **PBMCs and plasma for biorepository[i]** | X | | X | |
| **Stool for biorepository[j]** | X | | X | X |
| **Neurologic assessment[k]** | X | | | |
| **Record development of interval illness and final diagnosis** | | | X | |

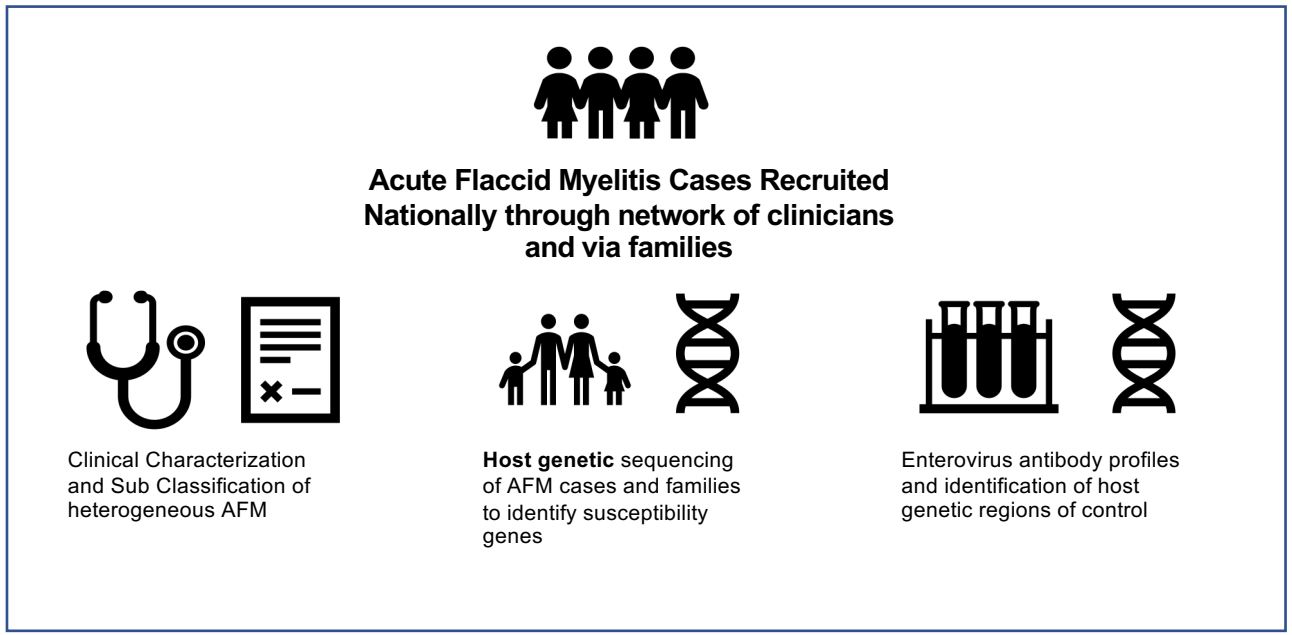
# Factors in Acute Flaccid Myelitis




Despite the presence of infection in the entire household only one younger member of the family is affected

- **Genetic predisposition?**

# Johns Hopkins AFM Case-Control Study
# 2014-present




Investigators from Johns Hopkins: **Priya Duggal**, Aaron Milstone, David Thomas, Matthew Elrick, Tom Crawford, Carlos Pardo, Ben Larman Plus an incredible national network of physicians dedicated to AFM

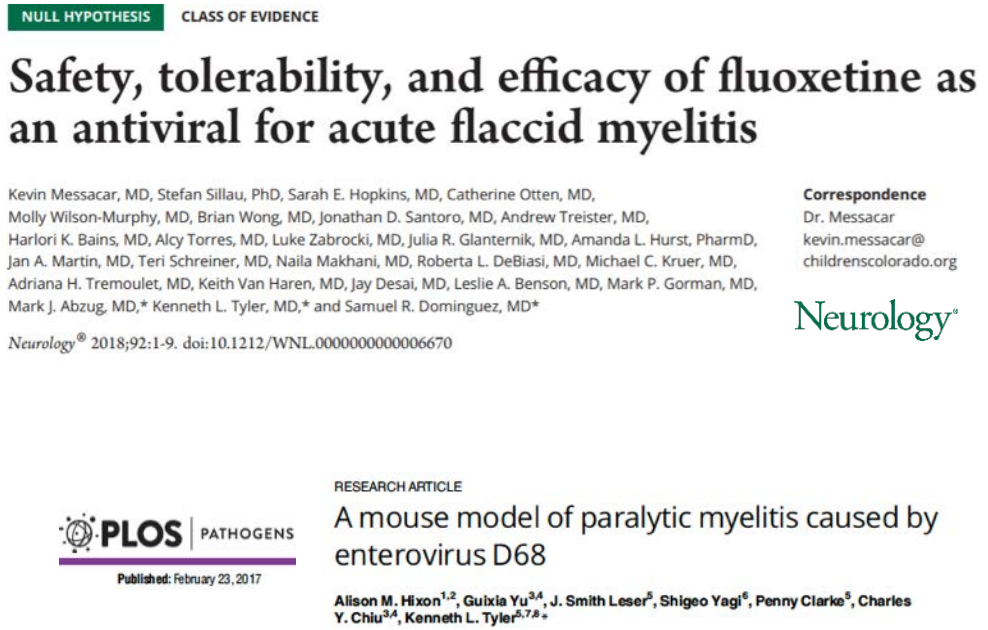
**SRNA Podcast series:** https://wearesrna.org/resources/genetic-study-of-afm/

# There is not a good treatment approach for AFM yet!!

**Treatment Approaches For Acute Flaccid Myelitis**

- Steroids??
- Plasma exchange??
- IVIG?
- Fluoxetine??

- **Rehabilitation!!**
- **Nerve transfers ?!**



NULL HYPOTHESIS CLASS OF EVIDENCE

**Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis**

Kevin Messacar, MD, Stefan Sillau, PhD, Sarah E. Hopkins, MD, Catherine Otten, MD, Molly Wilson-Murphy, MD, Brian Wong, MD, Jonathan D. Santoro, MD, Andrew Treister, MD, Harlori K. Bains, MD, Alcy Torres, MD, Luke Zabrocki, MD, Julia R. Glanternik, MD, Amanda L. Hurst, PharmD, Jan A. Martin, MD, Teri Schreiner, MD, Naila Makhani, MD, Roberta L. DeBiasi, MD, Michael C. Kruer, MD, Adriana H. Tremoulet, MD, Keith Van Haren, MD, Jay Desai, MD, Leslie A. Benson, MD, Mark P. Gorman, MD, Mark J. Abzug, MD,* Kenneth L. Tyler, MD,* and Samuel R. Dominguez, MD*

**Correspondence**
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*Neurology*® 2018;92:1-9. doi:10.1212/WNL.0000000000006670

Neurology®



PLOS | PATHOGENS

Published: February 23, 2017

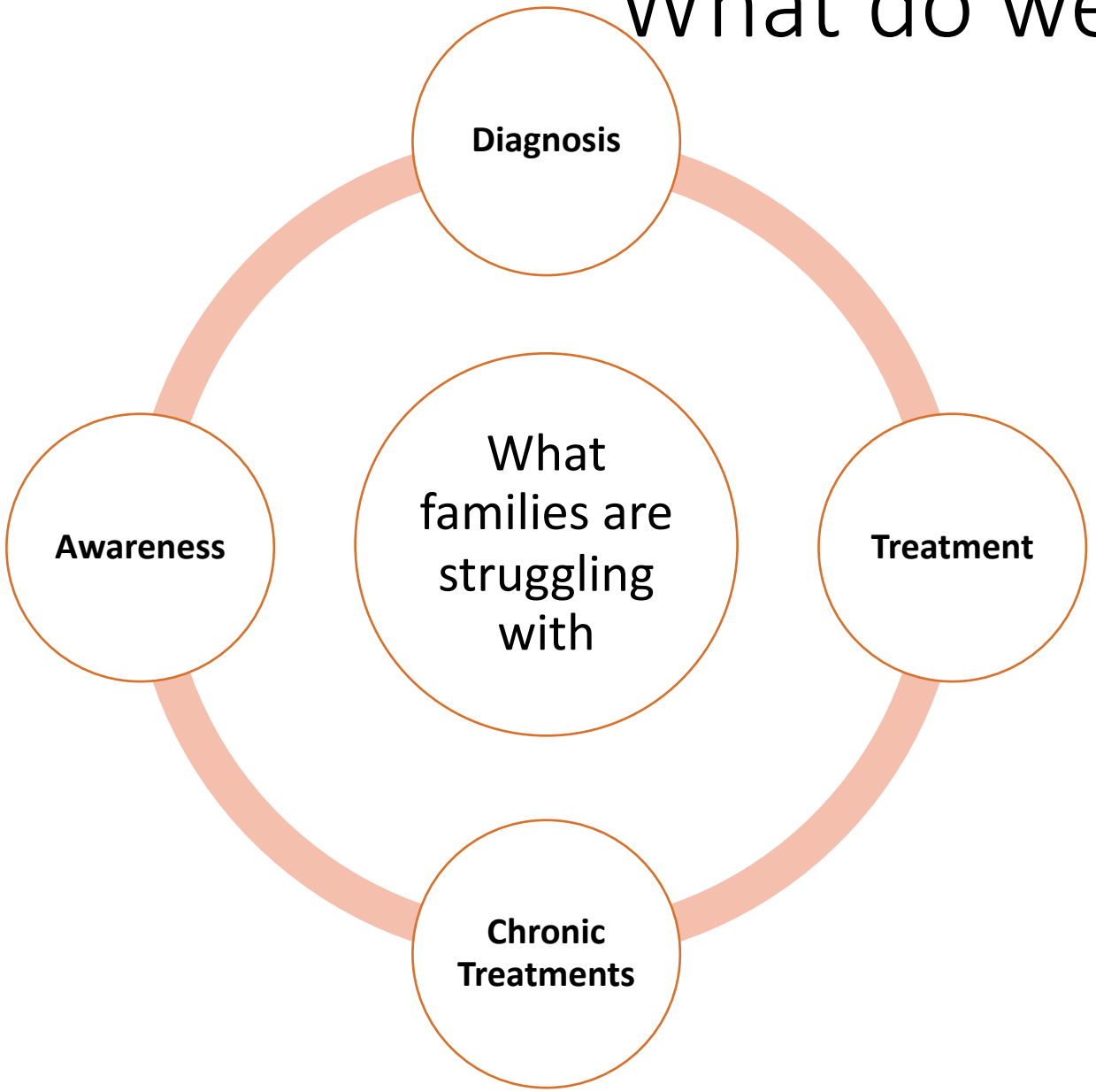
RESEARCH ARTICLE

A mouse model of paralytic myelitis caused by enterovirus D68

Alison M. Hixon[1,2], Guixia Yu[3,4], J. Smith Leser[5], Shigeo Yagi[6], Penny Clarke[5], Charles Y. Chiu[3,4], Kenneth L. Tyler[5,7,8]*

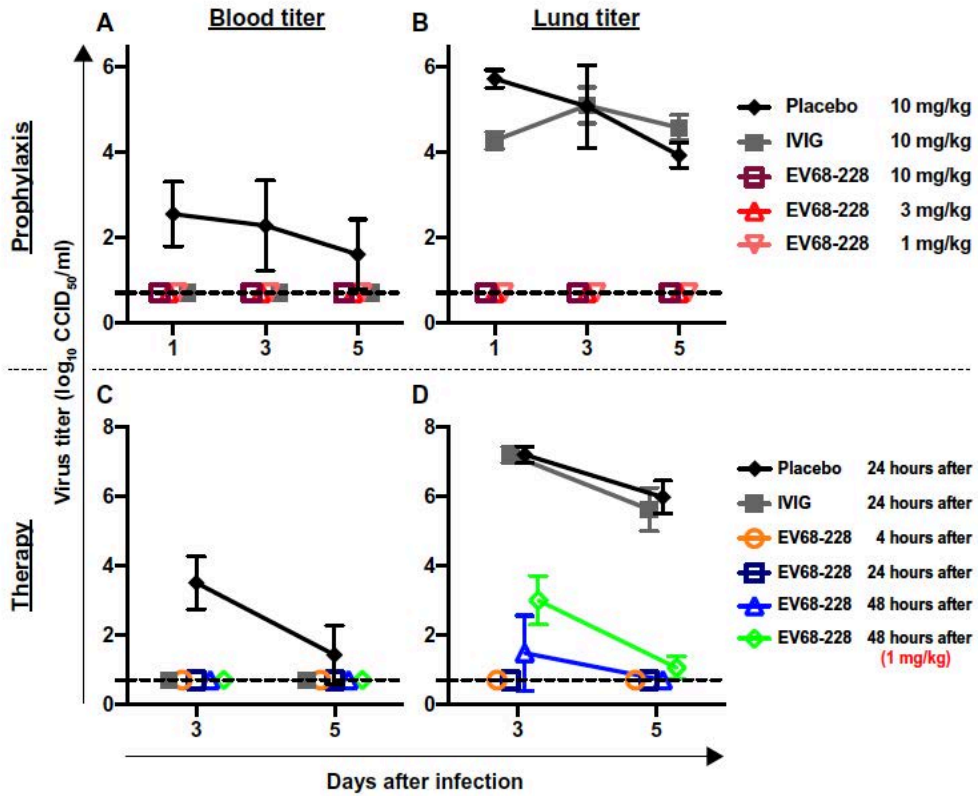
**Hixon AM, Clarke P, Tyler KL.** Evaluating Treatment Efficacy in a Mouse Model of Enterovirus D68-Associated Paralytic Myelitis. J Infect Dis. 2017 Dec 5;216(10):1245-1253

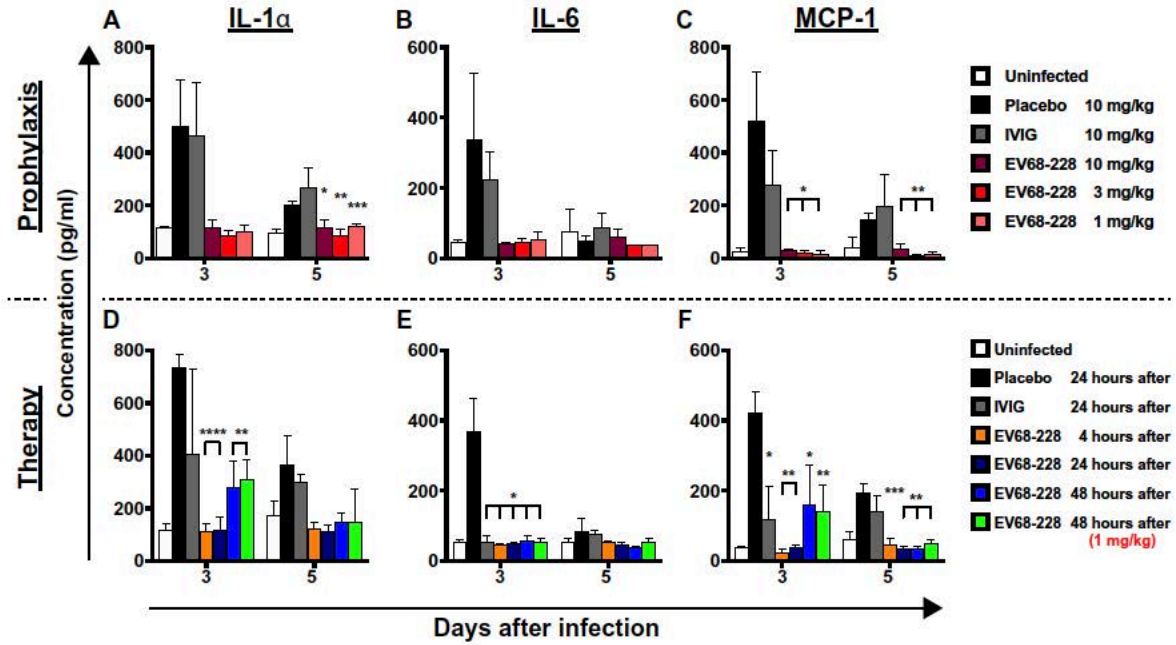
# What do we need?




**What is in the future of treatments?**

- Developments of new antiviral medications
- Use of specific antibodies for EV-D68
- Vaccines for EV-D68 and other pathogens
- New rehabilitation strategies
- Nerve and tendon transfers and surgeries




SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

INFECTIOUS DISEASES

# Human antibodies neutralize enterovirus D68 and protect against infection and paralytic disease

Matthew R. Vogt[1]*, Jianing Fu[2]*, Nurgun Kose[3], Lauren E. Williamson[4], Robin Bombardi[3], Ian Setliff[5], Ivelin S. Georgiev[3,4], Thomas Klose[2], Michael G. Rossmann[2†], Yury A. Bochkov[6], James E. Gern[6,7], Richard J. Kuhn[2], James E. Crowe Jr.[1,3,4,5‡]

# What do we need?