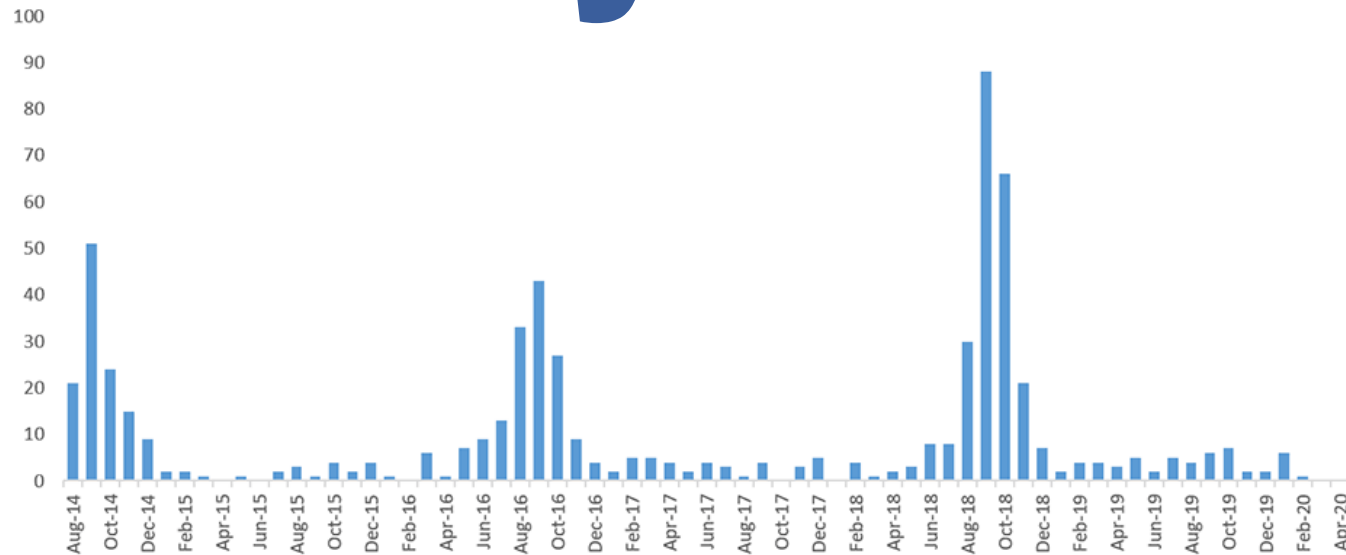


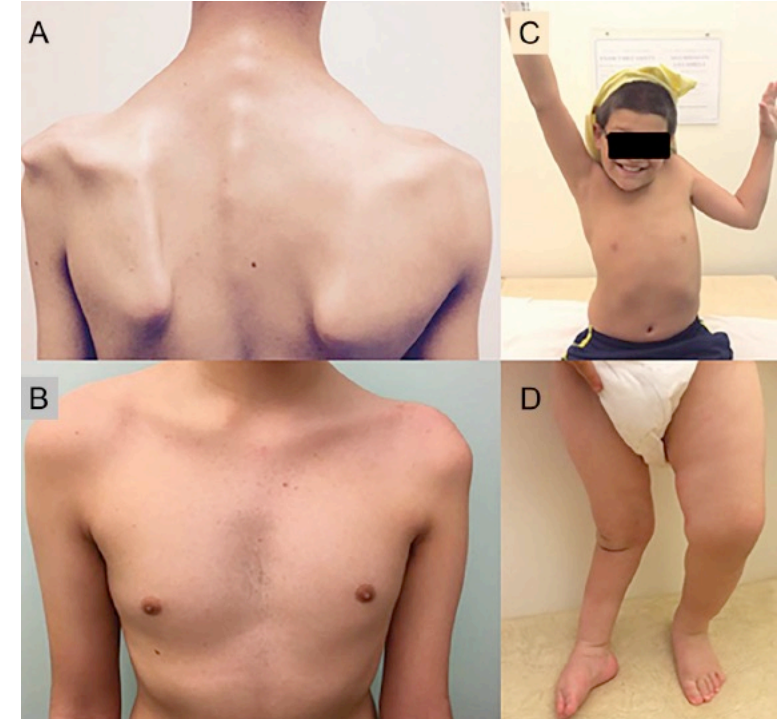
Acute Flaccid Myelitis



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Disclosures

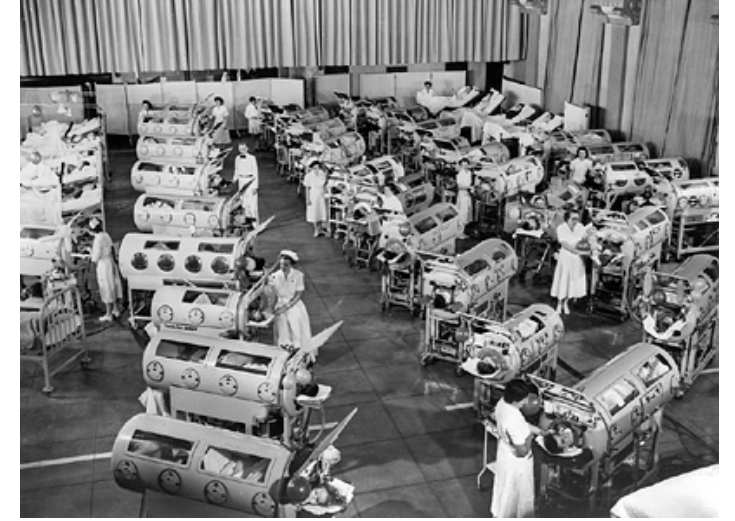
- No relevant financial disclosures or conflicts of interest
 - Supported by NIAID K23AI28069
- I will discuss off-label use of medications

Acknowledgments

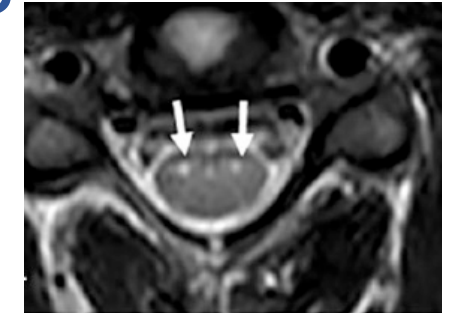
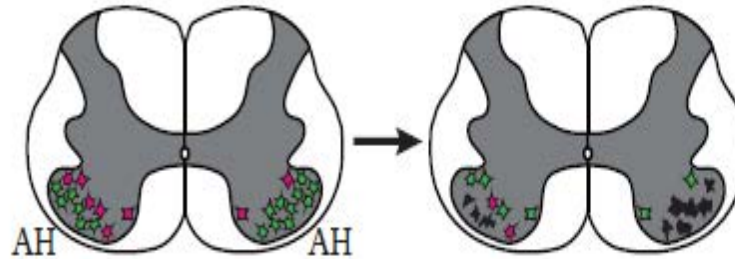
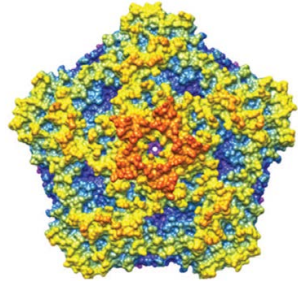
- Siegel Rare Neuroimmune Association, John Hopkins University, Kennedy Krieger Institute, and Acute Flaccid Myelitis Working Group
- Advances in this field have been driven by the dedication and hard-work of many basic scientists, clinicians, researchers, and public health experts working collaboratively
- **Thank you to the patients and families affected by AFM for teaching us and your contributions to research efforts**

Overview

- **The Past:** How far we have come...



- **The Present:** ...our current understanding of AFM...

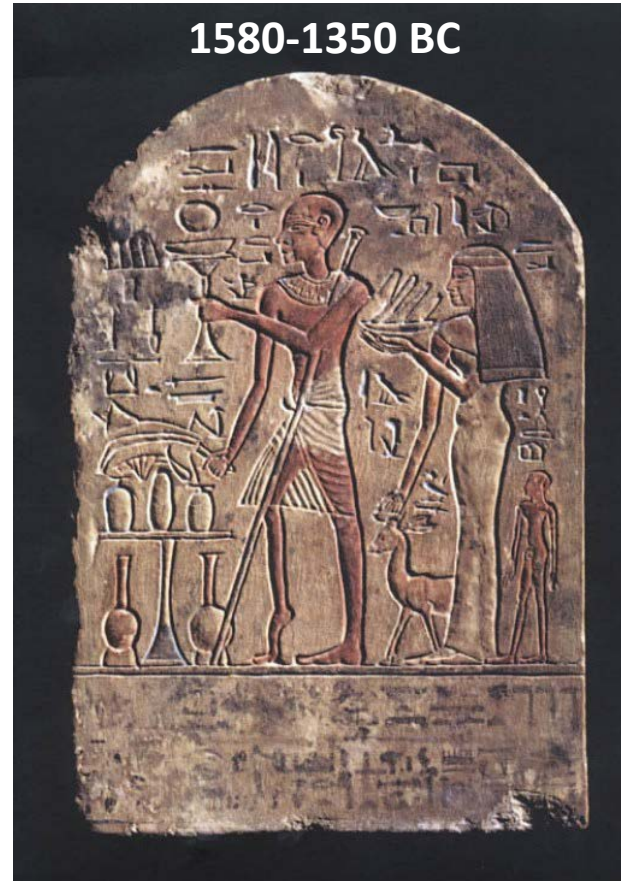


- **The Future:** ...how far we still need to go.



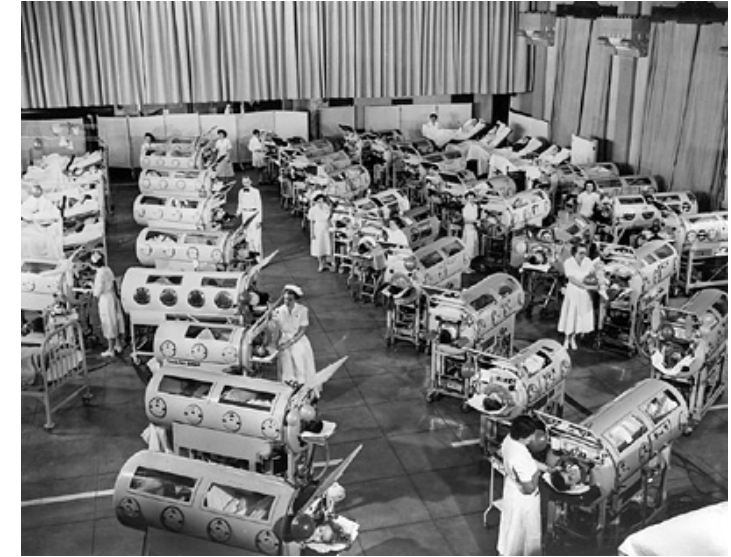
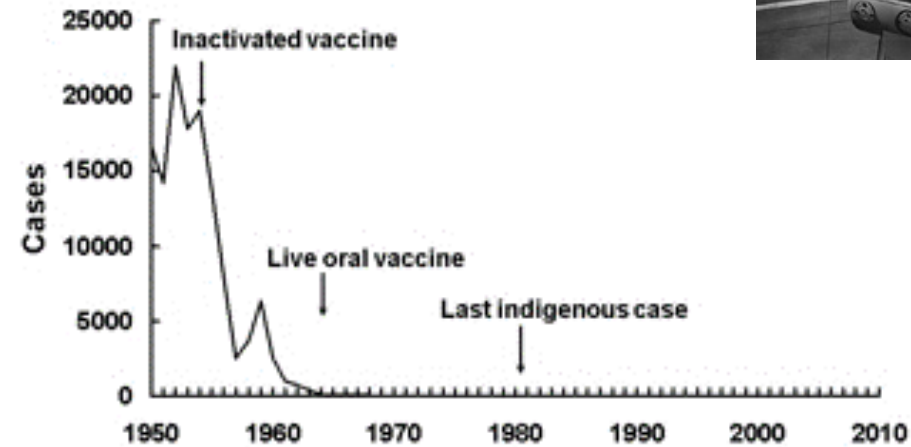
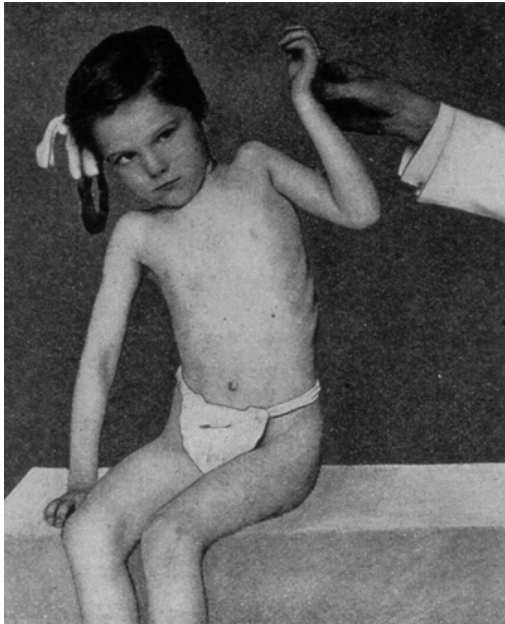
Historical Context

- Infantile paralysis



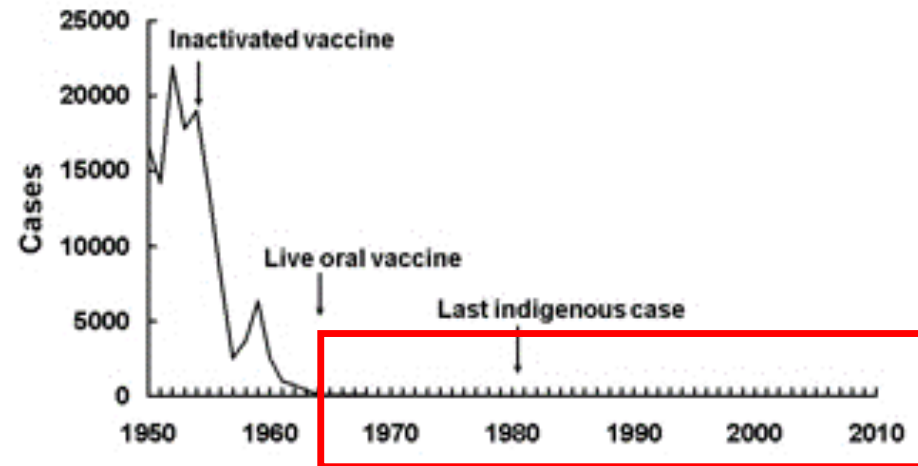
Historical Context

- Infantile paralysis
- Poliomyelitis



Historical Context

- Infantile paralysis
- Poliomyelitis
 - Poliovirus vaccine:

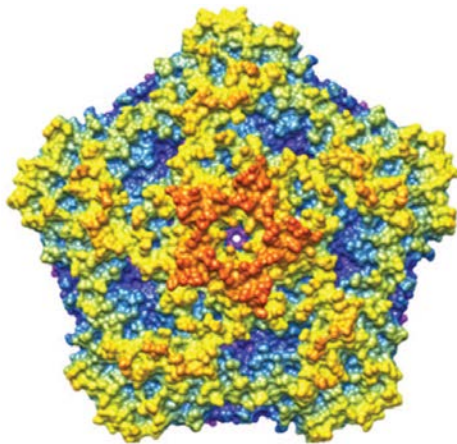


- Sporadic non-polio acute flaccid paralysis
 - Flaviviruses (West Nile virus, Japanese encephalitis virus)
 - Non-polio EVs (EV-A71, EV-D70)

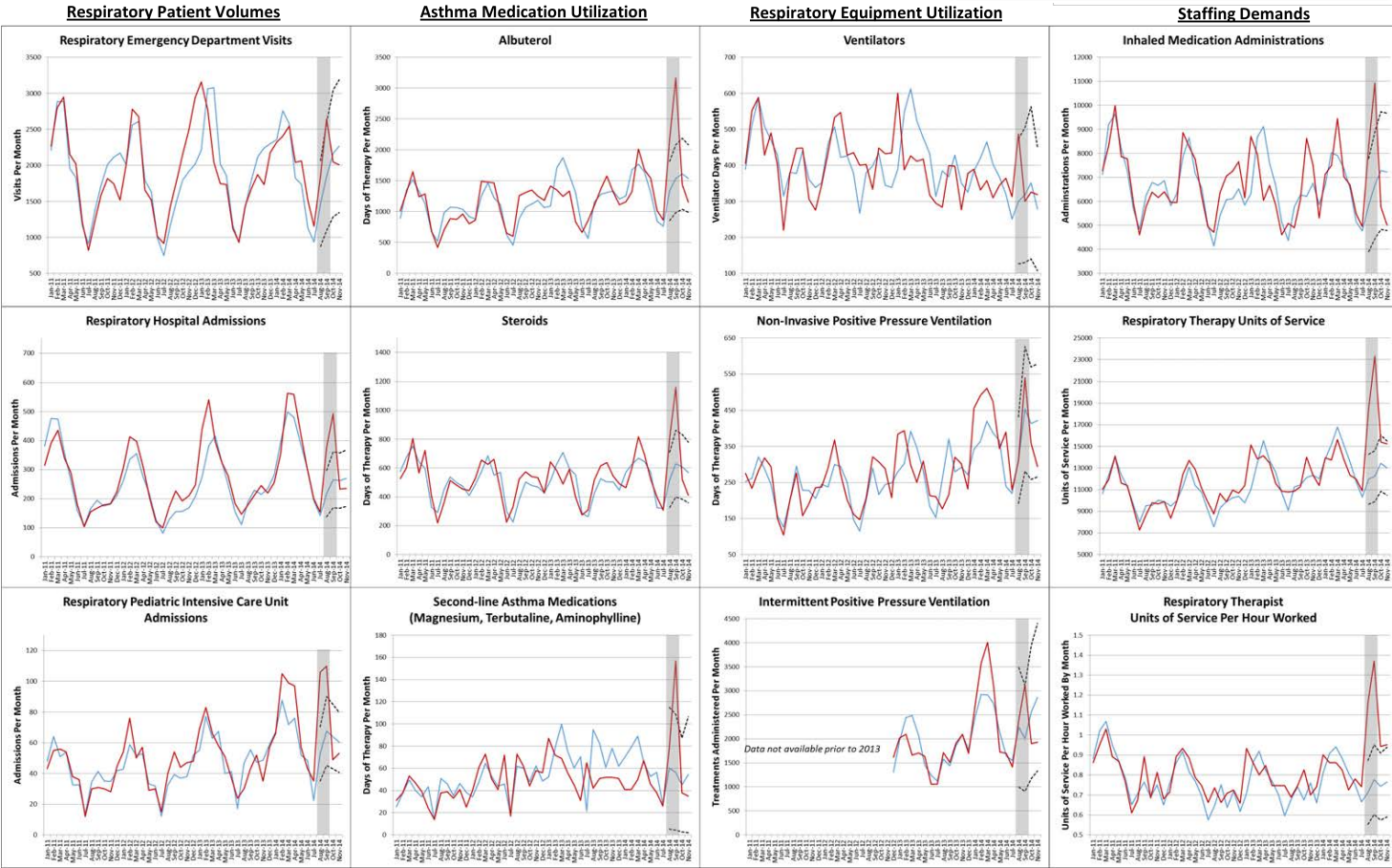
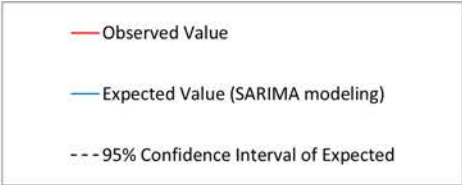
2012: Polio-like Illness Reports in CA

- 2012-13: Cluster of 5 pediatric cases of a polio-like syndrome reported to California Department of Public Health
 - All poliovirus vaccinated, all poliovirus testing negative
 - 3 with preceding respiratory illness
 - 2 tested positive for enterovirus D68
- August 2012: Passive statewide surveillance established in CA

Fall 2014 Enterovirus D68 Outbreak: An Unexpected Strain

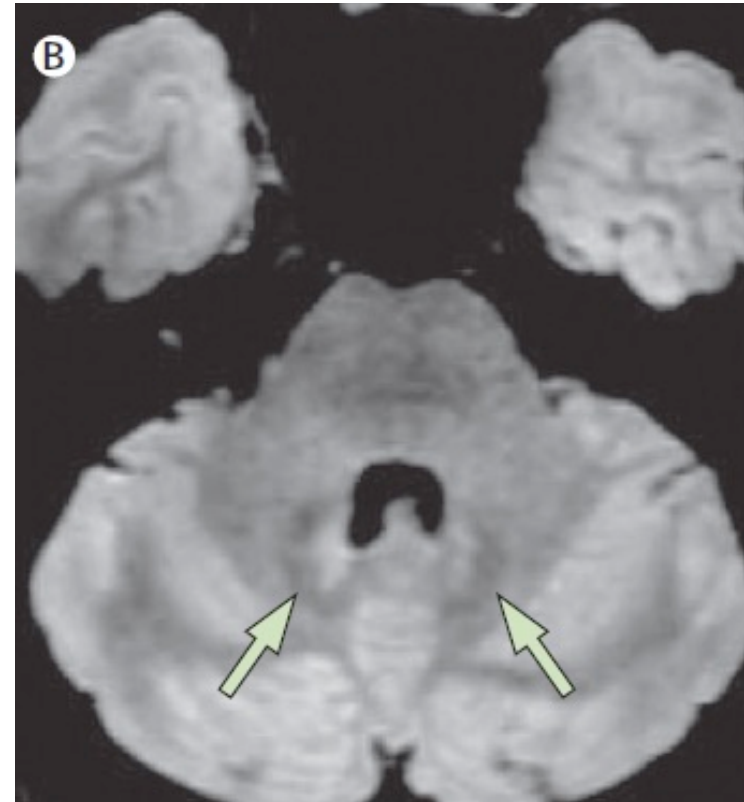


Observed vs. Expected Resource Utilization at Children’s Hospital Colorado Aug-Oct 2014 (gray)



In the midst of the outbreak...

- 18 yo M with fever, nasal congestion, cough, sore throat
- 7 days later develops headache, stiff neck, and cannot move his L arm
- CSF pleocytosis, MRI with longitudinal gray matter and brainstem lesions
- Within 24 hours intubated for airway protection due to bulbar paralysis
- No response to IVIG
- Tracheostomy, gastrostomy



2014 Co

Aug

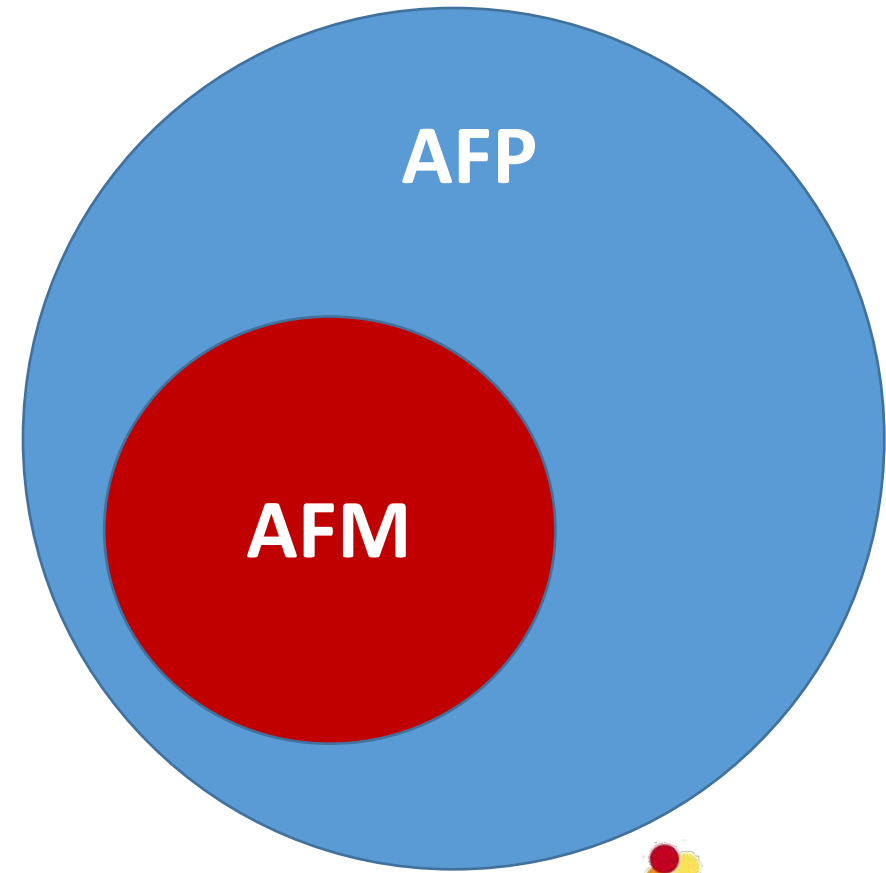


Case 12

Acute Flaccid Myelitis:

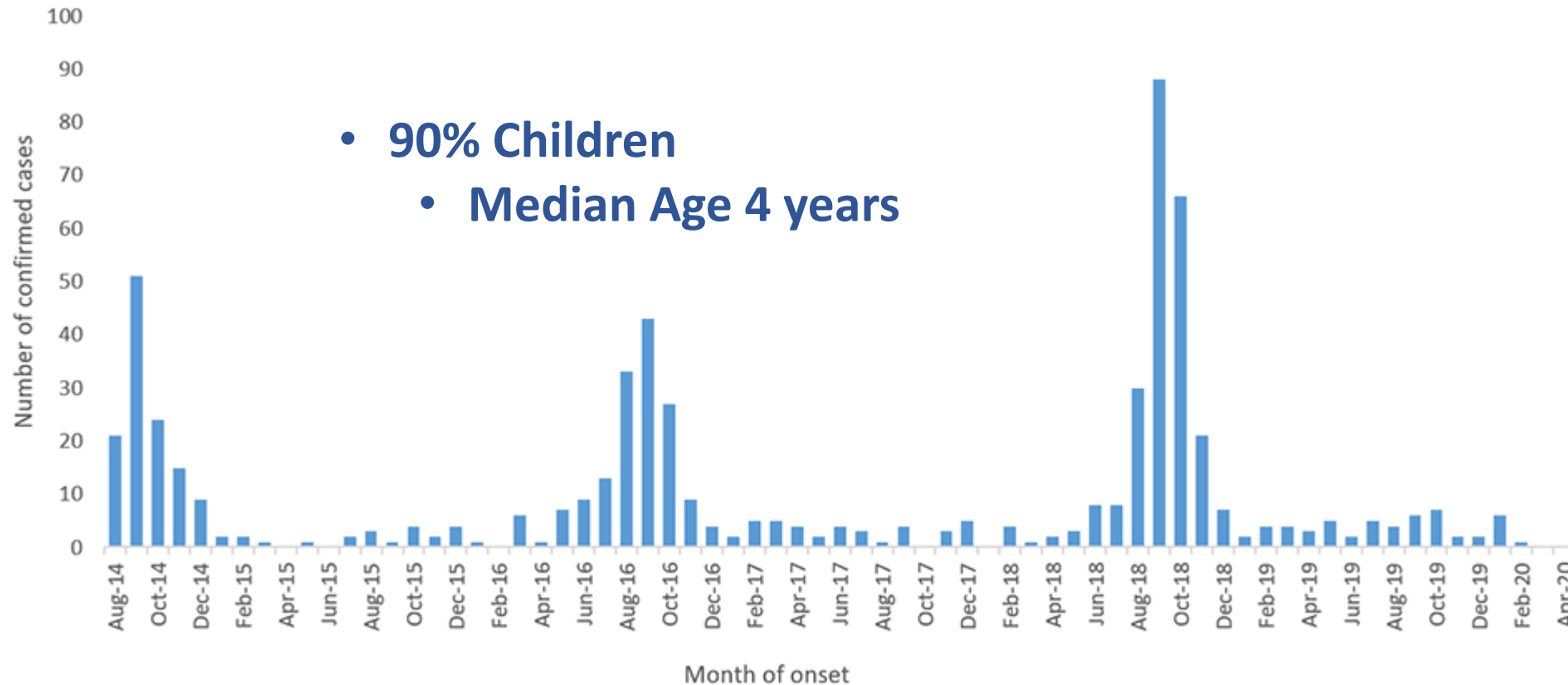
Surveillance Case Definition

- **Clinical criteria**: Acute onset flaccid limb weakness (AFP)
- + **Imaging criteria**: MRI with spinal cord lesion with predominant gray matter involvement spanning one or more vertebral segments





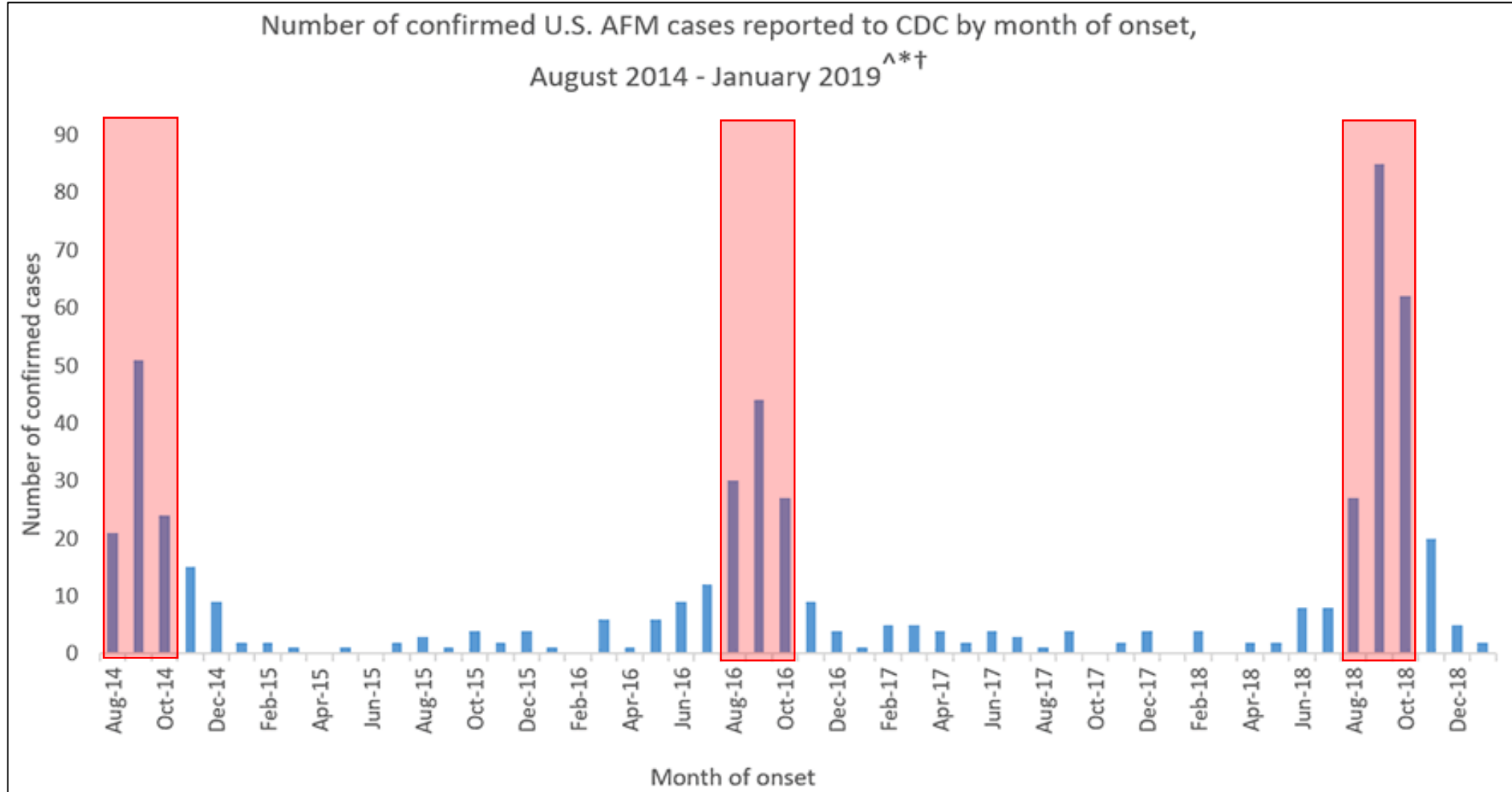
US AFM Epidemiology: 2014-Present



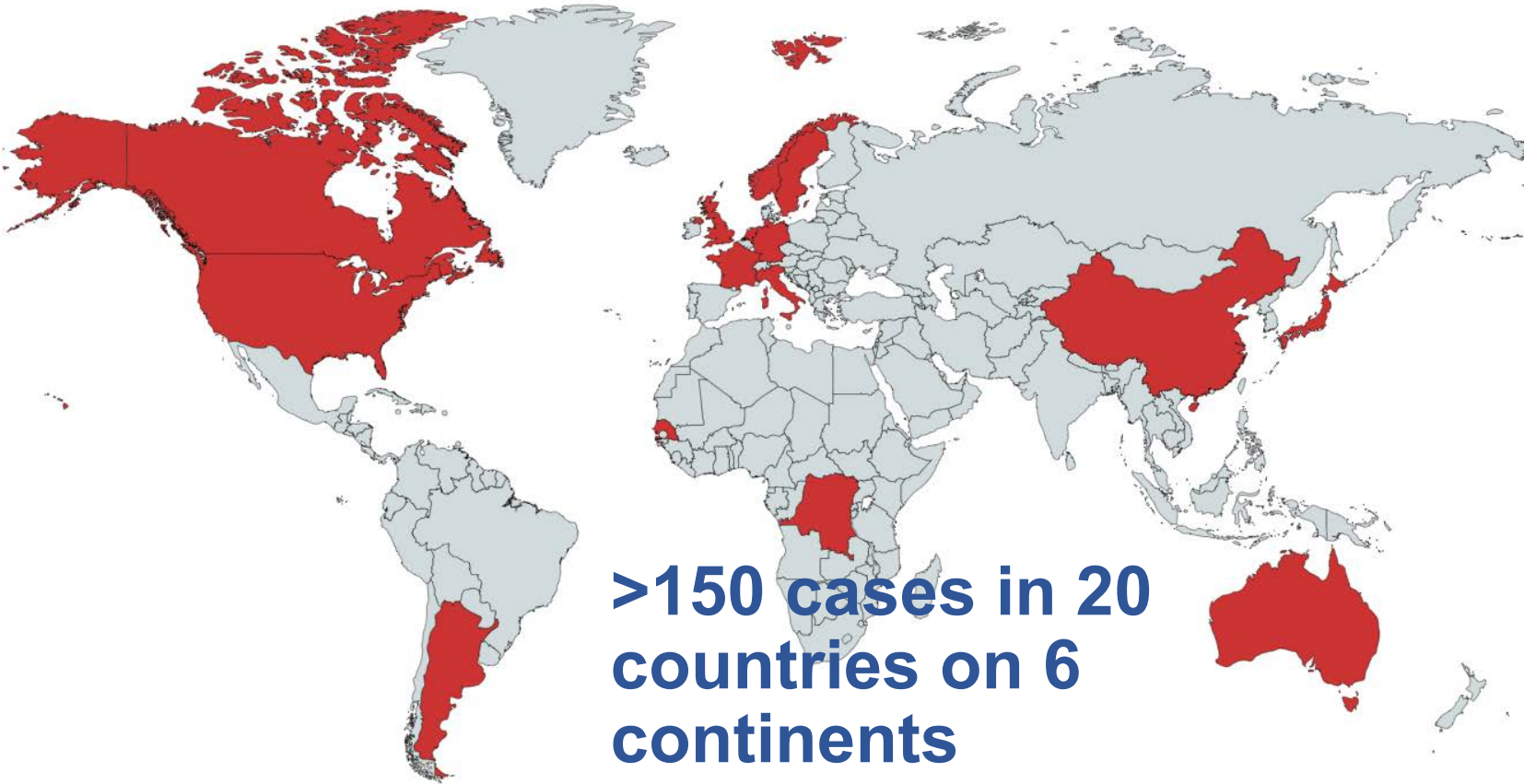
- **2014: 120 cases**
 - 34 states
- 2015: 22 cases
 - 17 states
- **2016: 153 cases**
 - 39 states
- 2017: 38 cases
 - 17 states
- **2018: 238 cases**
 - 42 states
- 2019: 46 cases
 - 18 states



Temporal Association Between AFM Cases and EV-D68 Circulation in US



Global Epidemiology: EV-D68 Acute Flaccid Myelitis

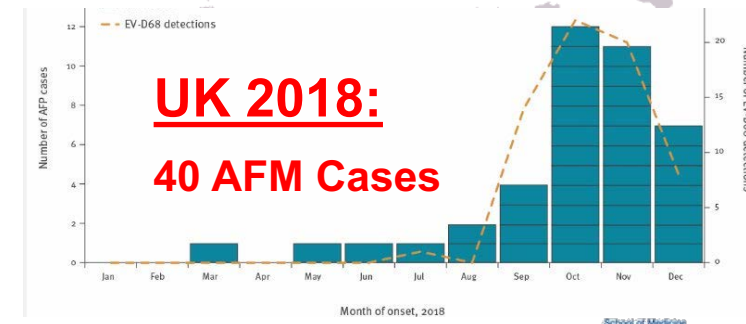
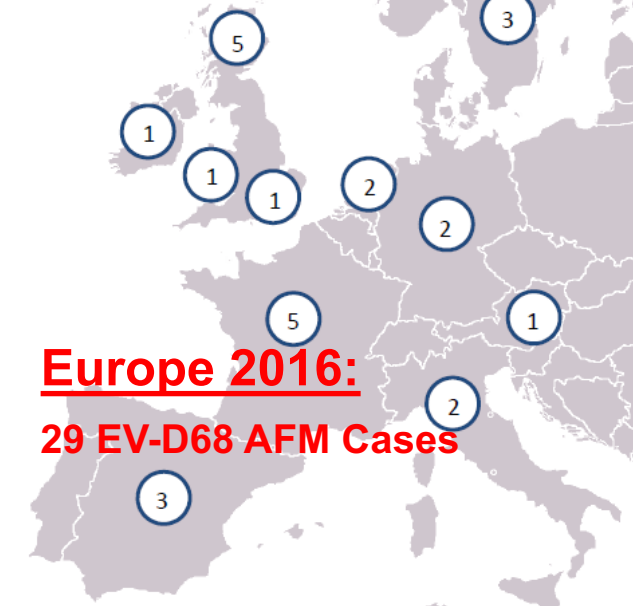
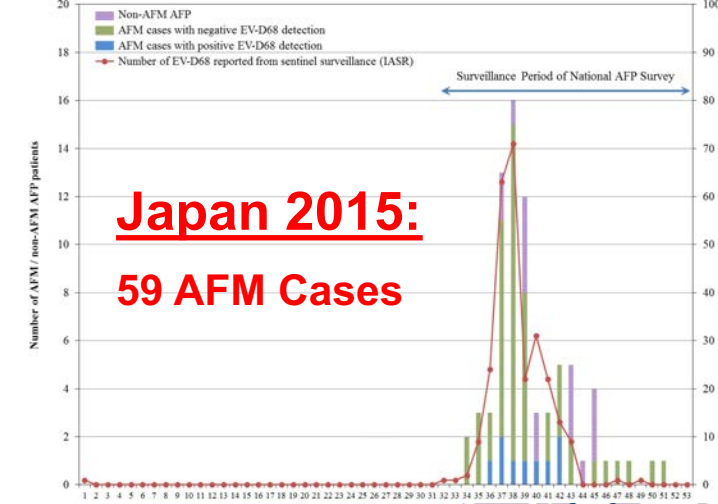


Messacar, K., et al. (2018). "Enterovirus D68 and acute flaccid myelitis-evaluating the evidence for causality." *Lancet Infect Dis*. Updated with new reported cases.

Chong, P. F., et al. (2017). "Clinical Features of Acute Flaccid Myelitis Temporally Associated with an Enterovirus D68 Outbreak: Results of a Nationwide Survey of Acute Flaccid Paralysis in Japan, August-December 2015." *Clin Infect Dis*.

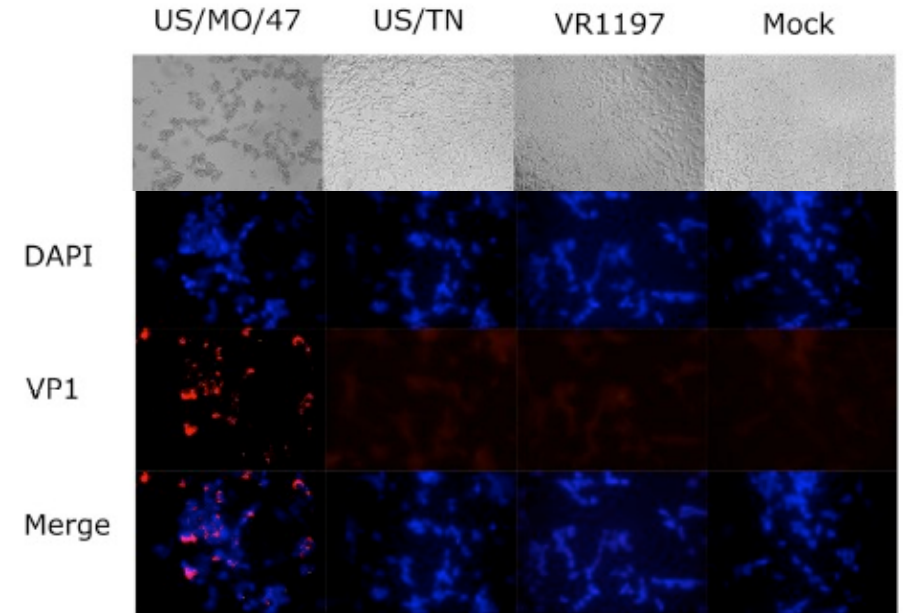
Knoester M, Helfferich J, Poelman R, et al. (2018) Twenty-Nine Cases of Enterovirus-D68 Associated Acute Flaccid Myelitis in Europe 2016; A Case Series and Epidemiologic Overview. *The Pediatric infectious disease journal*.

The United Kingdom Acute Flaccid Paralysis Afp Task, F. (2019). "An increase in reports of acute flaccid paralysis (AFP) in the United Kingdom, 1 January 2018-21 January 2019: early findings." *Euro Surveill* 24(6).



Research Advances: Enteroviruses and AFM

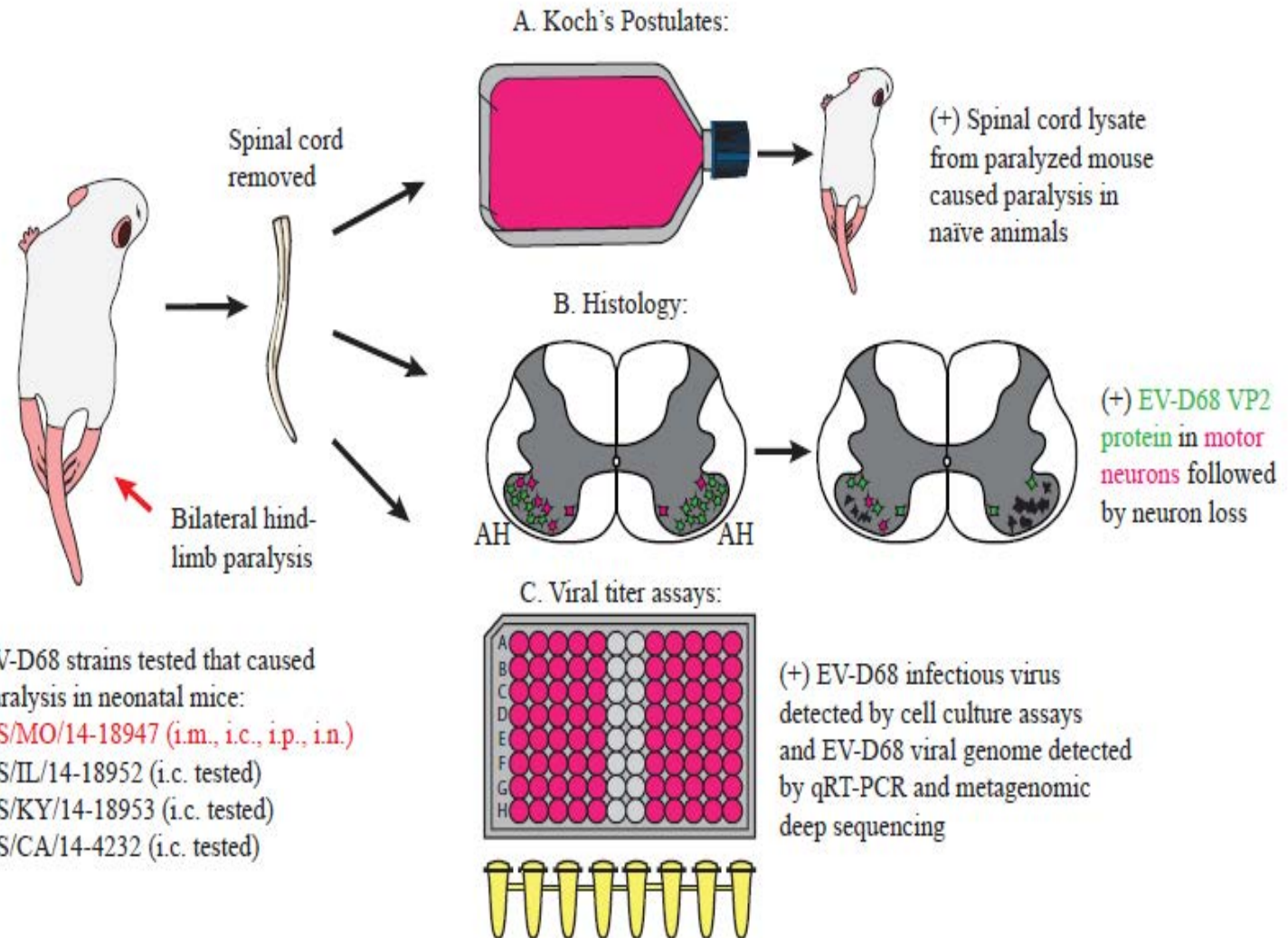
- EV-D68 infects motor neurons



**Neuroblastoma-derived
SH-SY5Y neuronal cell line**

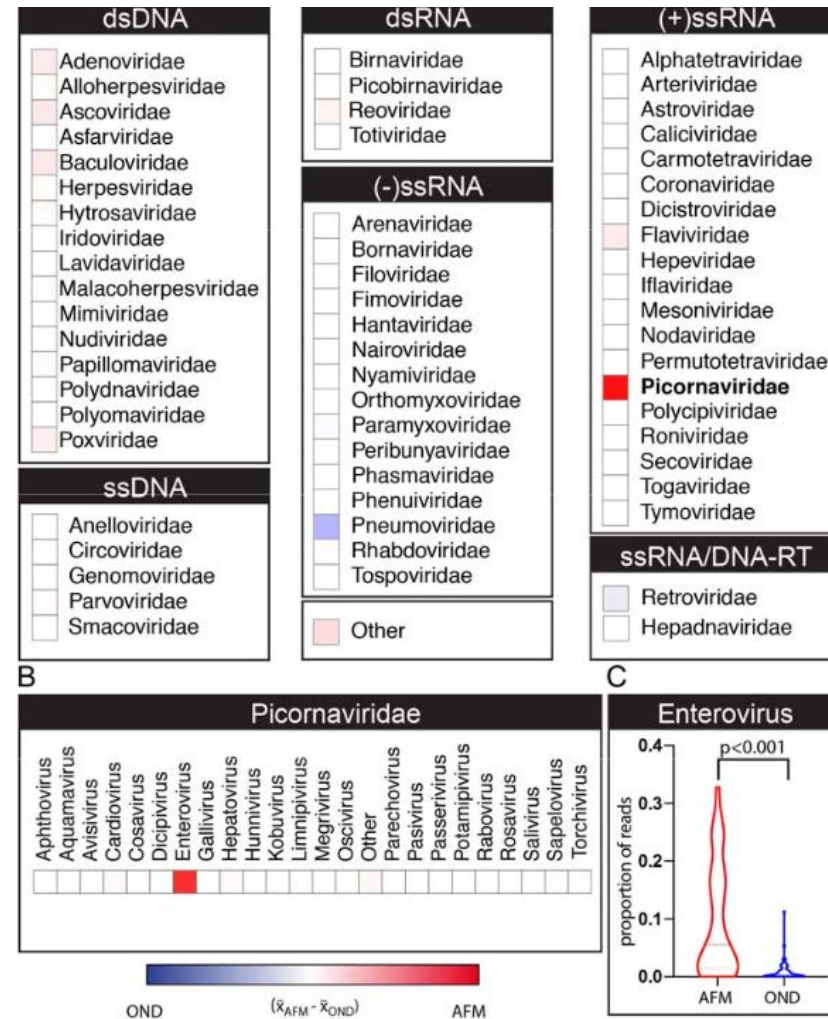
Research Advances: Enteroviruses and AFM

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice



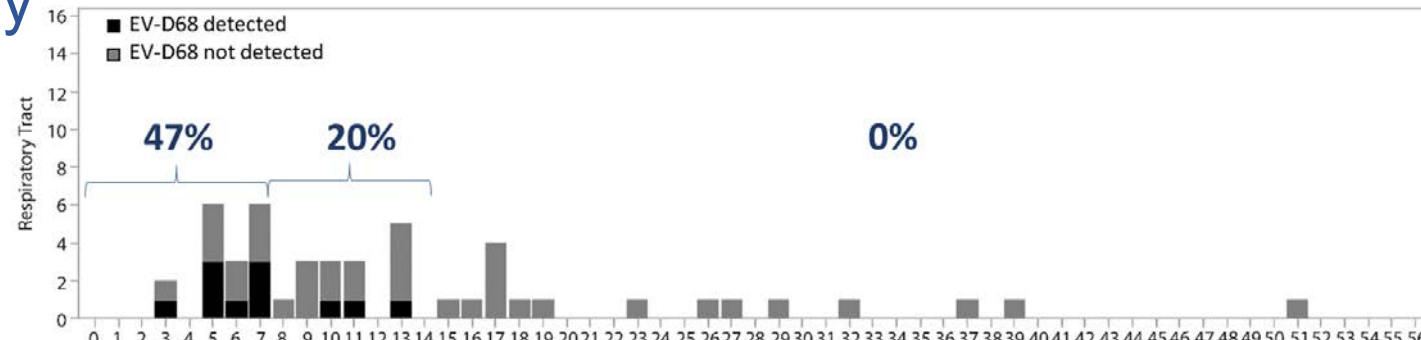
Research Advances: Enteroviruses and AFM

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice
- No viruses present in CSF
 - EV antibodies identified



Research Advances: Enteroviruses and AFM

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice
- No viruses present in CSF
 - EV antibodies identified
- EVs most commonly identified viruses in AFM cases
 - EV-D68: NP respiratory specimens
 - EV-A71: stool>OP>NP respiratory





AFM Natural History

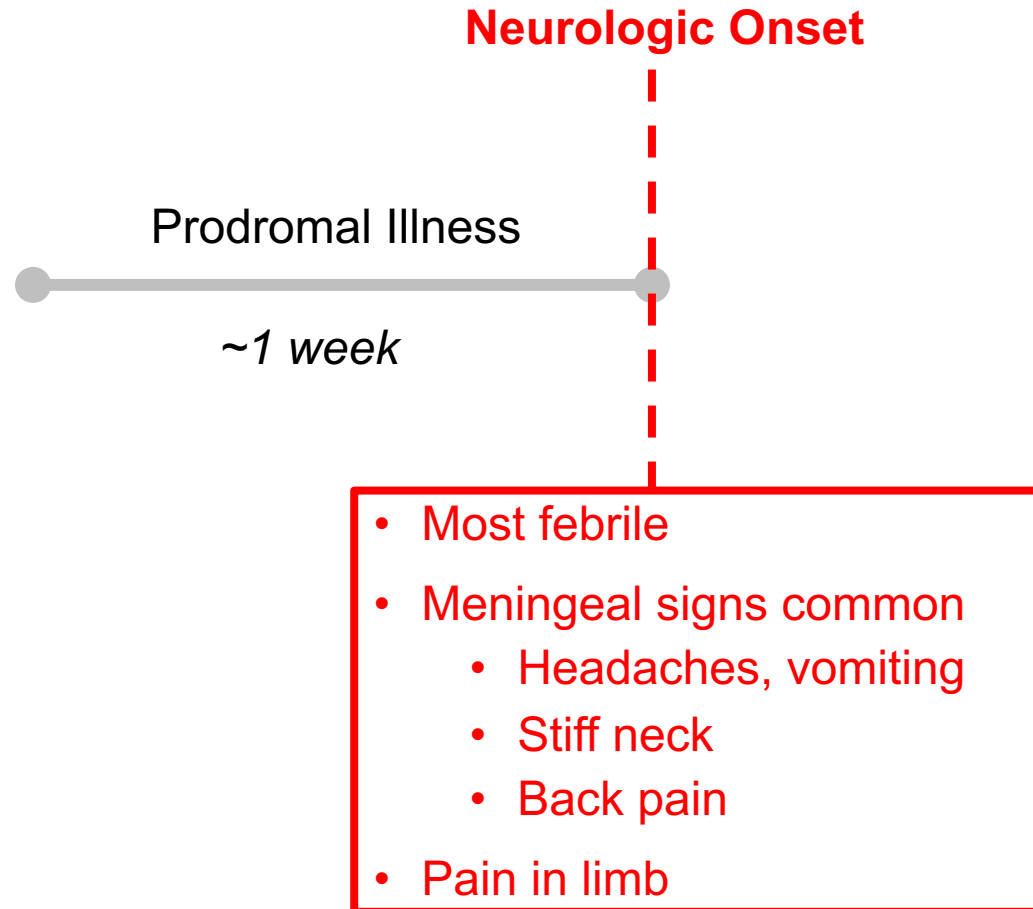
Prodromal Illness

~1 week



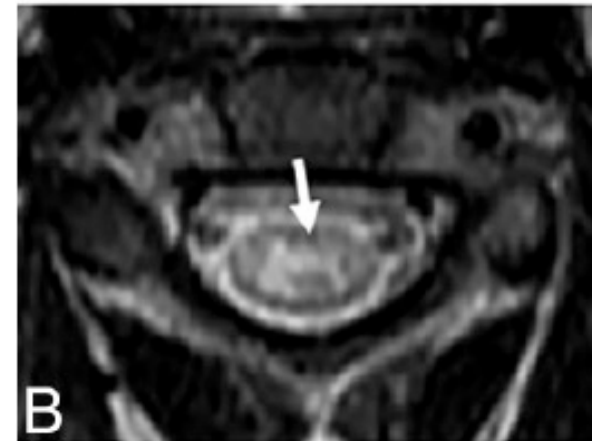
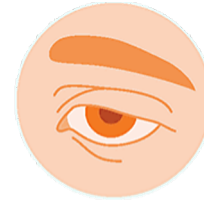
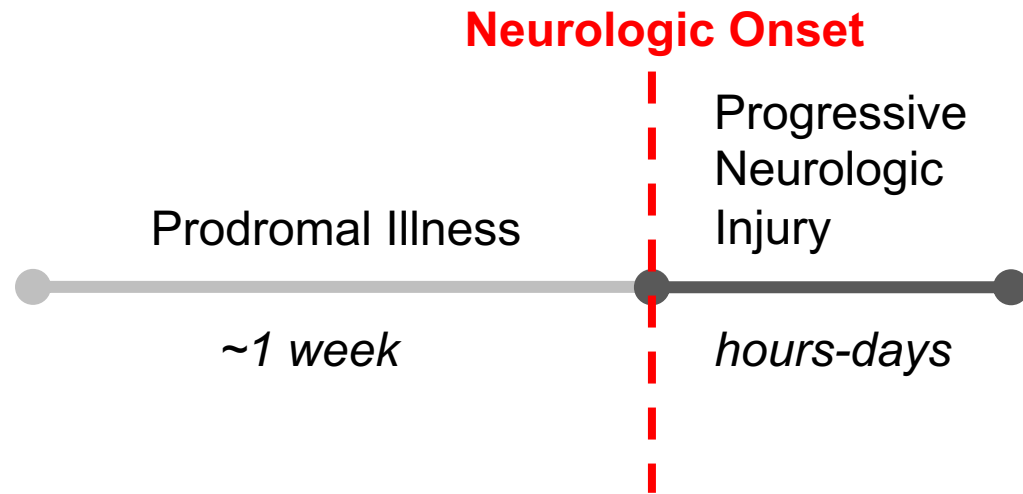


AFM Natural History



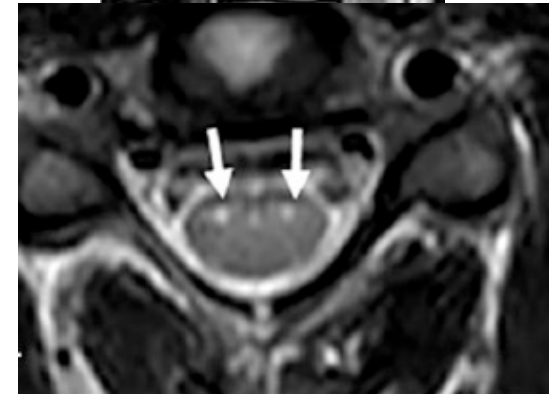
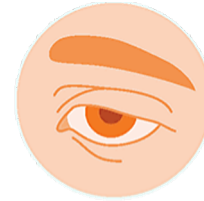
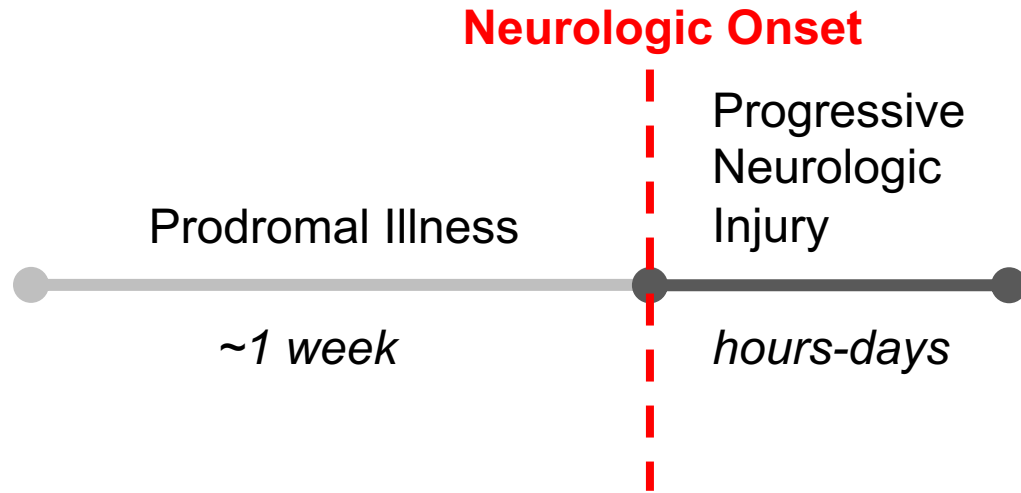


AFM Natural History



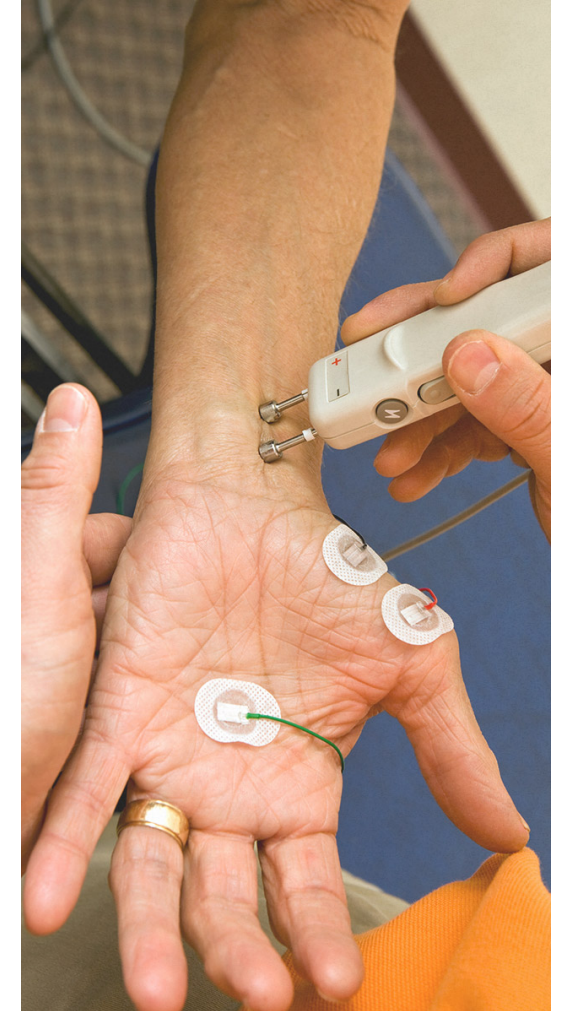
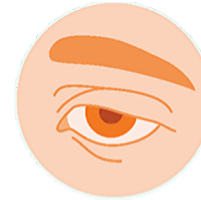
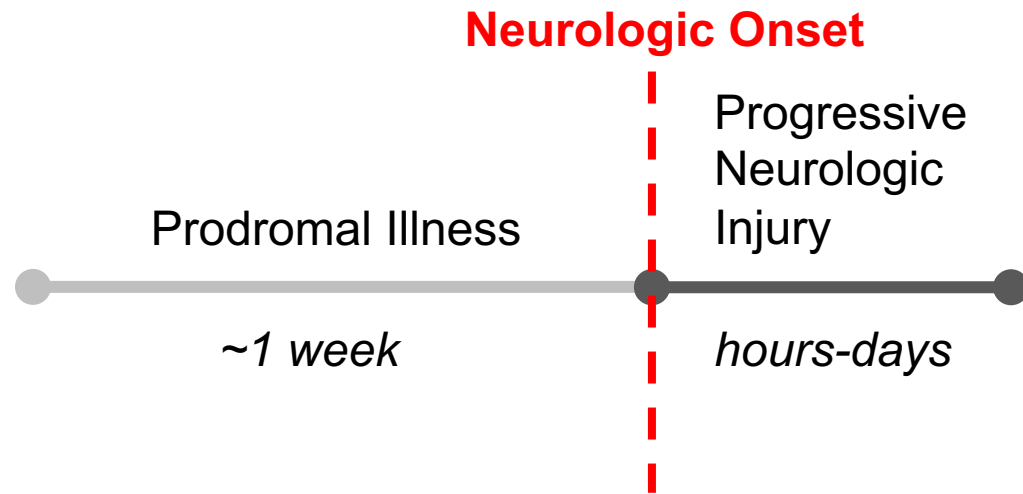


AFM Natural History



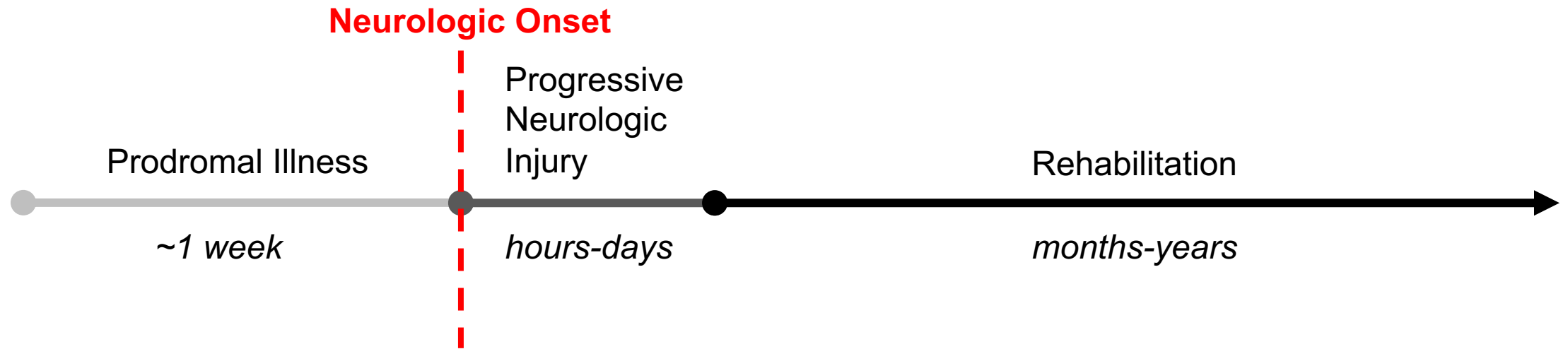


AFM Natural History





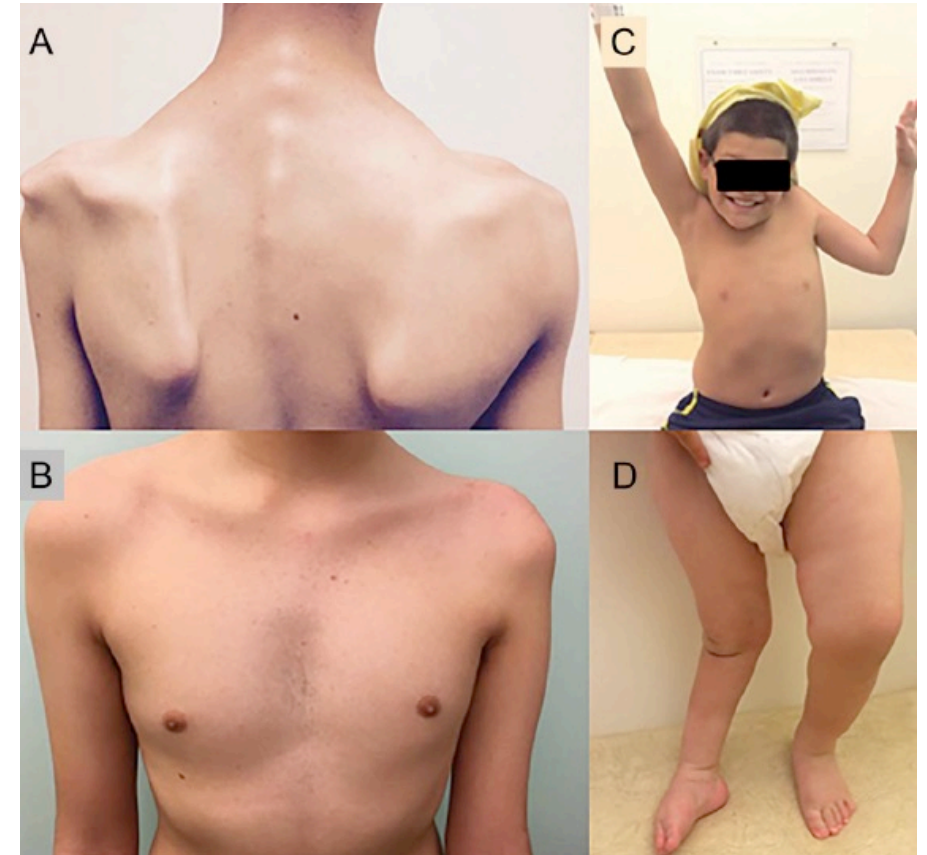
AFM Natural History





AFM Outcomes

- Functional improvements with rehabilitation therapies
 - Most recovery occurs early
 - Improvement still noted after 12 months
 - Distal, less-affected muscles > proximal, more-affected muscles > completely denervated muscles
- Motor deficits persist in ~75% at 1 year
- Nerve and tendon transplants → functional gains in certain patients

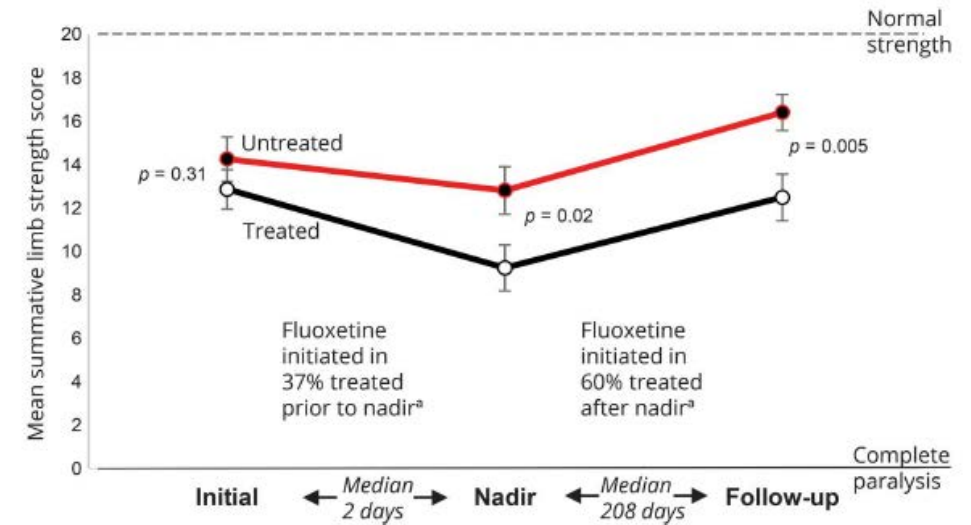


Polio-like muscle atrophy in affected limbs



Addressing AFM Future Challenges

- **Why are certain children affected?**
 - Host genetics studies
- **Role of infection vs. immune response?**
 - Basic science, NIH Natural History Study
- **Which treatments are most effective?**
 - No controlled human studies
 - EV-D68 monoclonal antibodies created
 - Screening antivirals *in vitro*, animal models
- **How can we prevent AFM?**
 - EV vaccine candidate identification underway



Observational study (2016):
Fluoxetine administered off-label
due to *in vitro* EV-D68 activity

- No signal of efficacy in retrospective analysis

Early Recognition: Key to AFM Advances

- **THINK AFM** in any patient with new onset weakness, particularly:
 - *Children with asymmetric, flaccid weakness in arms > legs*
 - *Following a febrile illness*
 - *Summer-fall season during enterovirus outbreaks*
- **DIAGNOSE AFM** by neurologic exam, neuroimaging, lumbar puncture
 - *Look for cause by collecting early biologic specimens (CSF, blood, stool, NP/OP)*
- **MANAGE AFM** with respiratory & 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 data and biological specimens using CDC Job Aid*

A Parent Perspective



Rachel Scott

AFM Parent and Co-Founder
Acute Flaccid Myelitis Association