Acute Flaccid Myelitis: What do we know?

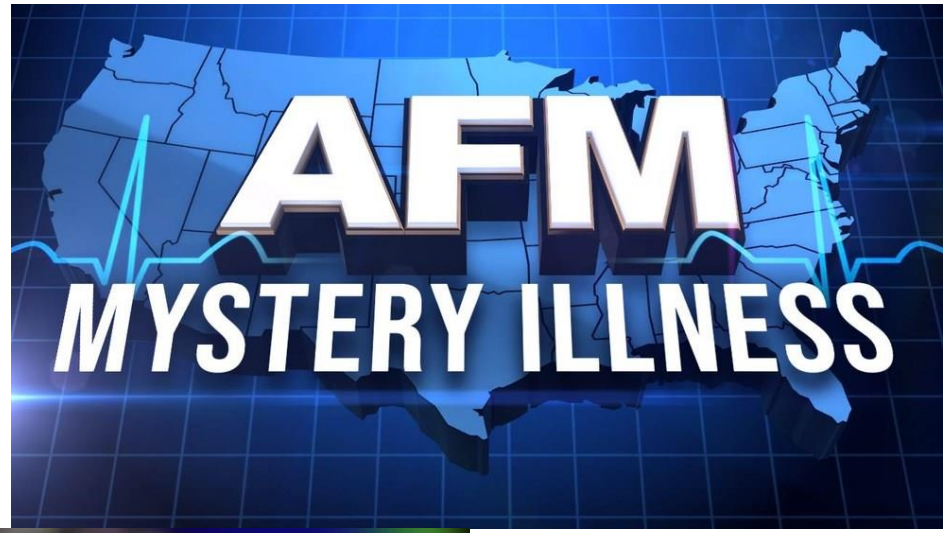
Rebecca Wallihan, MD

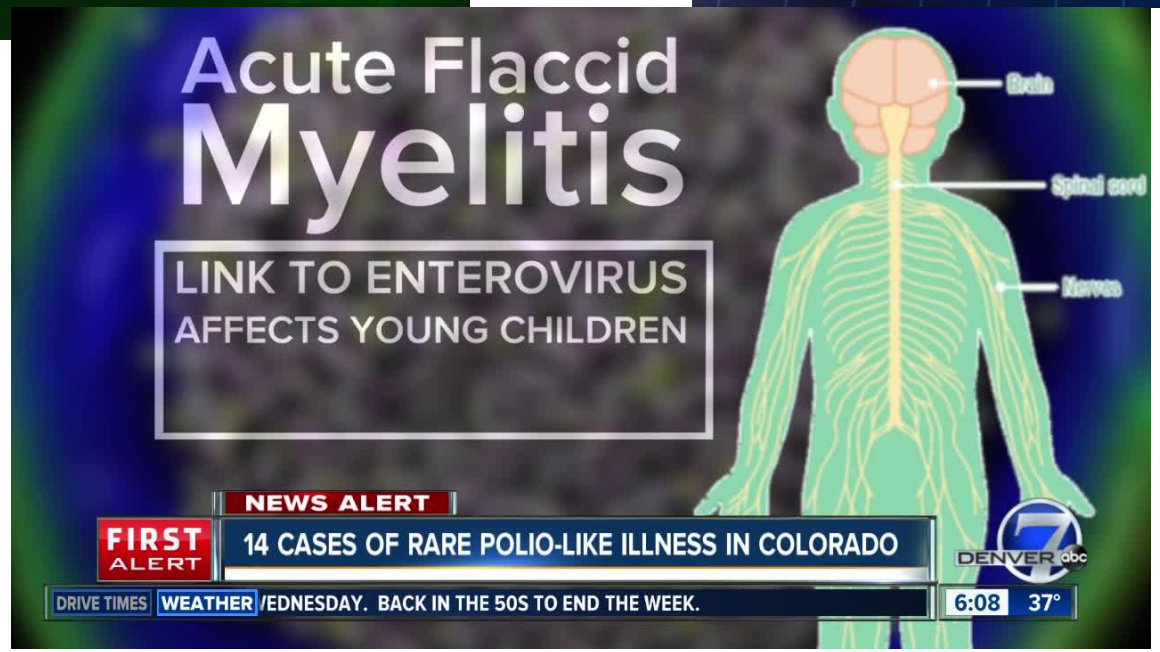
December 10, 2018

Disclosures

- None


'POLIO-LIKE'
illness


AFM
MYSTERY ILLNESS


Acute Flaccid
Myelitis
LINK TO ENTEROVIRUS
AFFECTS YOUNG CHILDREN
Brain
Spinal cord
Nerves
NEWS ALERT
FIRST ALERT
14 CASES OF RARE POLIO-LIKE ILLNESS IN COLORADO
DENVER 7 abc
DRIVE TIMES
WEATHER
/EDNESDAY. BACK IN THE 50S TO END THE WEEK.
6:08
37°

Objectives

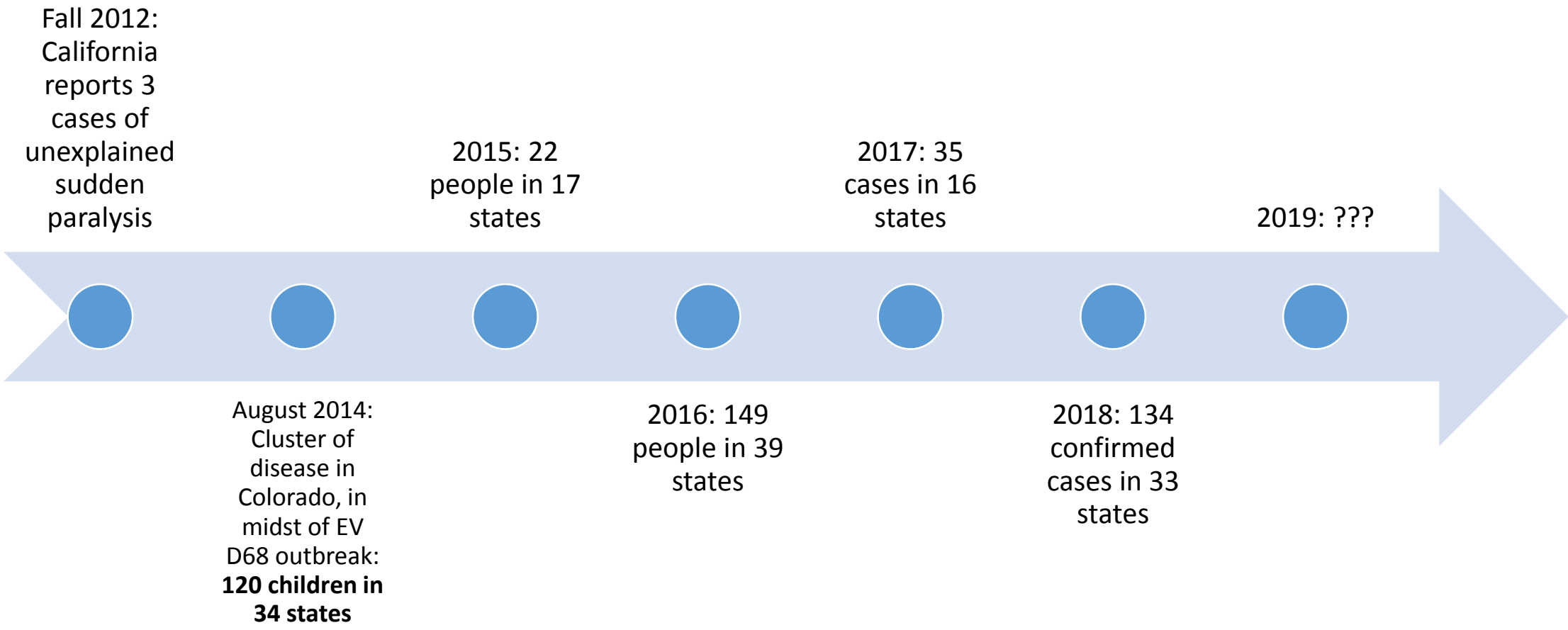
- Identify the clinical presentation of acute flaccid myelitis (AFM) in children
- Understand the epidemiology and potential etiologies of AFM
- Recognize potential outcomes of AFM in children

Mark’s Story

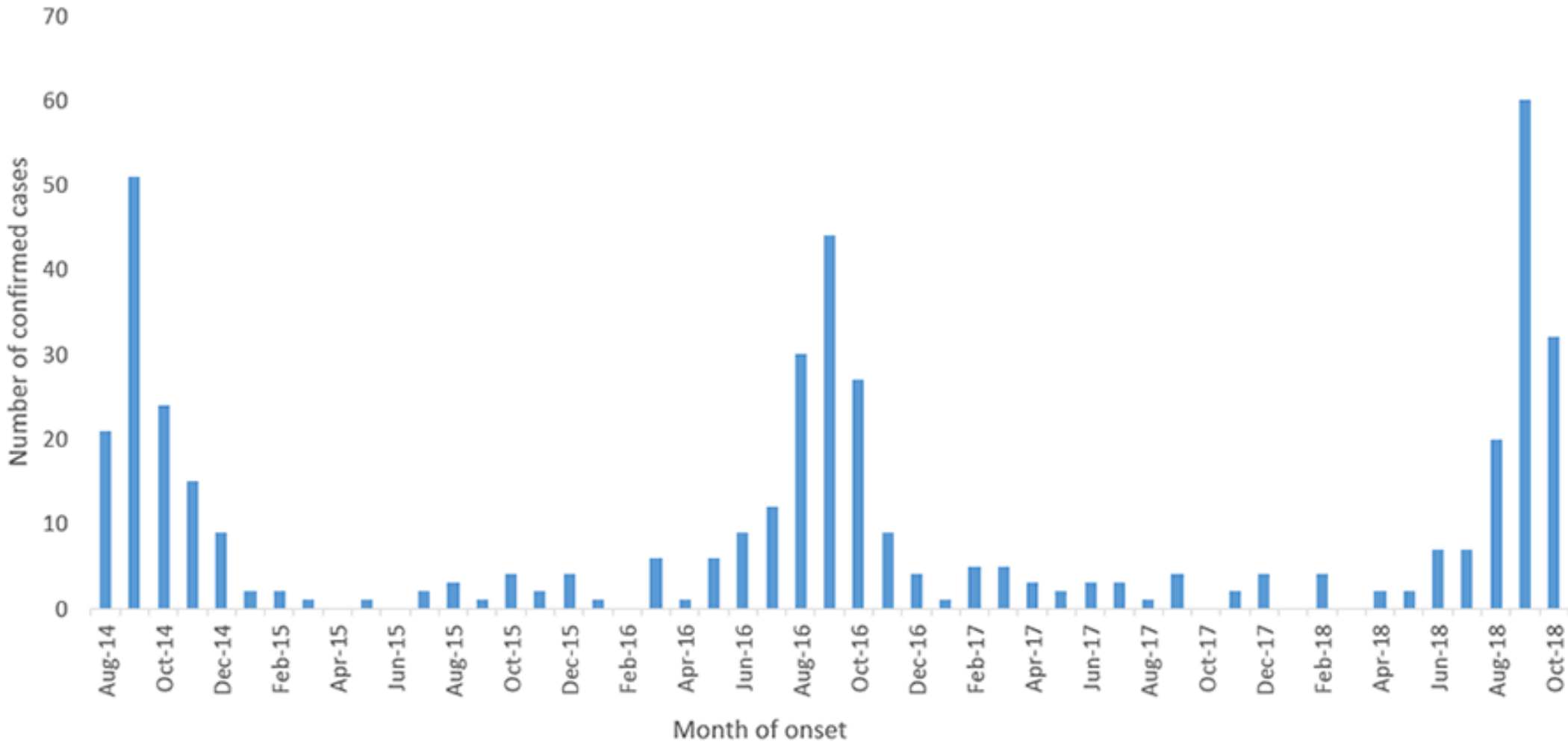
What is acute flaccid myelitis (AFM)?

- Illness with sudden onset of flaccid weakness in one or more extremities AND distinct grey matter lesions in the spinal cord
- CDC investigating since 2014
- Cause often unknown
  - Possibly caused by different viral pathogens including: enteroviruses (including poliovirus and EV-A71), flaviviruses like West Nile virus or Japanese encephalitis virus, herpesviruses, and adenoviruses

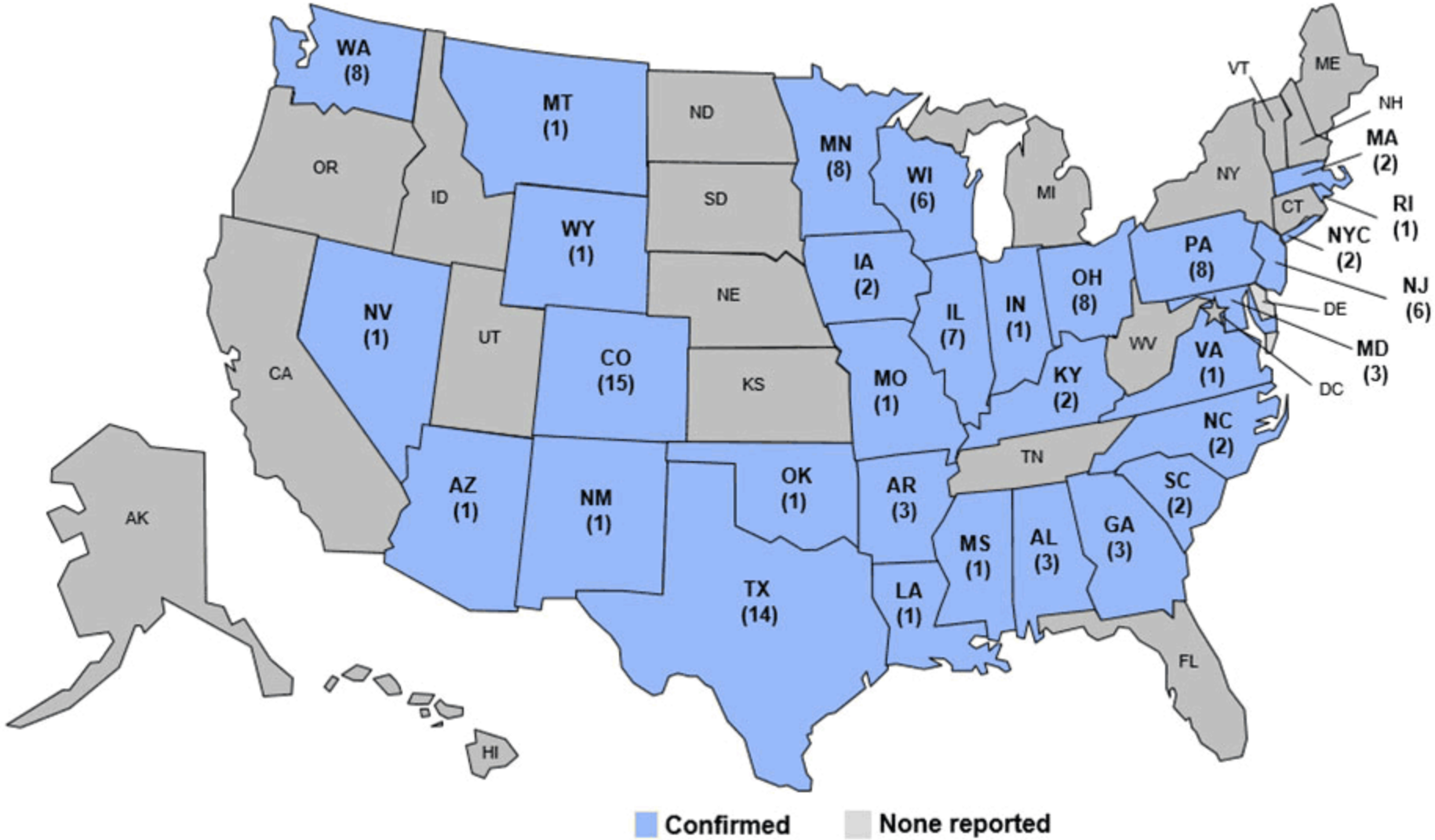
Acute flaccid myelitis in the US



Number of confirmed U.S. AFM cases reported to CDC by month of onset, August 2014 - October 2018^*†



2018 confirmed cases of acute flaccid myelitis (AFM) by state (N=116)*



*Confirmed AFM cases as of November 23, 2018. Patients under investigation are still being classified, and the case counts are subject to change. Case counts will be updated every Monday.

Demographics

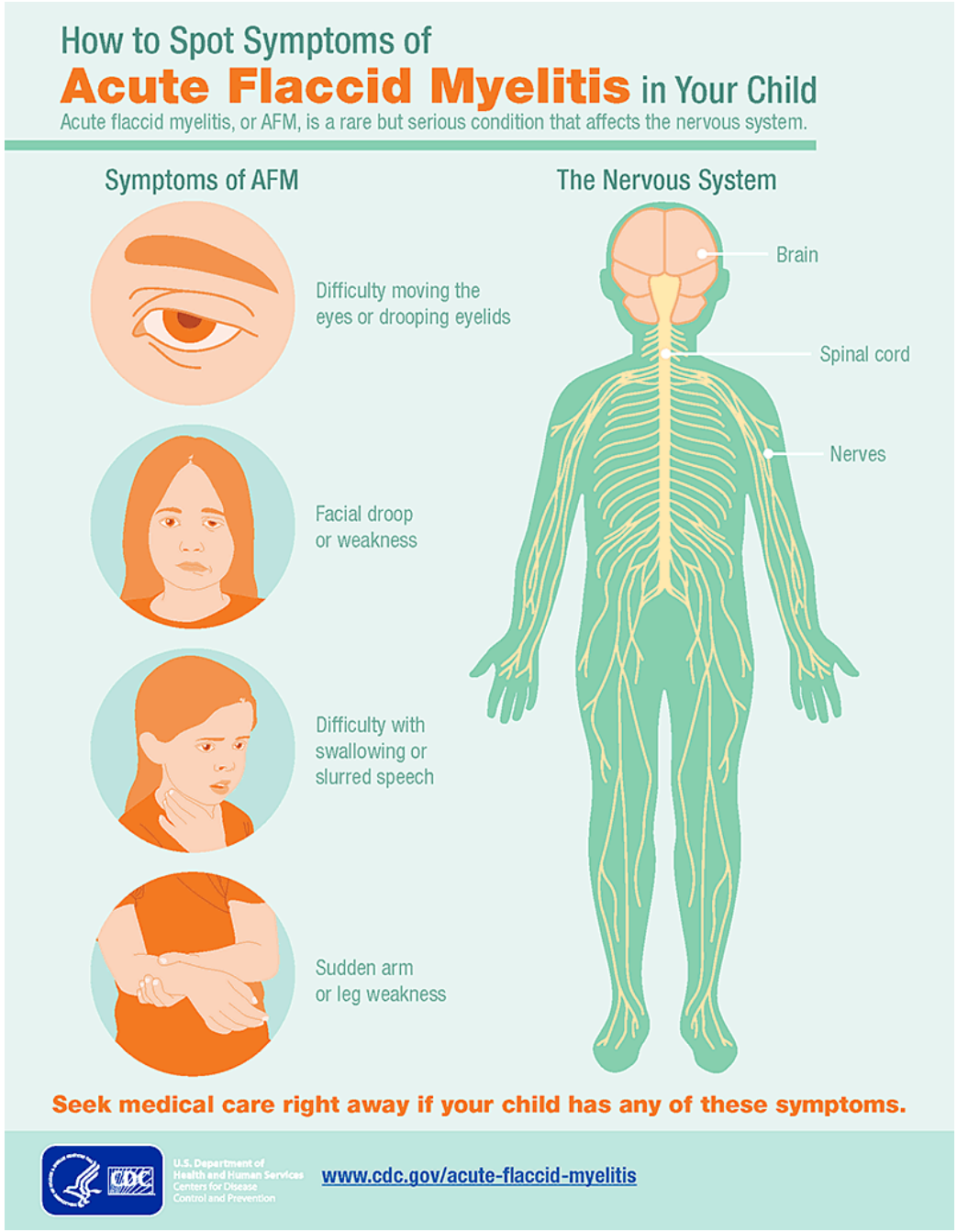
	2012-2015 CDC	2018 CDC
No. of cases	120	80
Sex (% male)	59	59
Median age, years (range)	7.1 (0.4-20.8)	4 (0.6-32)
Pre-existing conditions, %	21	NR
• Asthma	10	NR
• Immunocompromised	2	NR

Messacar et al, *Ann Neurol*, 2017
CDC, 2018

How does AFM present?

Symptoms

- Weakness in one or more limbs
  - may be accompanied by stiff neck, headache, or pain in the affected limb(s)
- Onset of weakness is rapid (hours to a few days)
- Cranial nerve abnormalities
  - Facial or eyelid droop
  - Difficulty swallowing or speaking
  - Hoarse or weak cry



Prodromal illness

	2012-2015 CDC	2018 CDC
Prodromal illness, %	90	99
• Fever	64	81
• Respiratory symptoms	81	78
• GI symptoms	NR	38

*Median 4.5 days from onset of illness to limb weakness

Messacar et al, *Ann Neurol*, 2017
CDC, 2018

Clinical presentation

	2012-2015 CDC	2018 CDC
Neurologic illness/deficits, %		
Altered mental status	11	NR
Limb weakness*	100	100
• UE weakness	77	48
• LE weakness	66	52
• Asymmetric	47	NR
Sensory involvement	21	NR
Cranial nerve dysfunction	28	NR

*Upper limb only in 48%, lower limb only in 9%

Messacar et al, *Ann Neurol*, 2017
CDC, 2018

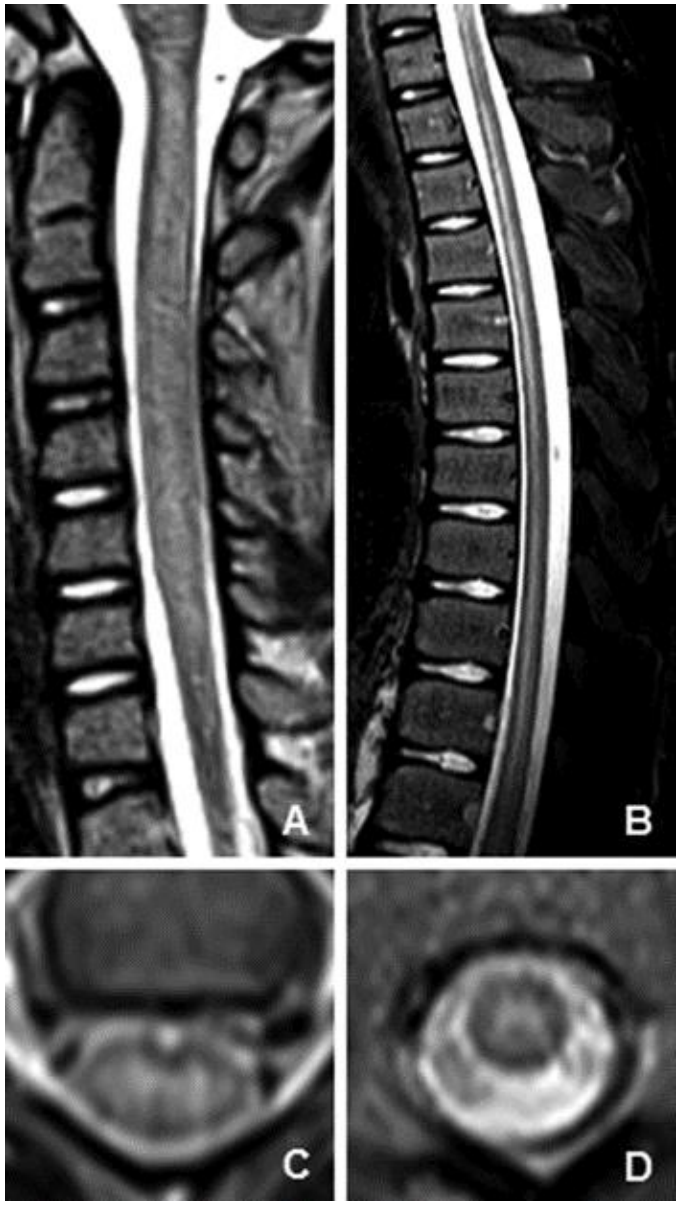
Laboratory findings

	2012-2015 CDC	2018 CDC
CSF pleocytosis, % (median, range)	81 (44, 0-664)	83 (103, 6-814)
CSF protein	43 (17-921)	47 (9-289)
Virus identified in CSF, %	2	1
EV D68 in respiratory specimen, %	20	22
Non-D68 rhino/enterovirus, %	21	31

Messacar et al, *Ann Neurol*, 2017
CDC, 2018

Imaging findings

- Grey matter lesions in > 1 spinal segment – mostly cervical
- Ventral (anterior horn) cells most commonly involved
  - May have entire central grey matter involved, producing characteristic “H” pattern on axial images
  - Ventral and dorsal nerve roots may demonstrate signal abnormality
  - Conus medullaris and cauda equina involvement frequent
- Hyperintensity on T2 and FLAIR weighted sequences and are usually non-enhancing
- Brainstem involvement possible



Messacar et al, *Ann Neurol*, 2017
CDC, 2018

Imaging findings

	CDPH (n=59)	CHCO (n=12)	PCH (n=11)	CDC (n=120)
T2 gray matter lesions spanning multiple vertebral levels on spinal cord MRI	90 (>3 levels)	100 (>3 levels)	91 (>3 levels)	96 (>1 level)
Nerve root enhancement on spinal cord MRI	20	40	NR	34
Brainstem lesions on brain MRI	NR	75	36	35
Supratentorial lesions on brain MRI	31	0	0	11

CDPH = California Department of Public Health. June 2012–July 2015.
CHCO = Children's Hospital Colorado. August 1, 2014–October 31, 2014.
PCH = Primary Children's Hospital. February 2014–January 2015.

Messacar et al, *Ann Neurol*, 2017

AFM differential diagnosis

- Synovitis
- Neuritis
- Limb injury
- Guillain-Barre syndrome (GBS)
- Transverse myelitis
- Stroke, including spinal stroke
- Tumor
- Acute cord compression
- Conversion disorder

Clinical Presentation of Acute Flaccid Myelitis Compared to Other Neurologic Syndromes With Acute Limb Weakness

		Acute Flaccid Myelitis Cases in the United States 2012–2015	Idiopathic Transverse Myelitis	Acute Inflammatory Demyelinating Polyneuropathy	Acute Disseminated Encephalomyelitis
Prodrome	Preceding illness	Febrile respiratory or gastrointestinal illness common, median of 7 days previous	Respiratory, gastrointestinal, or systemic illness common	Respiratory or gastrointestinal illness common 2 to 4 weeks previous	Febrile respiratory illness or vaccination common
	Associated symptoms at onset	Fever; meningeal signs; limb/neck/back pain common	Dysesthesia and paresthesias;back pain	Afebrile;no meningeal signs;leg pain, unsteady gait	Fever; meningeal signs; encephalopathy
Motor deficits	Progression	Progression over hours to days	Progression over hours to days	Ascending weakness over hours to days, nadir by 2 to 4 weeks	Progression of multifocal deficits over 4 to 7 days
	Distribution	Asymmetric; upper>lower limb	Symmetric or asymmetric; bilateral;below level of lesion	Symmetric	Commonly asymmetric
	Tone	Flaccid	Can be flaccid in acute phase, then spastic	Flaccid	Spastic
	Deep tendon reflexes	Decreased or absent	Can be decreased in acute phase, then increased	Decreased or absent	Increased
Associated deficits	Sensory deficits	Variably present in affected limb	Common, sensory level present	Distal paresthesias with little objective sensory loss; no sensory loss present in acute motor axonal neuropathy variant	Common
	Autonomic deficits	Bowel and bladder dysfunction possible	Common, especially bowel or bladder dysfunction	Common, especially cardiovascular instability	Possible
	Cranial nerve deficits	Common, especially bulbar dysfunction, diplopia, facial weakness	Uncommon	Uncommon, but may occur with variants (Miller Fischer variant)	Possible, especially optic neuritis

Fever & meningeal signs common

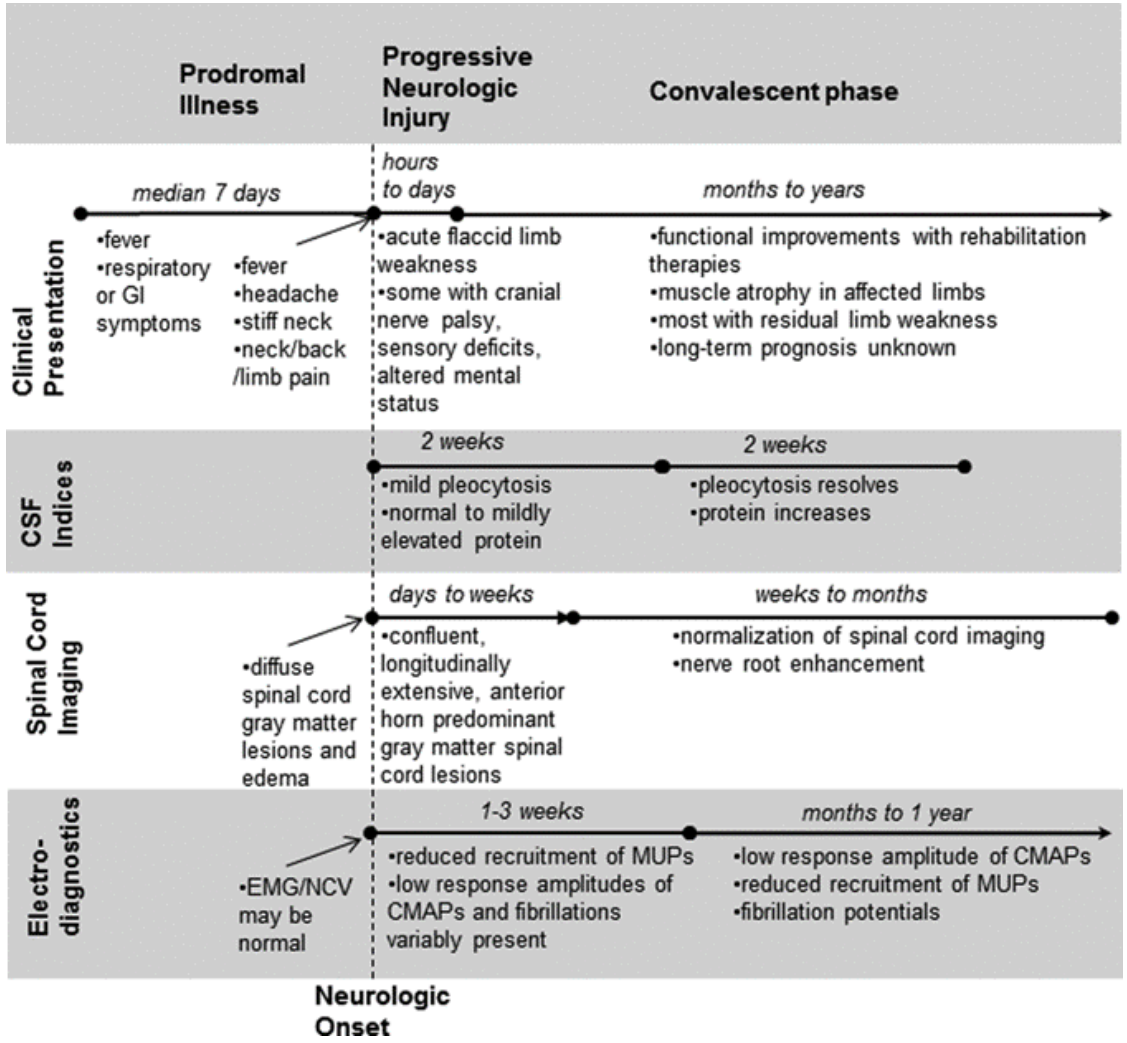
Flaccid (instead of spastic)

Cranial nerve deficits common

Messacar et al, *Ann Neurol*, 2017

Putting it all together

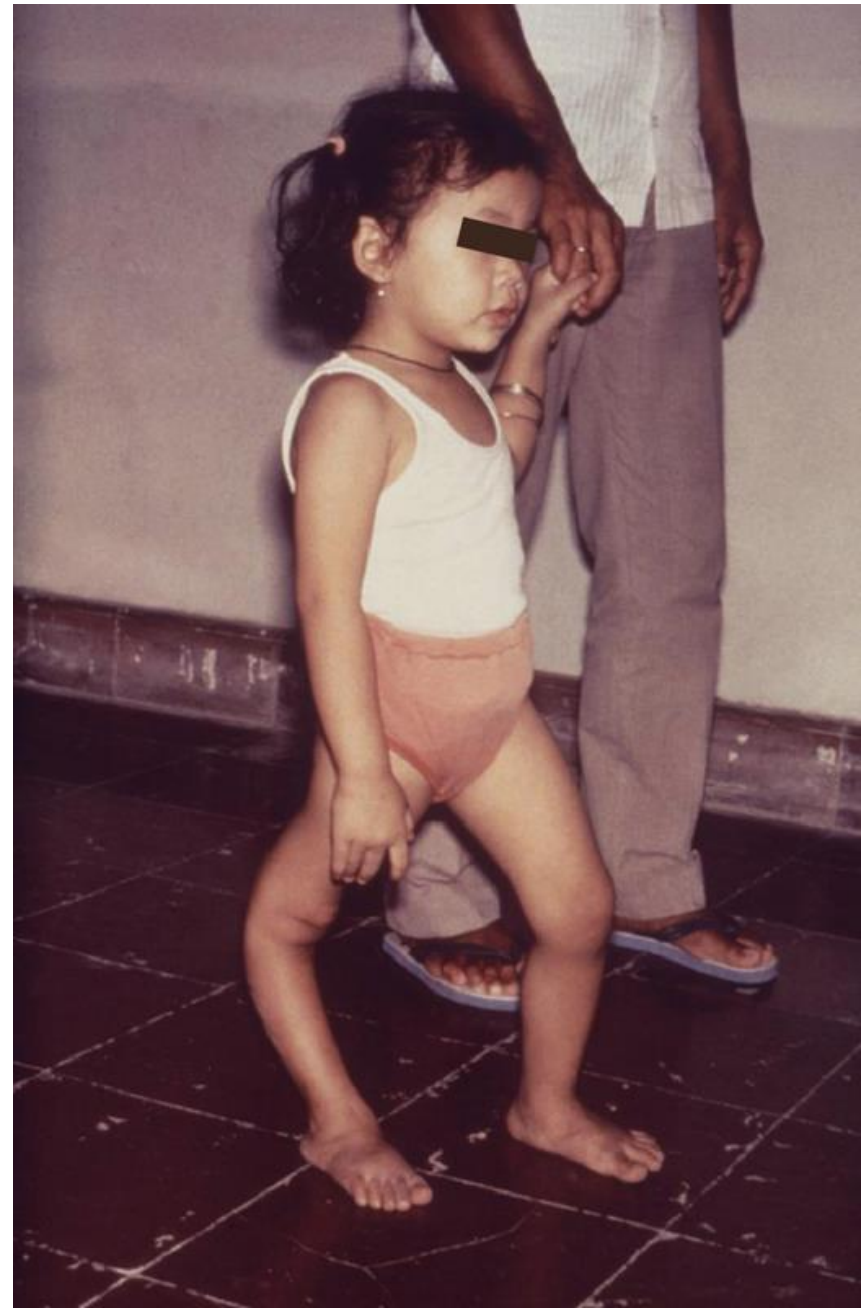
- Nonspecific prodromal illness
- Rapid onset weakness
- MRI findings in grey matter
- Recovery?



Messacar et al, *Ann Neurol*, 2017

What do we know about potential causes?


Rare Historical Photos.com



Enteroviruses?

- Enterovirus 71
  - Typically causes hand-foot-mouth disease
  - Known association with neurologic disease during outbreaks
    - Acute flaccid myelitis
    - Encephalomyelitis
- Enterovirus D68
  - First described in 1962
  - Respiratory illness

Pathogens	CSF	Respiratory	Serum/Plasma	Stool/Rectal Swab
Enterovirus/rhinovirus	1/55 (2)	24/56 (43)[a]	0/43 (0)	11/54[b] (20)
EV-D68	1/1 (100)	11/23 (48)	. . .	0/11 (0)
Non–EV-D68	0/1 (0)	12/23 (52)	. . .	11/11 (100)
Adenoviruses	0/48 (0)	0/44 (0)	1/39 (3)	5/47 (11)
Herpesviruses				
Herpes simplex virus 1	0/41 (0)	0/35 (0)	0/33 (0)	. . .
Herpes simplex virus 2	0/41 (0)	0/35 (0)	0/33 (0)	. . .
Varicella zoster virus	0/41 (0)	0/35 (0)	0/33 (0)	. . .
Epstein-Barr virus	1/41 (2)	3/35 (9)	2/31 (6)	. . .
Human herpesvirus 6A	0/39 (0)	. . .	0/29 (0)	. . .
Human herpesvirus 6B	0/39 (0)	. . .	0/29 (0)	. . .
Cytomegalovirus	0/38 (0)	. . .	0/26 (0)	. . .
Panviral PCR platform	0/31 (0)	2/9 (22)[c]	1/16 (6)[d]	1/7 (14)[e]
Metagenomic next-generation sequencing	14/35 (40)[f]	1/1 (100)[g]	7/12 (54)[h]	. . .
Arboviruses (IgM)				
West Nile	0/2 (0)	. . .	0/35 (0)[i]	. . .
St Louis encephalitis	0/2 (0)	. . .	0/35 (0)[i]	. . .
La Crosse	0/4 (0)	. . .	0/35 (0)[i]	. . .

Sejvar et al, CID, 2016

TABLE. Enterovirus/rhinovirus (EV/RV) type testing results* of specimens from patients with confirmed acute flaccid myelitis and specimens positive for EV/RV, by specimen type — United States, January–October 2018

Enterovirus and rhinovirus testing, by type	CDC laboratory results			
	CSF specimens (n = 21)	Respiratory specimens (n = 59)	Stool/Rectal swab specimens (n = 45)	Total (N = 125)
EV- or RV-positive no. (%)	**2 (10)**	**31 (53)**	**17 (38)**	**50**
Subtype, no. (%) positive†				
EV-A71	1 (50)	10 (32)	10 (59)	21 (42)
EV-D68	1 (50)	13 (42)	1 (6)	15 (30)
EV-D68/PeV-A6	0 —	1 (3)	0 —	1 (2)
RV-A38	0 —	1 (3)	0 —	1 (2)
RV-A101	0 —	1 (3)	0 —	1 (2)
RV-A24/PeV-A6	0 —	1 (3)	0 —	1 (2)
RV-A81	0 —	1 (3)	0 —	1 (2)
RV-A54	0 —	1 (3)	0 —	1 (2)
CVA2	0 —	0 —	1 (6)	1 (2)
CVA4	0 —	0 —	1 (6)	1 (2)
CVA9	0 —	0 —	1 (6)	1 (2)
CVA16	0 —	0 —	1 (6)	1 (2)
PeV-A1	0 —	0 —	1 (6)	1 (2)
Nontyped EV/RV	0 —	2 (6)	1 (6)	3 (6)

Abbreviations: CSF = cerebrospinal fluid; CVA = Coxsackie A virus; PeV-A6 = parechovirus A6.
* Specimens tested at CDC laboratory.
† Among EV- or RV-positive specimens.

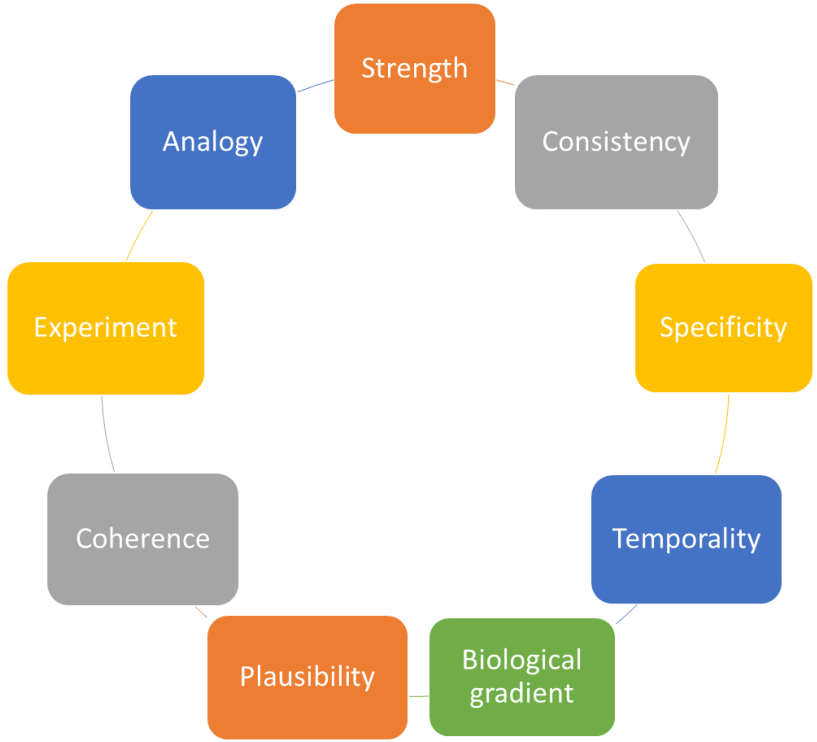
McKay et al, MMWR 2018

What about EV D68? – Bradford Hill Criteria

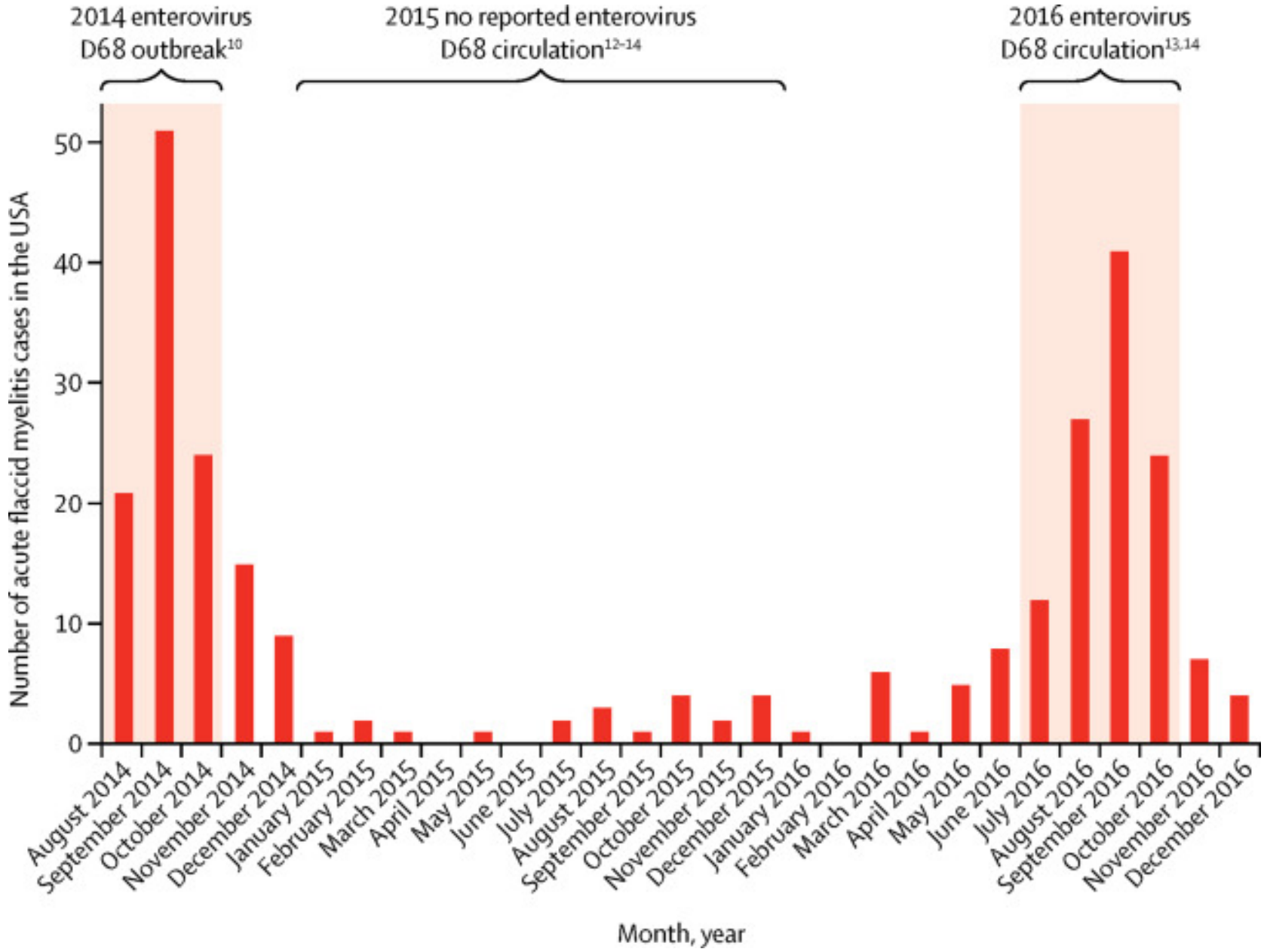
Dyda et al, *Euro Surveill*, 2018
Messacar et al, *Lancet*, 2018

Strength

- Exposure → higher risk of disease
- Increased AFM cases clustering during periods of EV D68 circulation in 2014 and 2016
- Sporadic AFM cases with no clustering in 2015 when EV D68 not circulating
- 4.5–10.3 greater odds of detection in AFM patients than respiratory controls in Colorado case control study



Dyda et al, *Euro Surveill*, 2018
Messacar et al, *Lancet*, 2018

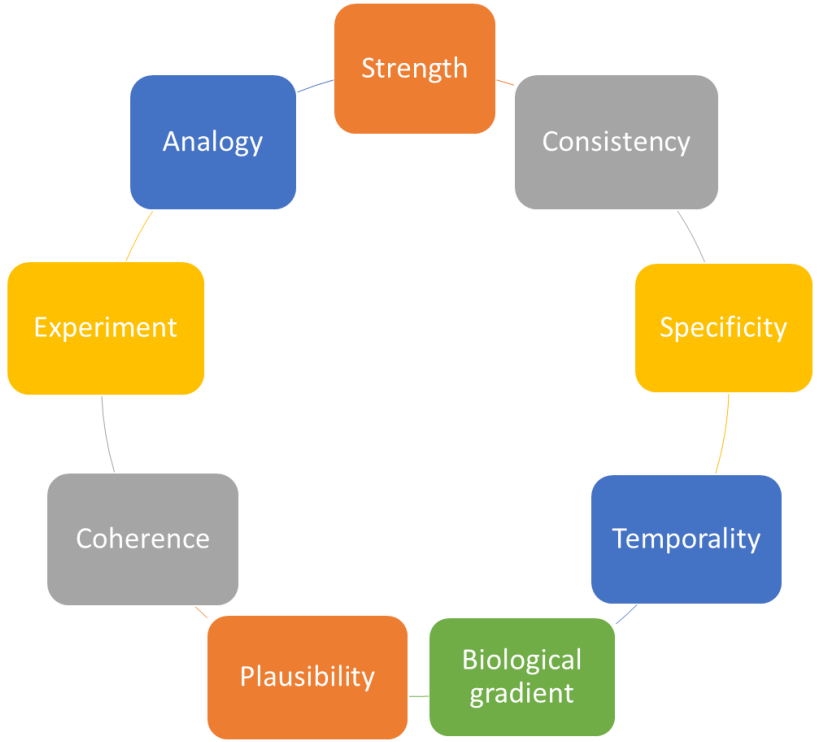


Messacar et al, *Lancet*, 2018

Consistency

- Repetition of findings

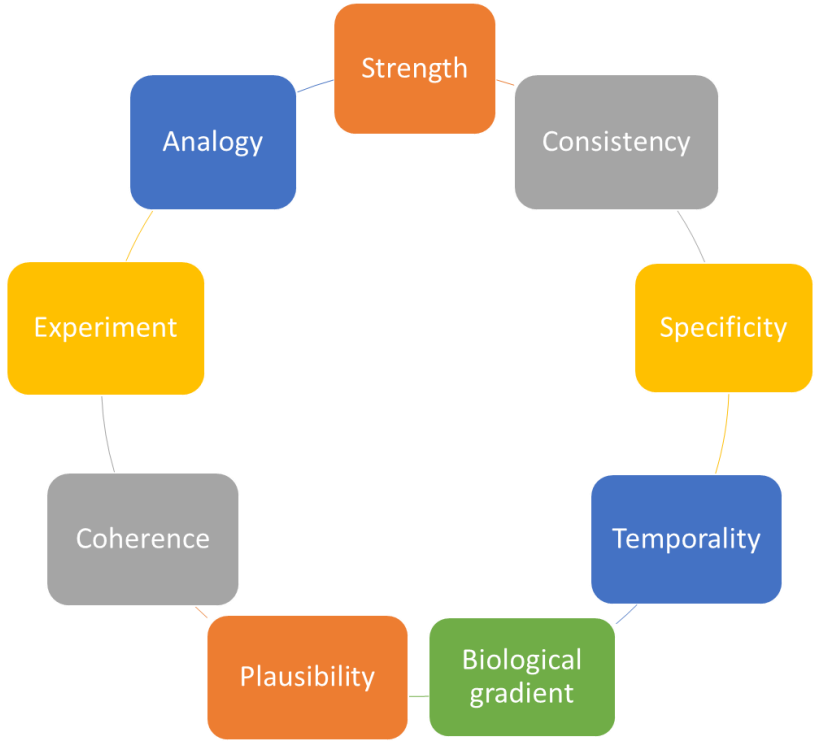
- Cases of paralysis with enterovirus D68 detection reported from
- 14 countries on six continents with consistent clinical presentation



Dyda et al, *Euro Surveill*, 2018
Messacar et al, *Lancet*, 2018

Specificity

- Exposure causes one specific disease or syndrome or specific population
- Partially fulfilled

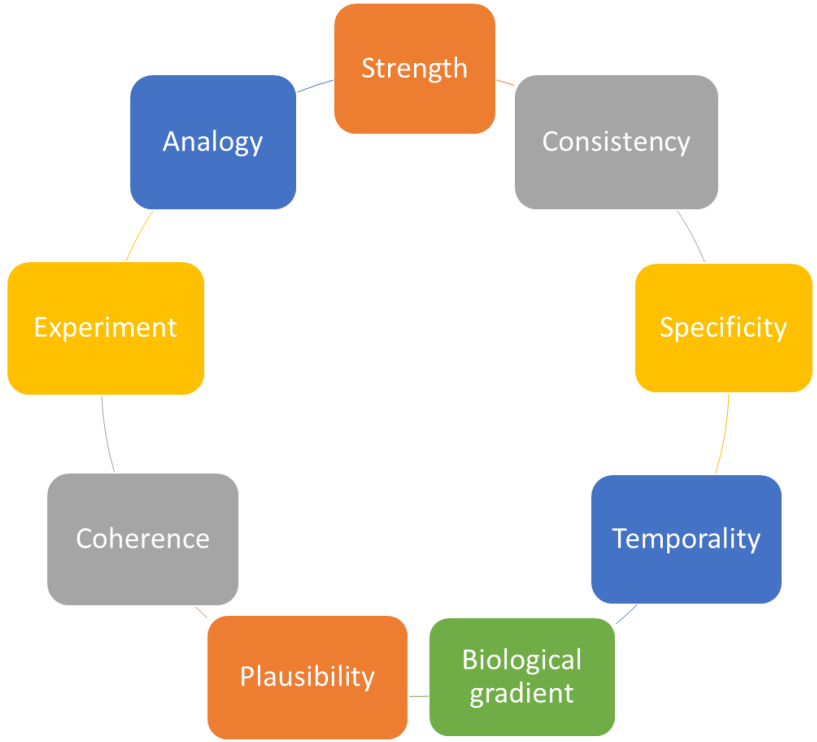


Dyda et al, *Euro Surveill*, 2018
Messacar et al, *Lancet*, 2018

Temporality

- Exposure occurs before disease

- Febrile respiratory prodrome precedes onset of neurological symptoms
- Cases with samples collected during respiratory prodrome positive before onset of neurological symptoms
- Frequency of EV D68 detection decreases with delayed sampling after AFM onset

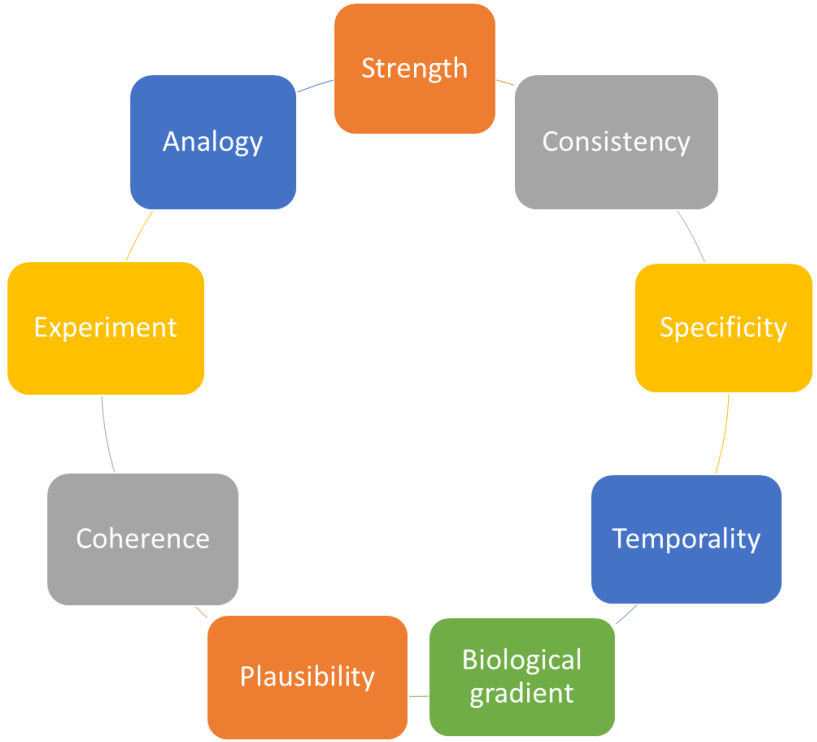


Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

Biological gradient

- Dose-response relationship

- No dose-response relationship noted and low level detection of in respiratory specimens of some severe AFM cases

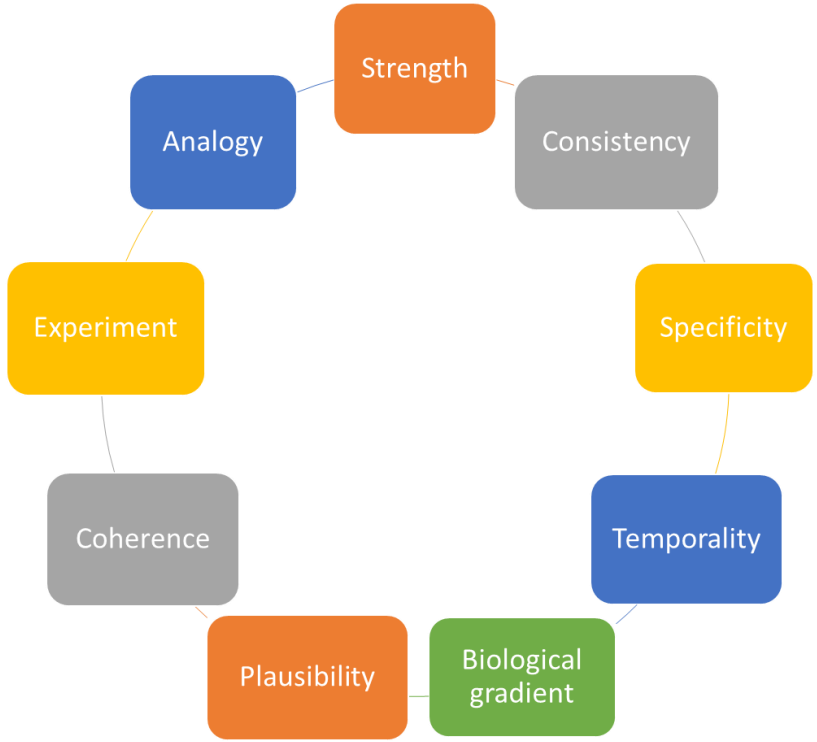


Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

Plausibility

- Conceivable mechanism

- 5 case reports of acute flaccid paralysis or AFM with EV D68 in CSF
- Most AFM cases with no EV D68 and no alternative pathogens in CSF
- One case with autopsy histopathology consistent with enterovirus and EV D68 in CSF

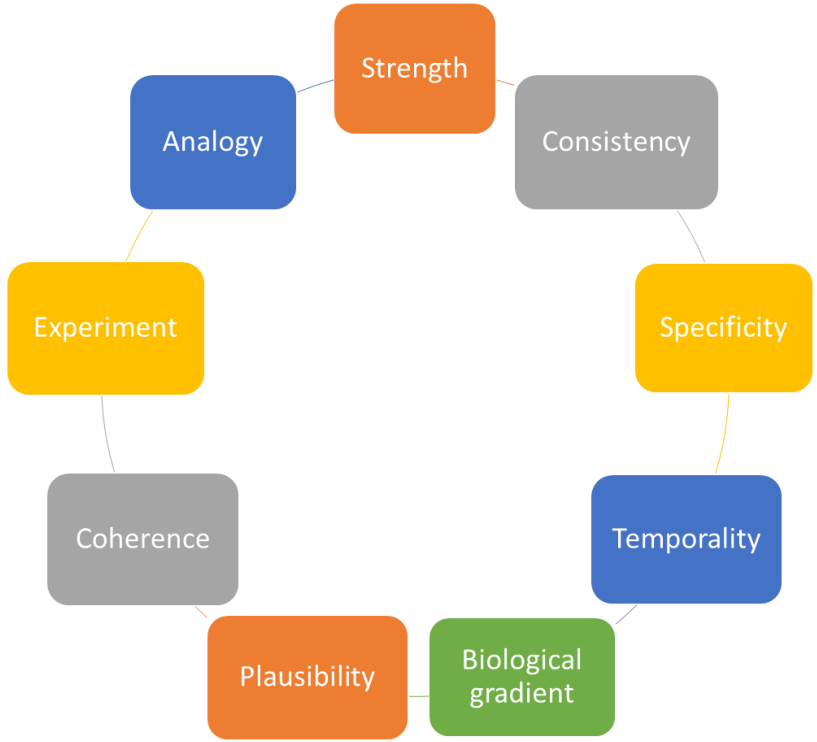


Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

Coherence

- Does not contradict previous knowledge

- Enteroviruses known to affect CNS
- EV A71 associated with neurological complications and encephalomyelitis

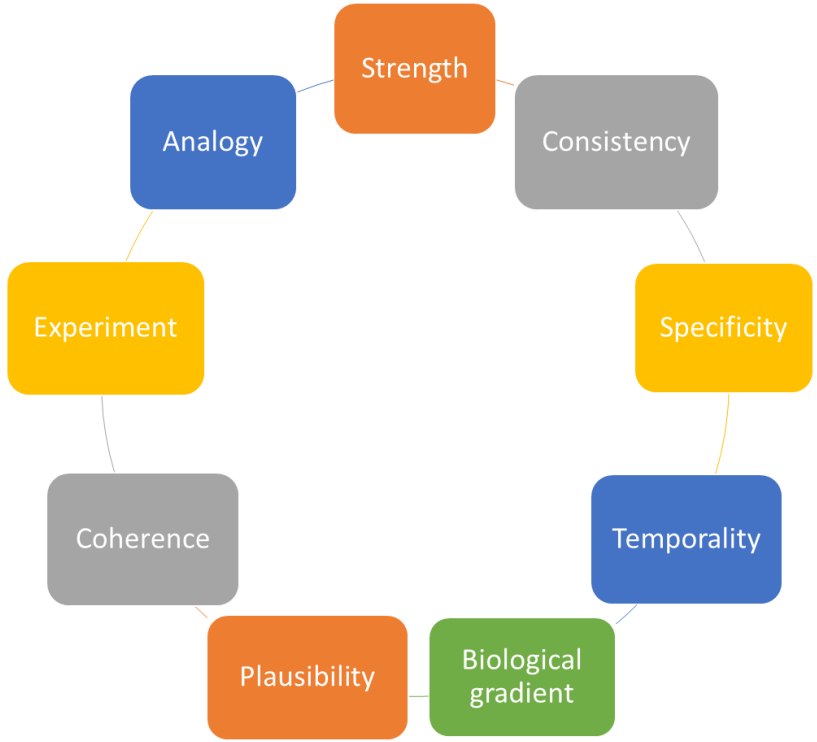


Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

Experiment

- Animal models

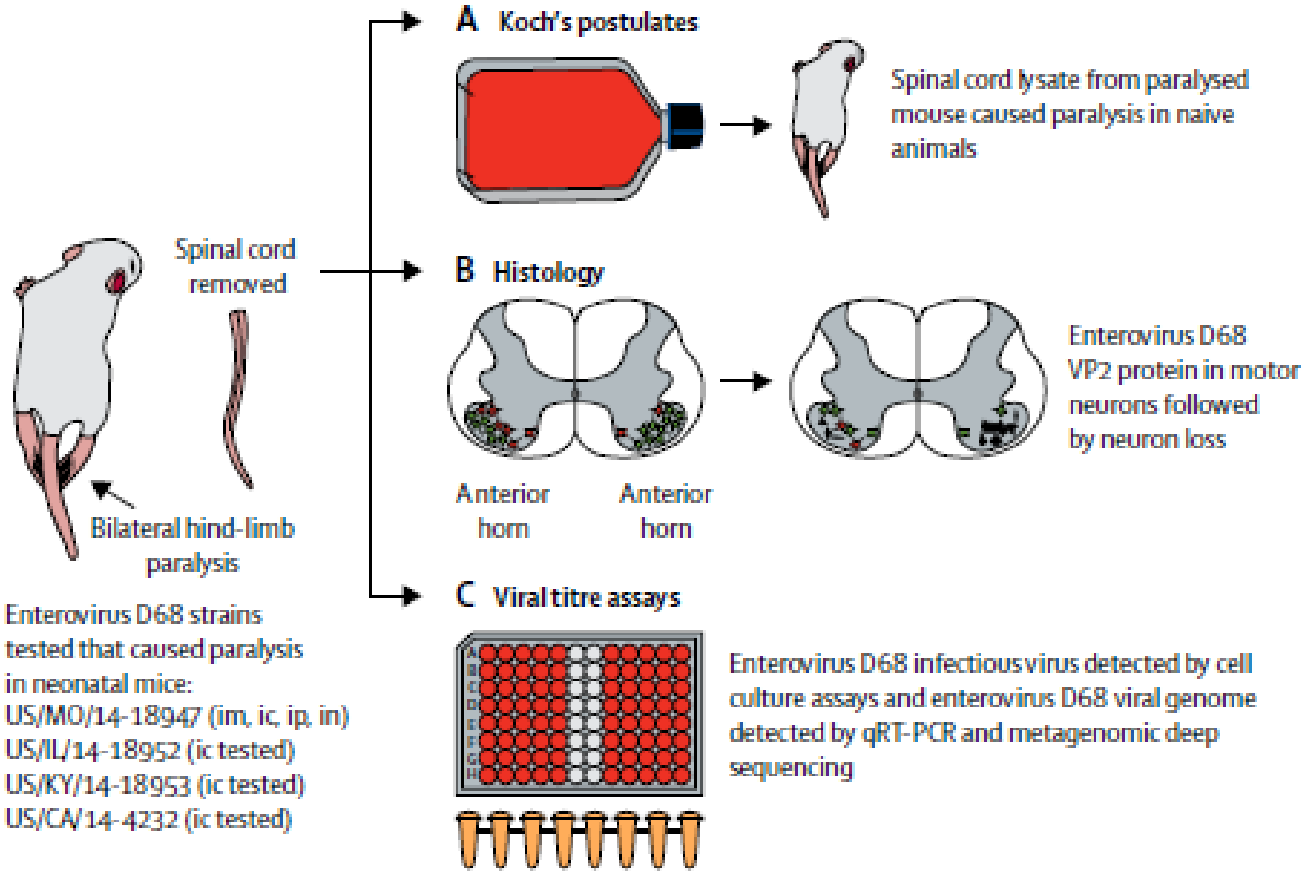
- Recent strains cause paralytic myelitis in mouse model, whereas historical strains do not
- Enterovirus D68 infects and causes loss of motor neurons in anterior horn of spinal cord in mice
- Enterovirus D68 antibodies protect against paralytic disease in mice, whereas immunosuppression leads to increased paralysis and mortality



Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

Evidence for Enterovirus D68

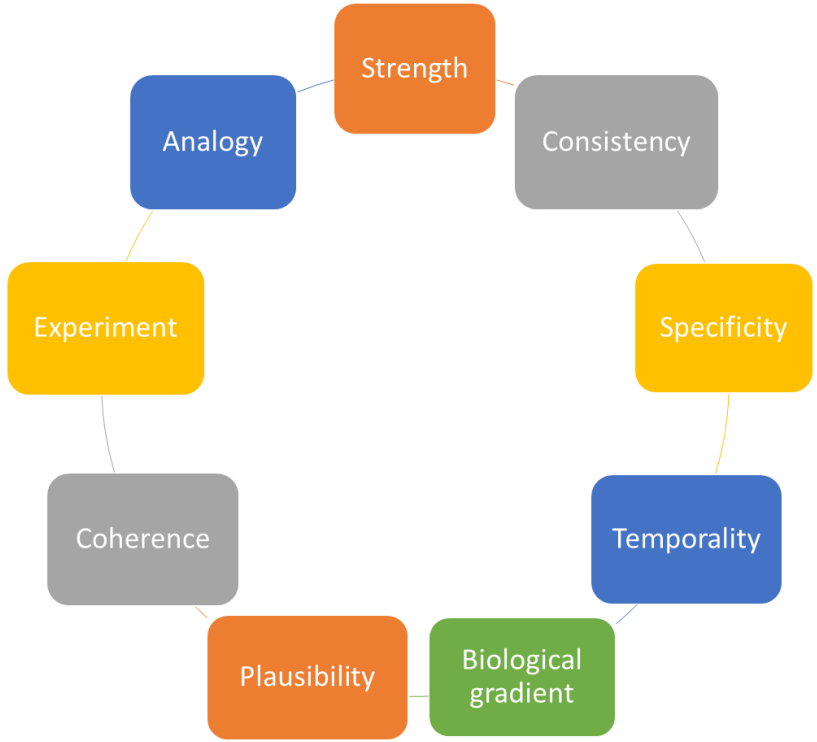
- Mouse model
- EV D68 strain caused paralysis by multiple routes of inoculation:
  - Intramuscular, 100%
  - Intracerebral, about 50%
  - Intraperitoneal, about 5%
  - Intranasal, about 3%



Messacar et al, *Lancet*, 2018

Analogy

- Association of similar exposure and disease outcome
- Clinical presentation, neuroimaging, electrophysiological findings similar to paralytic disease due to poliovirus and EV A71
- Enterovirus D68 found less commonly in CSF than poliovirus or EV A71
- Detection of poliovirus or enterovirus A71 from stool when absent in CSF analogous to EV D68 detection in respiratory specimens



Dyda et al, *Euro Surveill*, 2018
Messecar et al, *Lancet*, 2018

What can we do?

Potential Treatment Options

- Steroids
- IVIG
- Plasma exchange
- Antivirals
- Fluoxetine

Steroids

- Has often been given in combination with other therapies
- Higher mortality in mouse models
- Poorer outcomes with EV-71

- *There is no indication that corticosteroids should be either preferred or avoided in the treatment of AFM.*
- *There is no clear human evidence for efficacy of steroids in the treatment of AFM, and there is some evidence in a mouse model with EV-D68 that steroids may be harmful.*

IVIG

- Efficacy in prevention of progression to neuroinvasive disease in rodent models
- All AFM patients tolerated the treatment regimens well without major complications
- Neurologic improvement was seen in all patients regardless of treatment, but in all except one patient, deficits persisted

- *There is no indication that IVIG should be either preferred or avoided in the treatment of AFM.*
- *There is no clear human evidence for efficacy of IVIG in the treatment of AFM; evidence for efficacy is based on early treatment in animal models and it has not been given in a systematic manner to AFM patients to allow for measurements of efficacy.*

Plasma exchange

- Case reports

- *There is no indication that plasma exchange should be either preferred or avoided in the treatment of AFM.*
- *There is no clear human evidence for efficacy of plasma exchange in the treatment of AFM, and it has not been given in a systematic manner to AFM patients to allow for measurements of efficacy.*
- *Although there are inherent procedure-associated risks, there is no evidence that using plasma exchange for patients with AFM is likely to be harmful.*

Antivirals

- Specific pathogen from a sterile site not identified in the majority of AFM patients
- CDC testing revealed no activity against circulating strains of EV D68

- *There is no indication that antivirals should be used for the treatment of AFM, unless there is suspicion of herpesvirus infection (e.g., concomitant supra-tentorial disease or other clinical or radiologic features of herpesvirus infection).*

Treatment

No reported effect of any treatments…yet

	CDPH (n=59)	CHCO (n=12)	PCH (n=11)	CDC (n=120)
Intravenous immune globulin, %	73	75	82	73
Plasmapheresis, %	22	17	9	15
Intravenous steroids, %	71	42	55	54
Antivirals, %	3	17	0	NR

CDPH = California Department of Public Health. June 2012–July 2015.
CHCO = Children's Hospital Colorado. August 1, 2014–October 31, 2014.
PCH = Primary Children's Hospital. February 2014–January 2015.

Messacar et al, *Ann Neurol*, 2017

CDC Recommendations

- *For three main treatments used for AFM, intravenous immunoglobulin (IVIG), corticosteroids, and plasmapheresis, there is not enough human evidence to indicate a preference or an avoidance for their use at this time*
- *Treatment decisions should be made in conjunction with neurology and infectious diseases experts.*
- *The possible benefits of using corticosteroids for spinal cord edema or white matter involvement must be balanced by the possible harm due to immunosuppression in the setting of a possible viral infection.*
- *There is no indication for the use of other immunosuppressive agents in the management of AFM.*

Fluoxetine?

- Selective serotonin reuptake inhibitor
- Activity against enteroviruses in vitro
- Both in a mouse model and retrospective case comparison of AFM patients, neither showed improvement of neurologic outcomes

- *There is no indication that fluoxetine should be used for the treatment of AFM.*

What can we do?

- Steroids
- IVIG
- Plasma exchange
- Antivirals
- Fluoxetine
- **Supportive care**
- **Intensive rehabilitation therapy**

Supportive Care

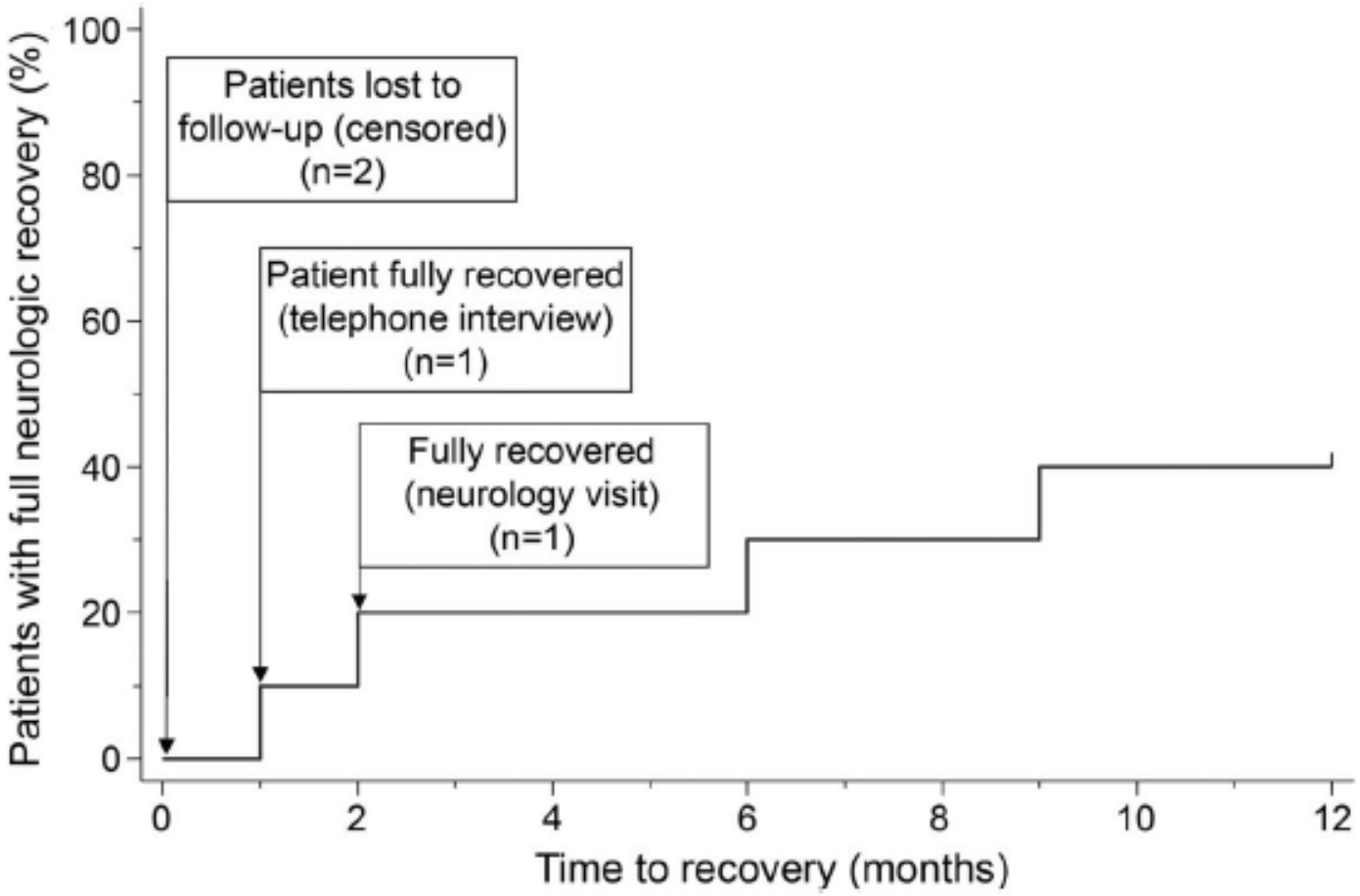
- Respiratory support
- Feeding
- Pain control
- Rehabilitation

What are the long term outcomes?

- Regain of function?
- Experimental surgery

Long term outcomes

Figure 2 Kaplan-Meier plot of time to neurologic recovery



40% full neurologic recovery at 12 months

Martin et al, *Neurol*, 2017

Long term outcomes

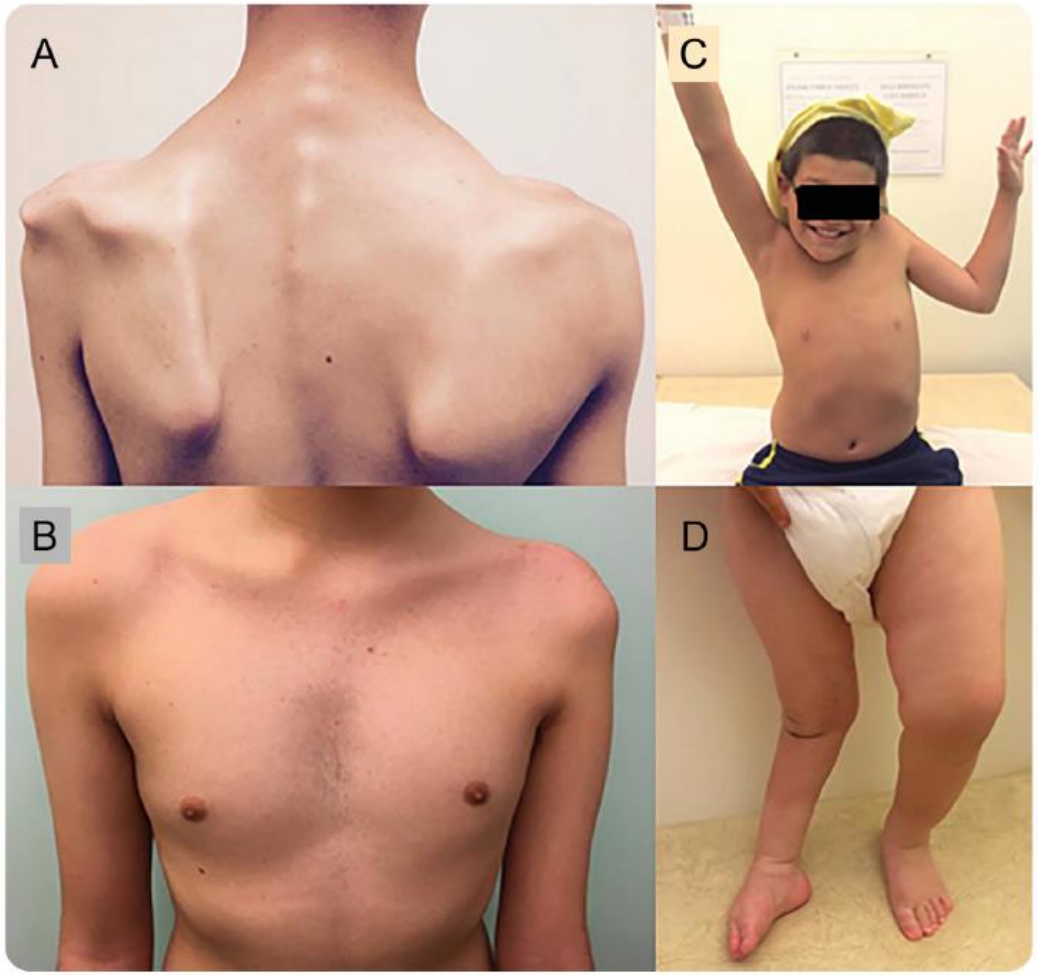
Table 1 Continued

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Function (clinical assessment)												
Onset	Horizontal diplopia, SCM weakness	R facial droop at rest, unable to fully close eye	Horizontal diplopia	Horizontal diplopia	Severe bulbar weakness, tracheostomy/ gastrostomy	Severe bulbar weakness, NIPPV, SCM weakness	Bilateral facial droop, unable to fully close eyes		Severe bulbar weakness, intubated, NG feeds	Subjective difficulty swallowing		
Six months	Normal vision and strength	Nasolabial fold flattening	a	a	Decannulated, hypophonia	Mild SCM weakness	R nasolabial fold flattening		a	Subjective difficulty swallowing		a
One year	Normal vision and strength	Nasolabial fold flattening	a	a	Hypophonia	Mild SCM weakness	Normal strength		a	Subjective difficulty swallowing		a

Martin et al, *Neurol*, 2017

Muscle atrophy

Muscle atrophy of affected limbs in children with acute flaccid myelitis (AFM)



Martin et al, *Neurol*, 2017

CBS NEWS / *October 11, 2018, 3:47 PM*

Doctors pioneer surgical treatment for rare, polio-like virus

Health officials are investigating a disturbing uptick in cases of paralysis in children from a rare illness in several states. Acute flaccid myelitis, also known as AFM, affects the nervous system and causes the muscles and reflexes in the body to become weak.

Its symptoms are likened to those caused by polio, which was eradicated in the U.S. thanks to the polio vaccine.

The illness is thought to attack the body's nervous system, although it's not well understood why. It can lead to paralysis and even death.

The U.S. Centers for Disease Control and Prevention said there have been 38 confirmed cases of AFM this year through the end of September. Fourteen cases have been reported in Colorado and six in Minnesota, most of them children. Earlier this week, three new cases were reported in patients being treated in Pittsburgh. CBS Chicago also reported that a 2-year-old in Chicago is recovering from the illness.

There is no specific treatment for AFM, but doctors at Children's Hospital Los Angeles are pioneering a new therapy to help patients regain movement.

"About half of kids with AFM will strengthen up enough on their own that they won't require any form of surgical intervention for their nerves. The other half won't," Dr. Mitchel Seruya, director of the Brachial Plexus and Peripheral Nerve Center at Children's Hospital Los Angeles, told CBS News.

Seruya is working on a nerve transfer surgery to help these patients.

Four-year-old Maipele Burns is one of the children receiving the treatment. She was born with chronic asthma, but an attack just before her second birthday was different

Conclusions

- We do not yet fully understand the pathogenesis of AFM
- Presentations variable and range from mild to severe
- Treatments have not been given systematically → difficult to determine efficacy
- Long term outcomes unknown, but many patients have residual deficits
- Published data limited

Advice for practitioners

- When AFM is suspected, hospitalization is recommended
  - Do not ignore limb weakness!
- Monitor closely, consider ICU care
  - Potential for rapid deterioration of weakness and respiratory compromise
- Obtain brain and spine MRI
- Immediate consultation with neurology and ID

Mark – where is he now?

Questions