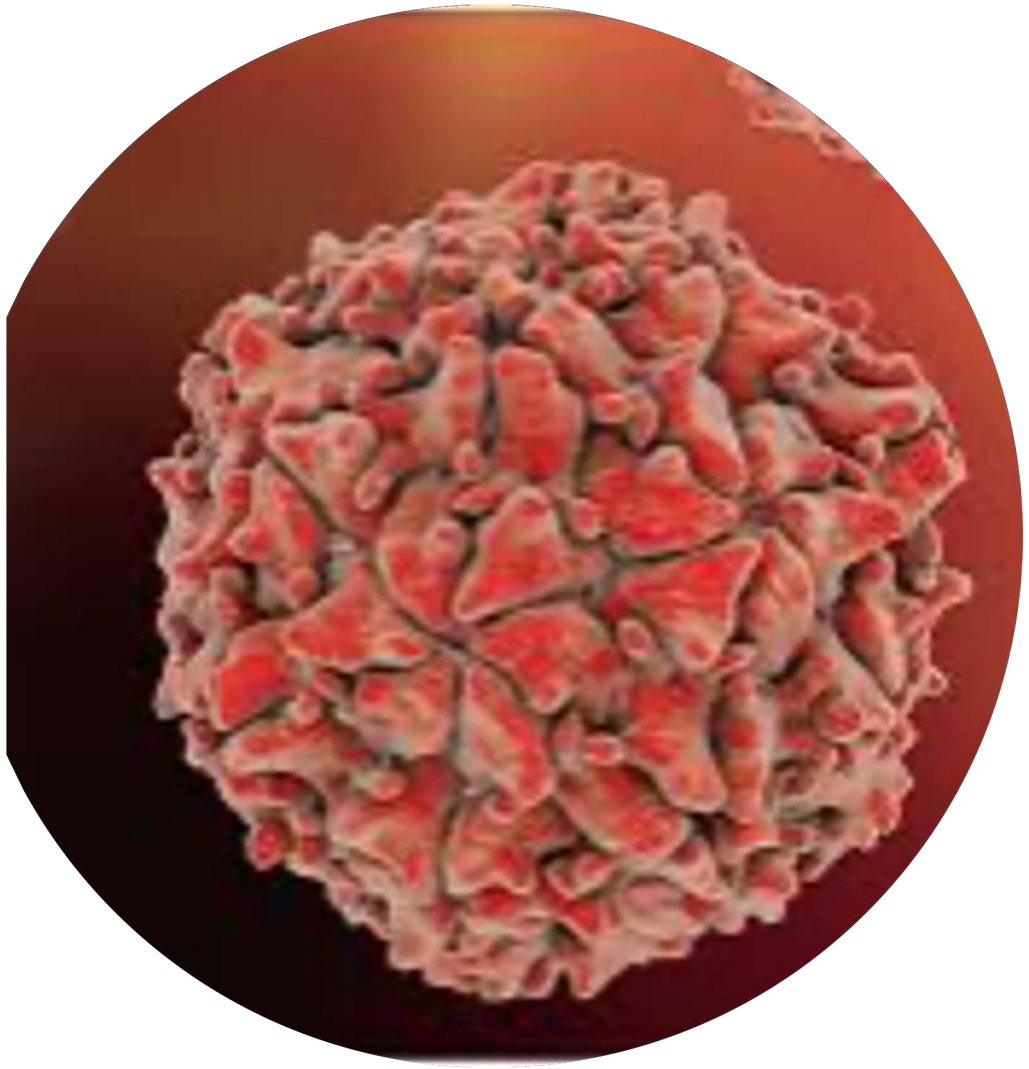

Host Genetics and Acute Flaccid Myelitis

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Why do we care?

If we can understand why people have different outcomes---we will better understand the immune response and eventually exploit this understanding for therapeutics and vaccines.

Our goals…are still to *better understand disease* so we can prevent and treat.

Things we look for to see if genetics might be playing a role…

- **Disease Heterogeneity**
  - not explained by other risk factors (sex, age, comorbidities)
- **Familial aggregation**
  - Hard to assess with infectious diseases because of transmission
- **Pathogen Dose and Environment not major players**
- **Similar to other diseases in pathology**

1. Heterogeneity

Does it matter?
Everyone gets infections.

Everyone.

Tuberculosis

~1/3 of world infected with mycobacteria, but only ~10% will develop clinical disease.

Hepatitis B

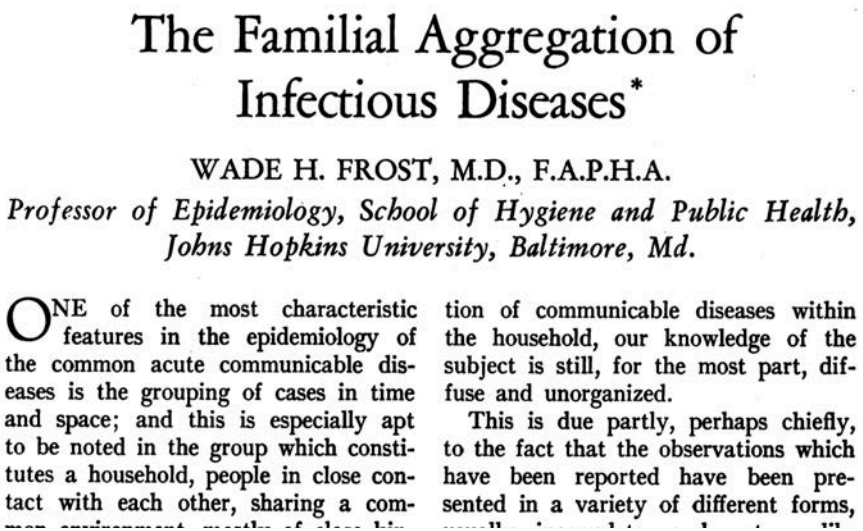
2 billion people (1/3 world) infected with HBV, but only ~10% will develop chronic disease.

HIV/AIDS

Variability in time to AIDS (in the pre-HAART and controlled post-HAART era)

2. Familial Aggregation and Twin Studies

1938



The Familial Aggregation of Infectious Diseases*

WADE H. FROST, M.D., F.A.P.H.A.

Professor of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md.

ONE of the most characteristic features in the epidemiology of the common acute communicable diseases is the grouping of cases in time and space; and this is especially apt to be noted in the group which constitutes a household, people in close contact with each other, sharing a com-

tion of communicable diseases within the household, our knowledge of the subject is still, for the most part, diffuse and unorganized.

This is due partly, perhaps chiefly, to the fact that the observations which have been reported have been presented in a variety of different forms,

Disease	MZ Concordance	DZ Concordance	Country of Study	Reference
Leprosy*	52	22	India	Chakravarti and Vogel 1973
HBV	35	4	Taiwan	Lin, Anticancer Research, 1979
TB	65	25	Germany	Diehl, 1936
	32	14	UK	Comstock, Am, Rev Respir Dis, 1978

* In cases where both twins had leprosy, the type of leprosy—tuberculoid or lepromataus was more likely to be concordant if the pair was monozygotic

** We expect MZ > DZ since they share the same alleles

3. Controlling Dose: We learn from our mistakes…

- 1926, Lubeck Germany
- 249 babies injected with the same live dose of virulent M. tuberculosis instead of BCG.
- Babies too young to have significant prior exposure to mycobacteria, and not previously vaccinated to BCG.
- All got the same strain, same dose.

76 babies died, 173 babies survived

Dubos, The White Plague 1952

4. Paralyzed with Fear

Yankees Even World Series By Taking 7-1 Victory

The Daily Tar Heel

POLIO FORCES CANCELATION OF TWO GAMES

Douglas To Be Speaker Here

Eisenhower, McGrath Also May Give Talks

Coeds Note Rush Change

BULLETIN

Status Of Cobb Is Left Vague By Legislature

NEWS IN BRIEF

One Grid Player, 3 Others Stricken

Attempts Will Be Made To Re-Schedule Georgia And State Later This Season

Yugoslavian Cosmopolitan Prexy Elect

Dormitory Adviser's Bicycle Goes Astray

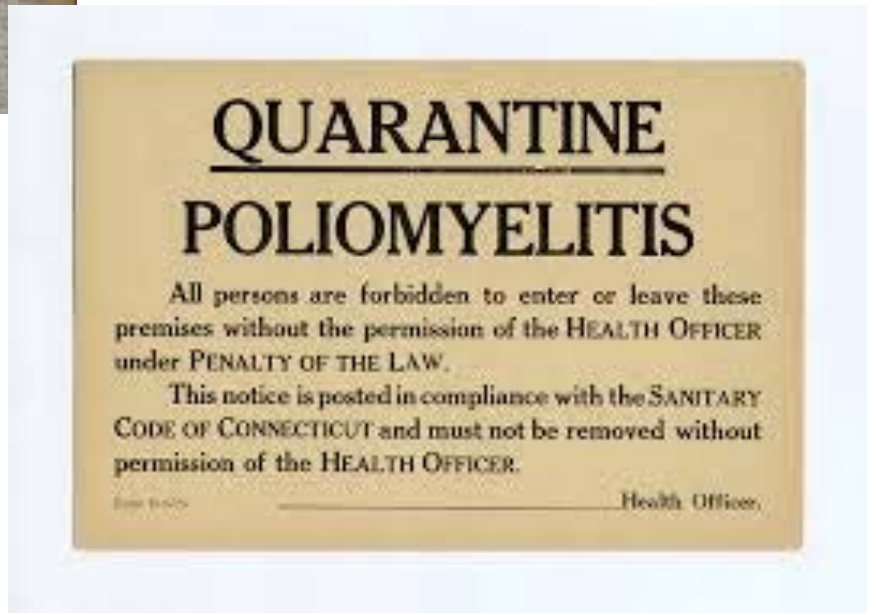
Evening Telegraph

BOY OF 4 MAKES POLIO TOTAL 26

Second Case Outside Schemes

Short Time For NCR

Polio Nursing Institute Set At Hospital



QUARANTINE

POLIOMYELITIS

All persons are forbidden to enter or leave these premises without the permission of the HEALTH OFFICER under PENALTY OF THE LAW.

This notice is posted in compliance with the SANITARY CODE OF CONNECTICUT and must not be removed without permission of the HEALTH OFFICER.

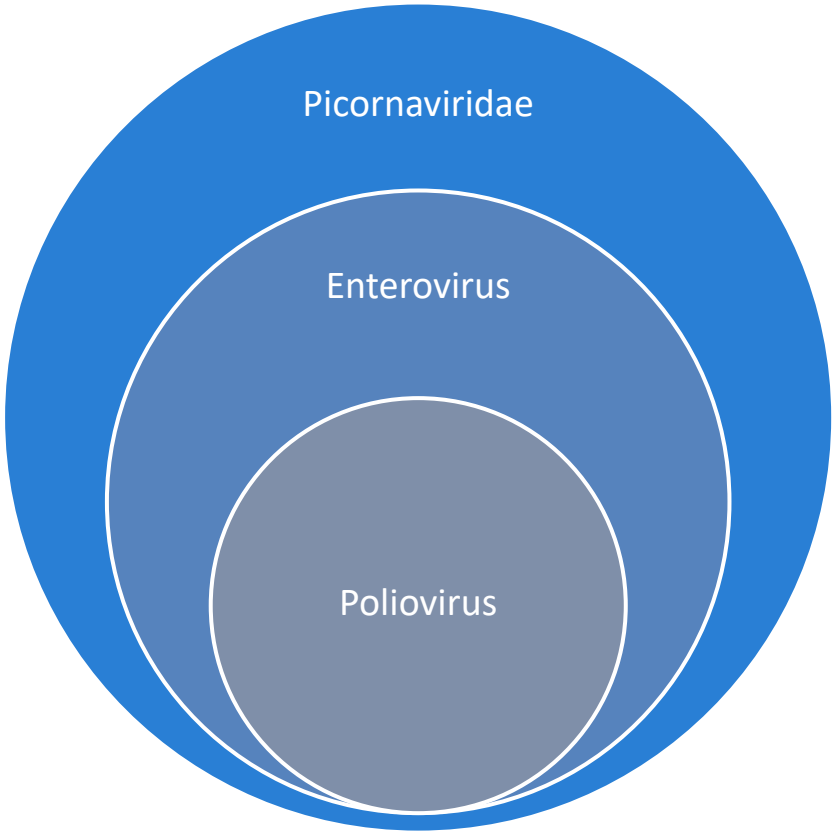
Health Officer.

As polio eradication is within reach…
…in 2014 a new disease emerged

Health & Science

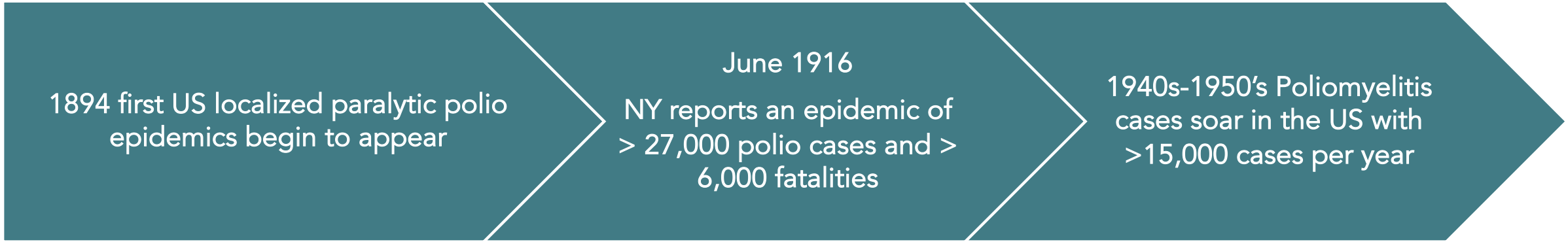
Mystery paralysis in children is perplexing parents — and researchers

Poliovirus



- Polio= grey and Myelon= marrow
- Poliomyelitis affects the grey matter, There is extensive damage to the anterior horn cells of the spinal cord. This causes limb paralysis.
- The incubation period ranges from 2 to 35 days.
- Widespread muscular atrophy occurs leading to flaccid paralysis. Death usually occurs due to respiratory paralysis in extreme cases.

Poliomyelitis in US



The Vaccine changed everything.
In one year the number of cases went from 58,000 to 5,600.

But we still did not learn what caused polio paralysis.

What can tragedy teach us? (Dose and Virus)

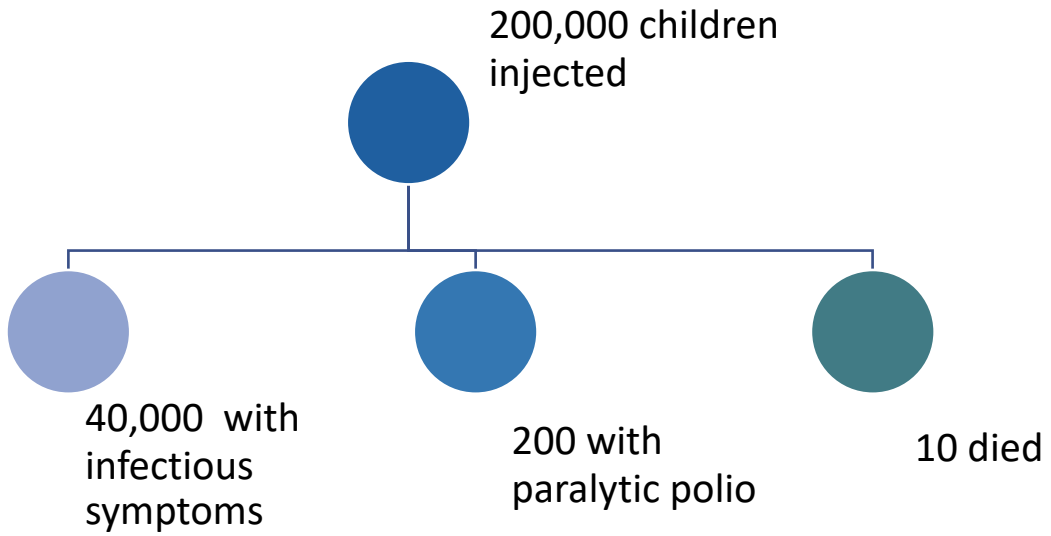
The Cutter Incident

Polio vaccine administered that was not inactivated to school age children

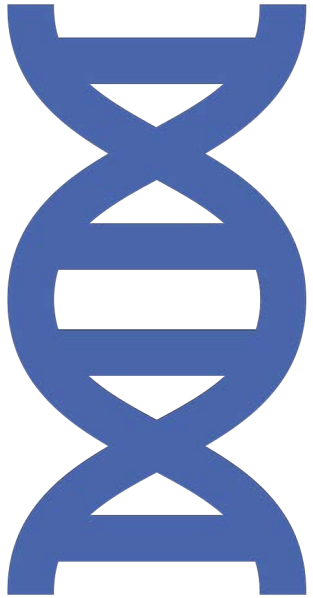
Same active virus administered but with different outcomes

Why, if everyone got a similar infectious dose of live virus did not everyone get infected?

Why did not everyone get paralysis?



What can poliomyelitis teach us? (Familial Aggregation)

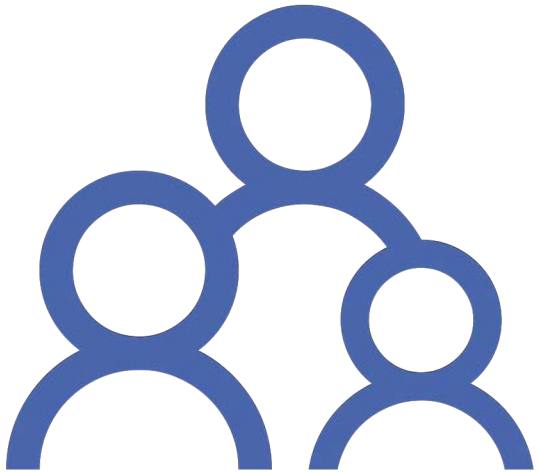


Twins and Polio (American Journal of Human Genetics 1951)

- Evaluated presumed monozygotic and dizygotic twins.
  - 5/14 "monozygotic" twin pairs had paralytic polio (36%)
  - 2/33 dizygotic twin pairs had paralytic polio (6%)
  - No parents had a history of poliomyelitis. No known intermarriage
  - Suggested that this was a recessive gene with relatively high frequency in the population.

Lesson for AFM: Evidence of genetic heritability for poliomyelitis. Even among those twins, the penetrance of the putative genes is not 100% suggesting it may be modified by other genes, or non-genetic factors. (36%).

What can poliomyelitis teach us? (Familial Aggregation)



1942 Addair and Snyder

- Polio cases in West Virginia. All 29 cases over 50 years occurred in 25 related families

1982-1987 Wyatt

•Evaluated original notes of 1,072 Maltese cases of poliomyelitits from 1909-1964. Traced relatives

•956 polio cases, 54% were related as sibs, 1st or 2nd cousins.

•13 pairs of sibs where both had paralytic polio. But the younger siblings was born months or years after first sibling was paralyzed suggesting dosage was not a factor.

Lesson for AFM: Familial aggregation of disease, but specifically in 1st and 2nd degree relatives.

Disease Heterogeneity

Age

Theory: Older individuals have waning immune systems

More children affected. Age may play a role, but not clear what role it is playing.

Sex

Theory: Biologic differences in immune responses due to sex and hormones

We see more children affected and not a huge skewing to boys.

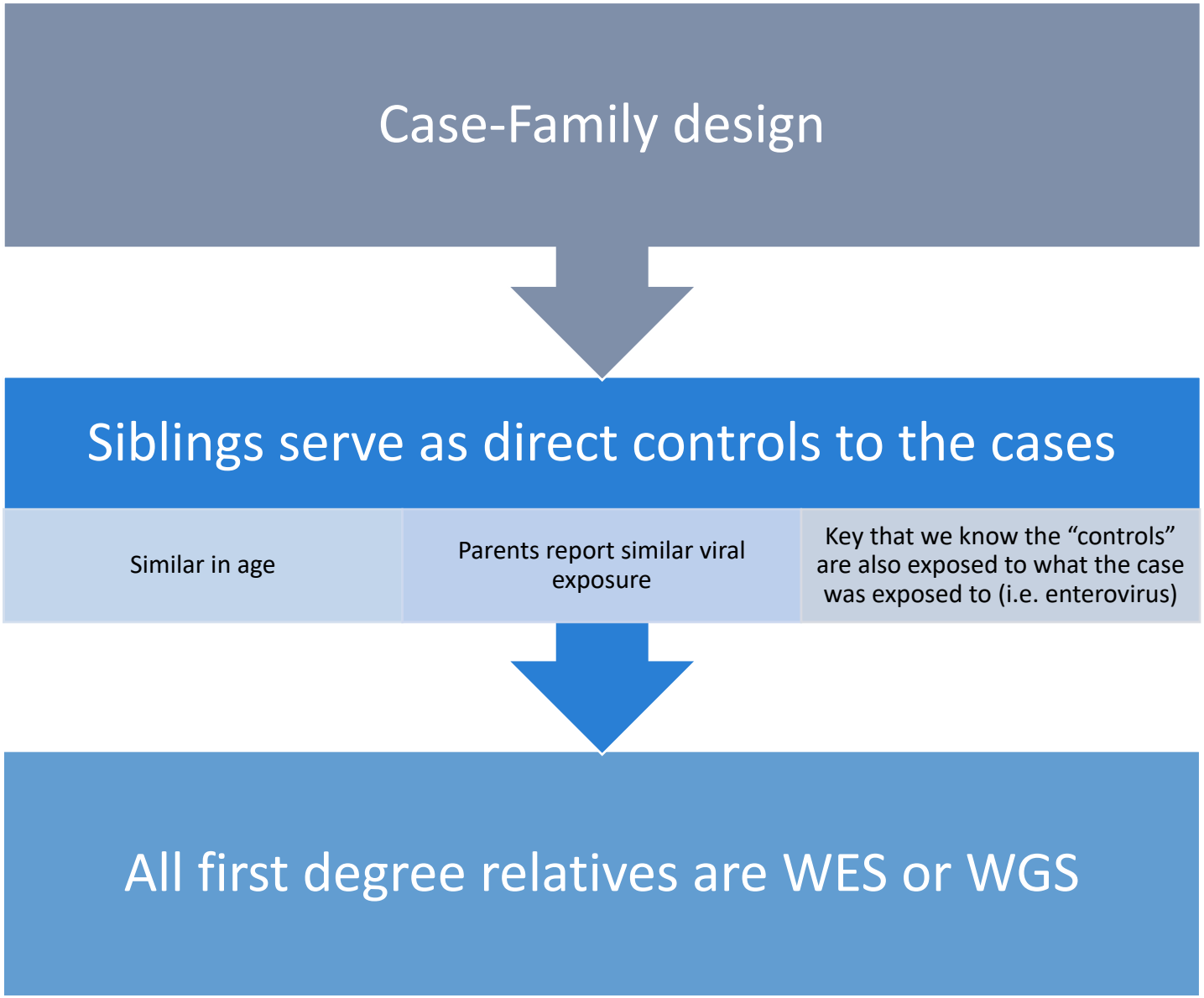
Co-infections/Co-morbidities

Theory: co-I or co-morbidities exacerbate disease and susceptibility

Most children reported to have AFM are healthy and in general do not have underlying immune related or neurologic conditions.

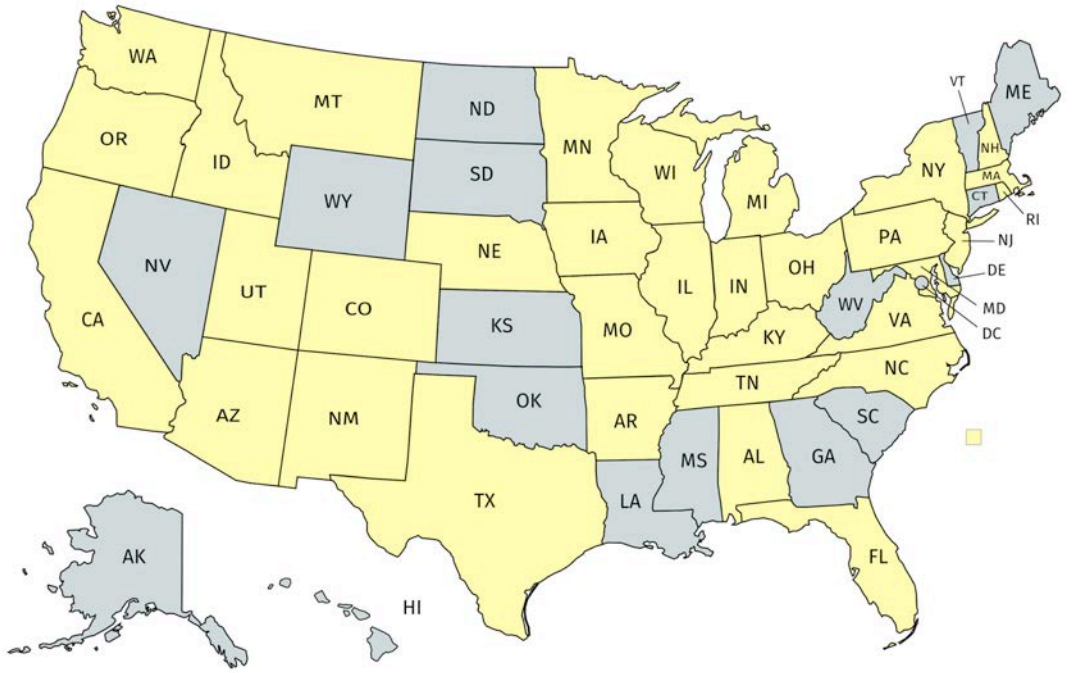
What else may be playing a role?

Genetics Study Design



100 AFM cases 2012-2019*

Mean age of child cases	5.0 years (SD 4.2)
Mean age of adult cases (n=4)	30.0 years (SD 1.0)
Sex M:F	61:39
Number with Limb Paralysis	
1-3 limbs	82
All Limbs	18
Self Reported Race/Ethnicity	
White	53%
Black	1%
Asian	2%
Native American	1%
Hispanic	1%
Other/Mixed	42%



JHU Host Genetics and AFM

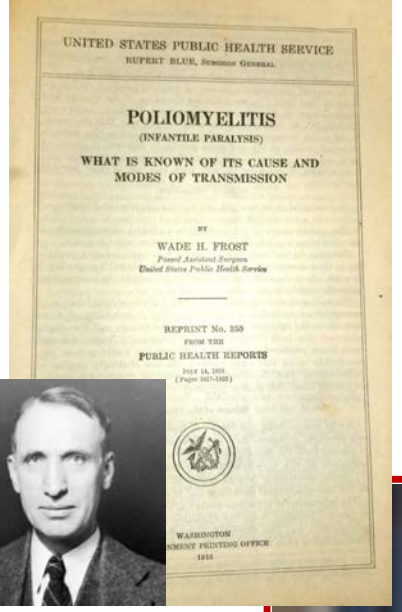
- AFM cases have family members with polio
- Evaluating *de novo* mutations, we see enrichment of loss of function mutations (LOF) in the AFM cases (expected 1, observed 18).
- However, we do not see common genes across the first 21 cases.
- Replication studies underway with AFM case trios and we also plan to evaluate polio survivors.

What can we do? Can genetics help?

Acute Flaccid Myelitis seems to be mirroring what we saw in the early days of poliomyelitis	• Sporadic Global Cases --->will there be a large scale epidemic?
Not everyone exposed to polio or enteroviruses will be paralyzed.	• Who is at risk? What can we do?
How do we prevent large numbers of AFM cases?	• Poliomyelitis was stopped via vaccine

Acute Flaccid Myelitis Acknowledgements

- Aaron Milstone, David Thomas, Carlos Pardo, **Matthew Elrick**, **Olwen Murphy**, Tom Crawford, **Hannah Manley**, Ani Voskertchian, **Cristian Valencia**, Andy Pekosz, Ben Larman
- Numerous physicians across the US that have been critical to the collection and enrollment of these cases.
- Incredible national AFM working group dedicated to trying to answer these critical questions working with CDC/NIH
- Funding:
  - Johns Hopkins Catalyst Award
  - NIH Sequencing Center


UNITED STATES PUBLIC HEALTH SERVICE

POLIOMYELITIS

(INFANTILE PARALYSIS)

WHAT IS KNOWN OF ITS CAUSE AND MODES OF TRANSMISSION

WADE H. FROST

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FROM THE

PUBLIC HEALTH REPORTS

AFM, enteroviruses and vaccines

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