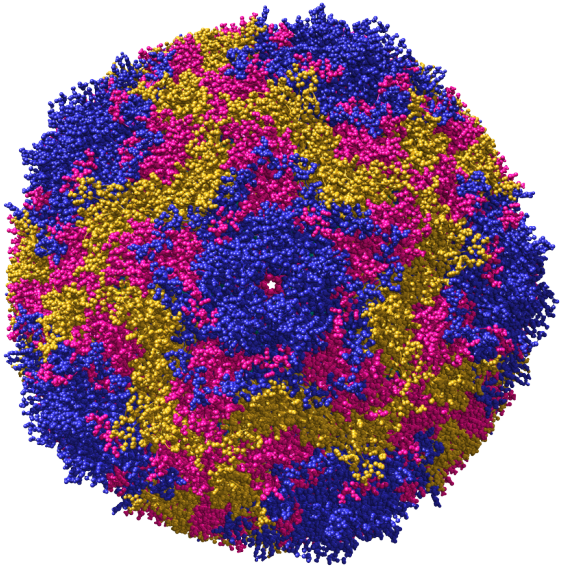
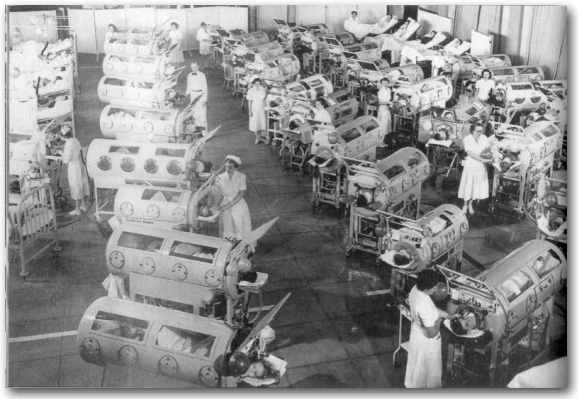
The Emergence and Eradication of Poliomyelitis

Emerging Infectious Disease
Fall 2019

You can find these slides at http://www.virology.ws/EID_2019.pdf





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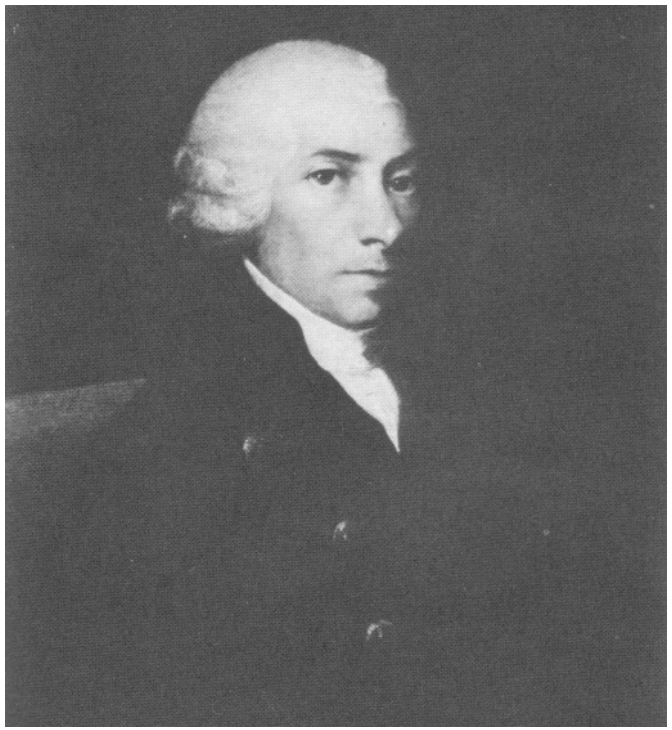
Poliomyelitis

- **Polio** (grey), **myelon** (marrow) = Greek
- **itis** (inflammation of) = Latin
- "A common, acute viral disease characterized clinically by a brief febrile illness with sore throat, headache and vomiting, and often with stiffness of the neck and back. In many cases a lower neuron paralysis develops in the early days of illness"

—J.R. Paul, Poliomyelitis (Infantile Paralysis), in A Textbook of Medicine, 1959.

Poliomyelitis has afflicted humans for thousands of years

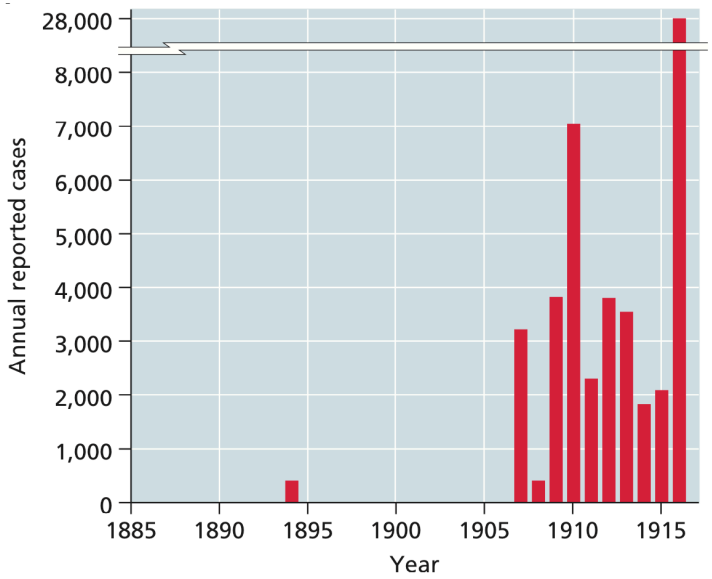
Egyptian stele
Eighteenth Dynasty
(1580-1350 B.C.)



Michael Underwood (1738-1810), London pediatrician

1789 - First intelligible clinical account of poliomyelitis, in *Treatise on Diseases of Children*

Epidemic poliomyelitis

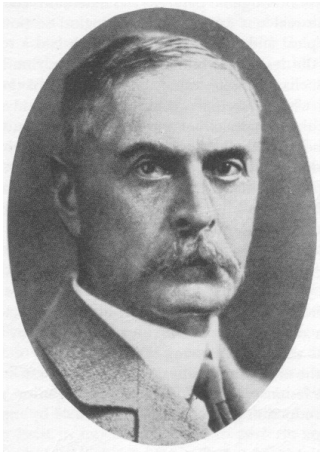


- First epidemics of poliomyelitis occurred in Sweden: 1868 (14 cases), 1881 (13 cases)
- Rutland, VT 1894, 132 cases
- Medin (1887) notes initial systemic phase: fever, malaise; involvement of the central nervous system seemed a complication

A disease of modern sanitation

- Pre-1900, poliovirus circulated freely and infected most shortly after birth
- Maternal antibodies prevent paralysis
- Improved sanitation delayed infection until later in life

Karl Landsteiner, MD



- Isolated poliovirus, 1908
- Injected two Old World monkeys with sterile filtrate from spinal cord of boy who had died of polio
- Sections of monkey spinal cord revealed lesions of poliomyelitis
- Suggested a viral etiology; was passed from monkey to monkey

Picornaviridae

- **Genus:** *Aalivirus*
- **Genus:** *Ampivirus*
- **Genus:** *Aphthovirus*
- **Genus:** *Aquamavirus*
- **Genus:** *Avihepatovirus*
- **Genus:** *Avisivirus*
- **Genus:** *Bopivirus*
- **Genus:** *Cardiovirus*
- **Genus:** *Cosavirus*
- **Genus:** *Crohivirus*
- **Genus:** *Dicipivirus*
- **Genus:** *Enterovirus*
- **Genus:** *Erbovirus*
- **Genus:** *Gallivirus*
- **Genus:** *Harkavirus*
- **Genus:** *Hepatovirus*
- **Genus:** *Hunnivirus*
- **Genus:** *Kobuvirus*
- **Genus:** *Kunsagivirus*
- **Genus:** *Limnipivirus*
- **Genus:** *Megrivirus*
- **Genus:** *Mischivirus*
- **Genus:** *Mosavirus*
- **Genus:** *Orivirus*
- **Genus:** *Oscivirus*
- **Genus:** *Parechovirus*
- **Genus:** *Pasivirus*
- **Genus:** *Passerivirus*
- **Genus:** *Potamipivirus*
- **Genus:** *Rabovirus*
- **Genus:** *Rosavirus*
- **Genus:** *Sakobuvirus*
- **Genus:** *Salivirus*
- **Genus:** *Sapelovirus*
- **Genus:** *Senecavirus*
- **Genus:** *Shanbavirus*
- **Genus:** *Sicinivirus*
- **Genus:** *Teschovirus*
- **Genus:** *Torchivirus*
- **Genus:** *Tremovirus*

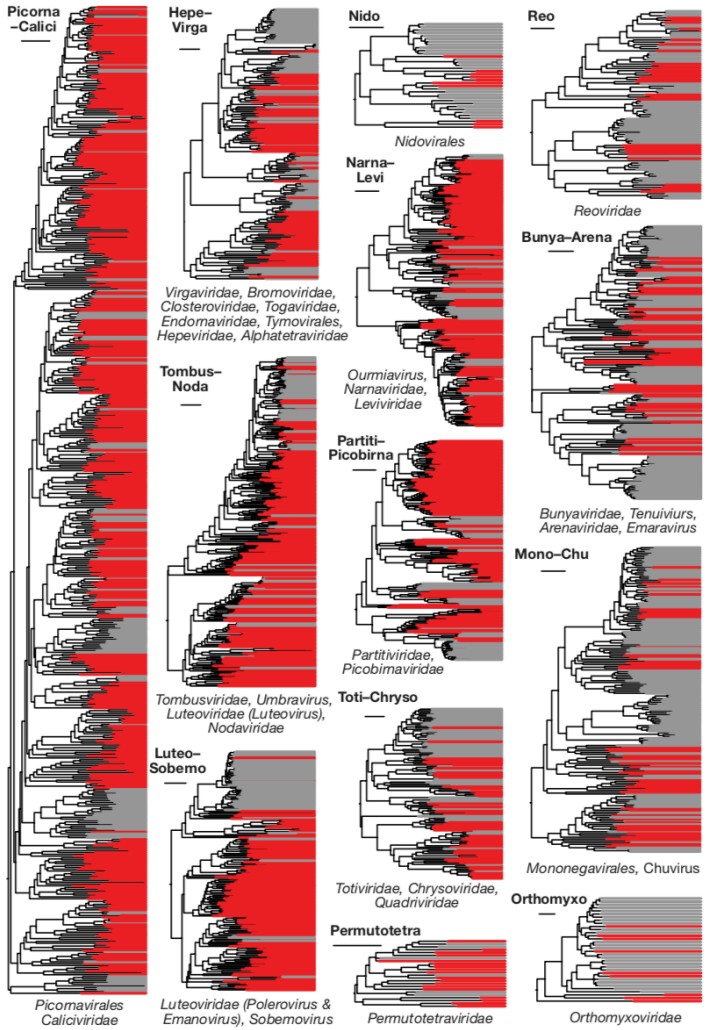
40 genera

- **Species:** *Enterovirus A* ⇨ Enterovirus A71, Coxsackievirus A16
- **Species:** *Enterovirus B* ⇨ Coxsackievirus B, Echovirus 1
- **Species:** *Enterovirus C* ⇨ Poliovirus 1, 2, 3
- **Species:** *Enterovirus D* ⇨ Enterovirus D-68
- **Species:** *Enterovirus E*
- **Species:** *Enterovirus F*
- **Species:** *Enterovirus G*
- **Species:** *Enterovirus H*
- **Species:** *Enterovirus I*
- **Species:** *Enterovirus J*
- **Species:** *Enterovirus K*
- **Species:** *Enterovirus L*
- **Species:** *Rhinovirus A*
- **Species:** *Rhinovirus B*
- **Species:** *Rhinovirus C*

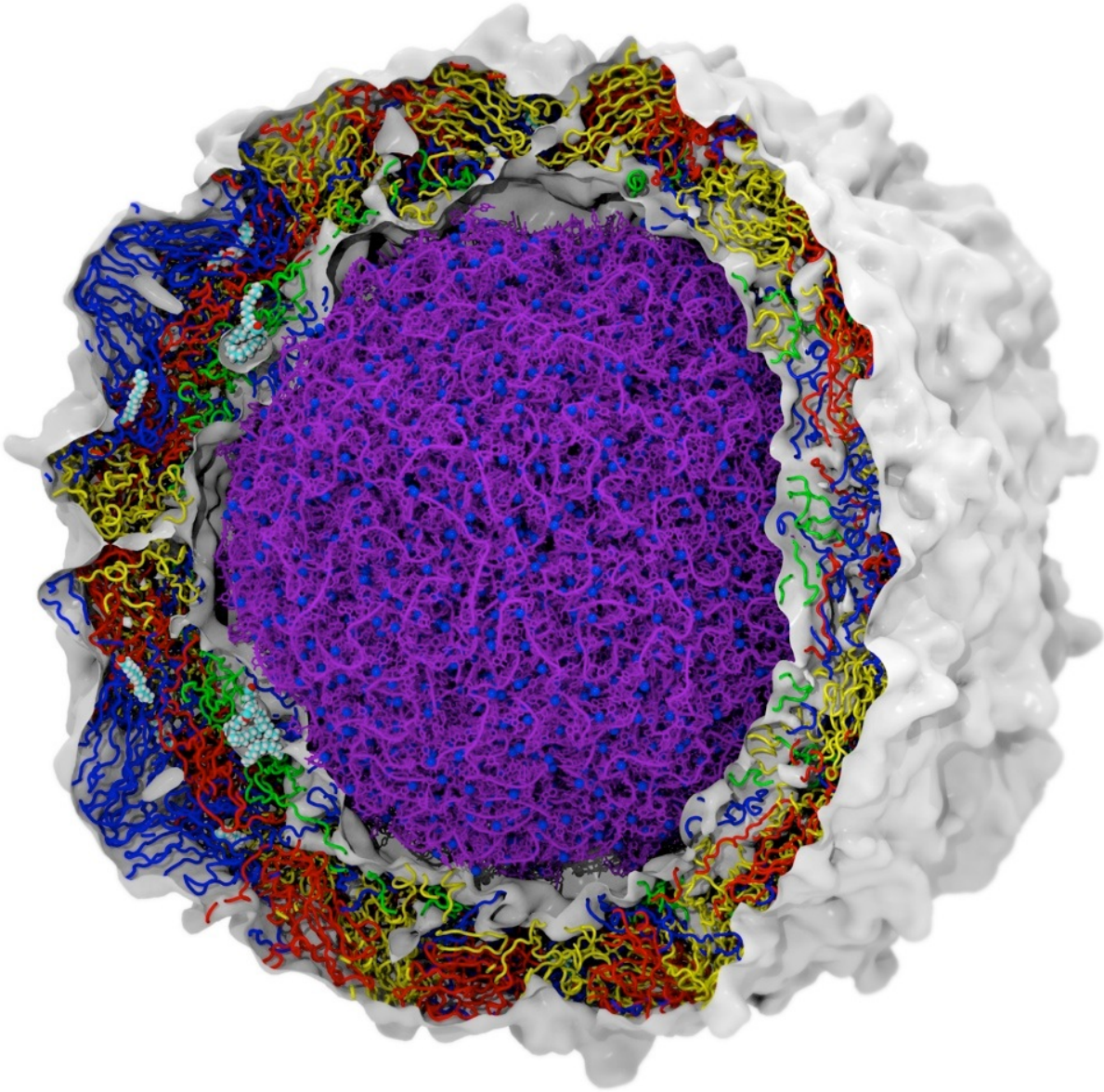
Invertebrate RNA virome

220 invertebrate species/1,445 RNA viruses

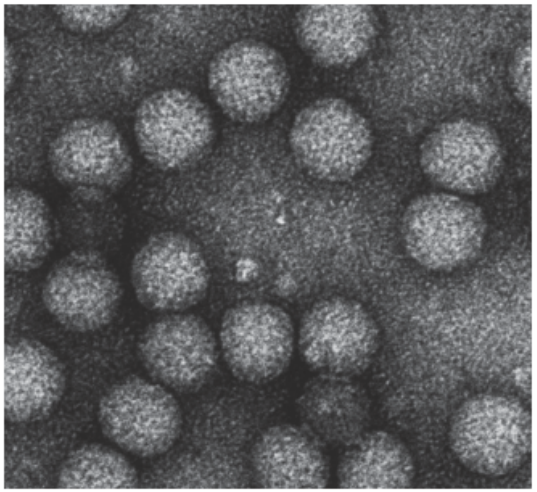
doi:10.1038/nature20167

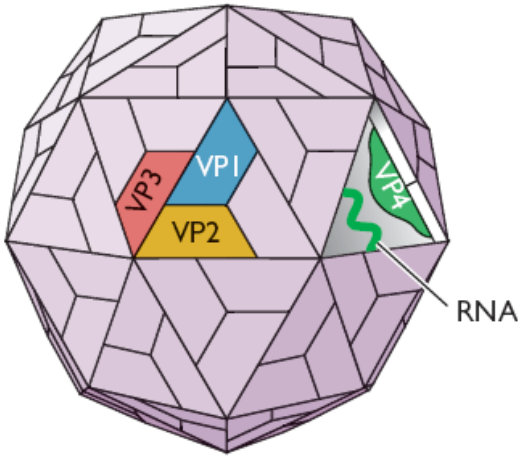


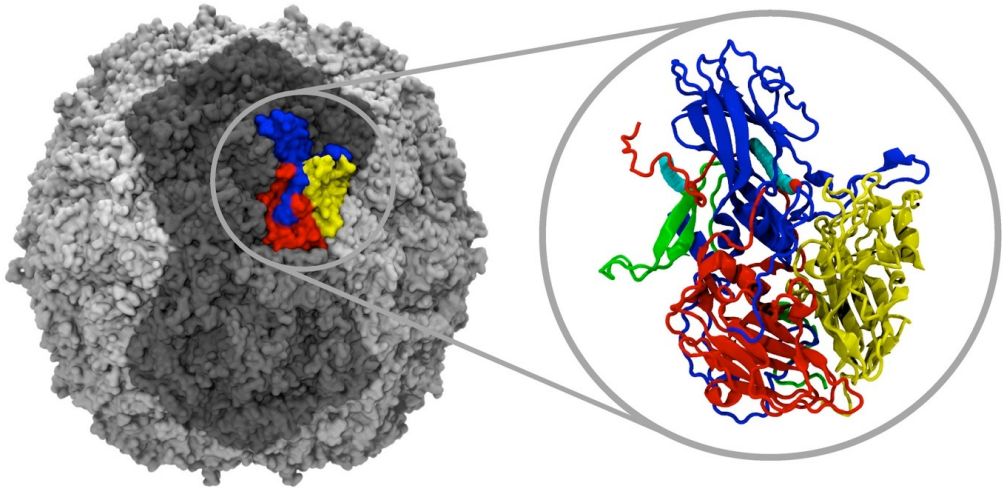
poliovirus



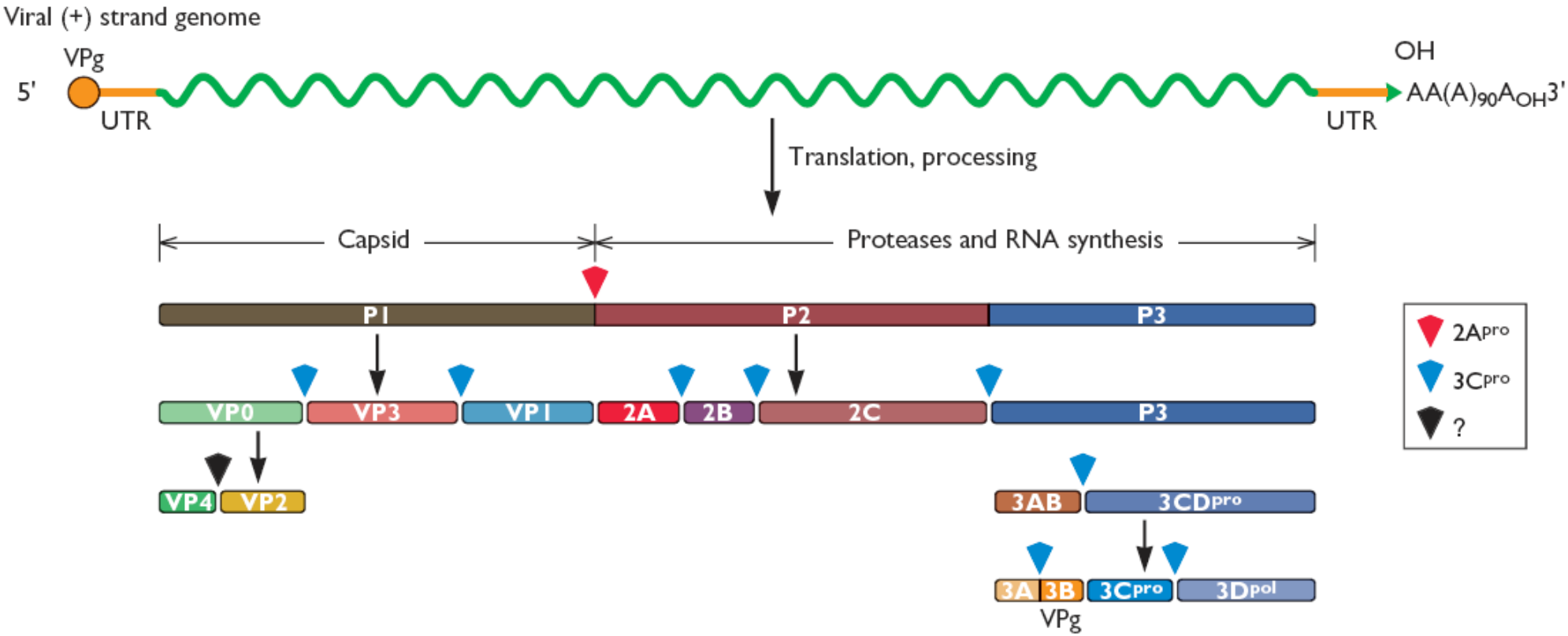
Poliovirus structure



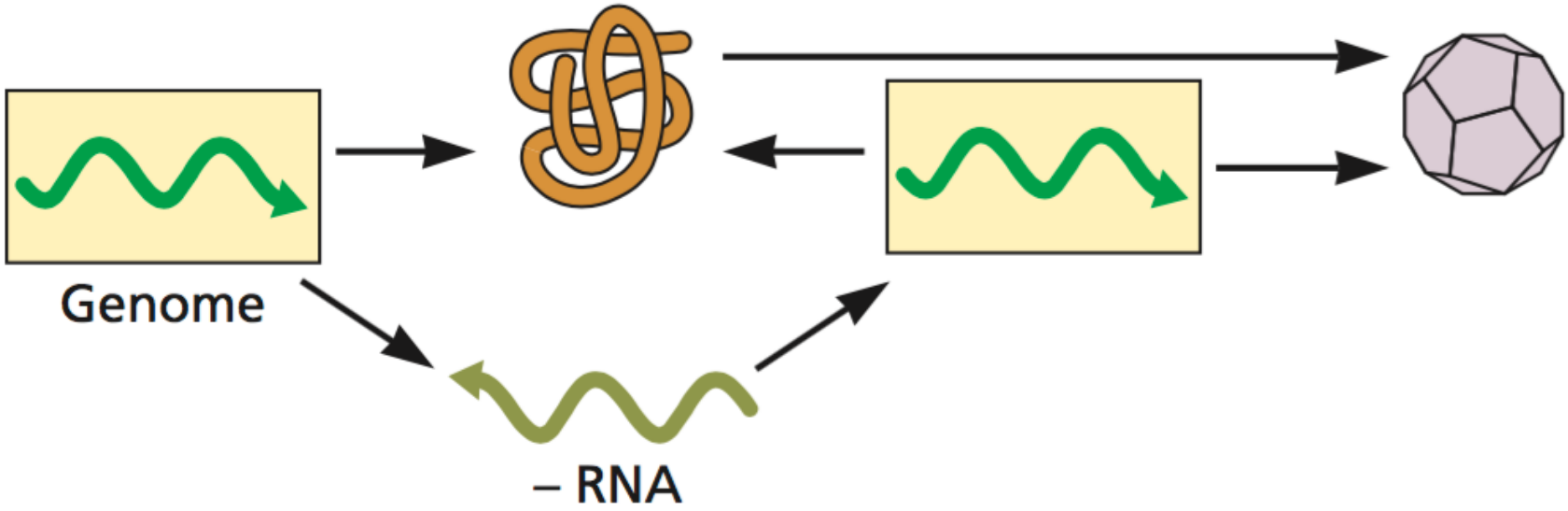


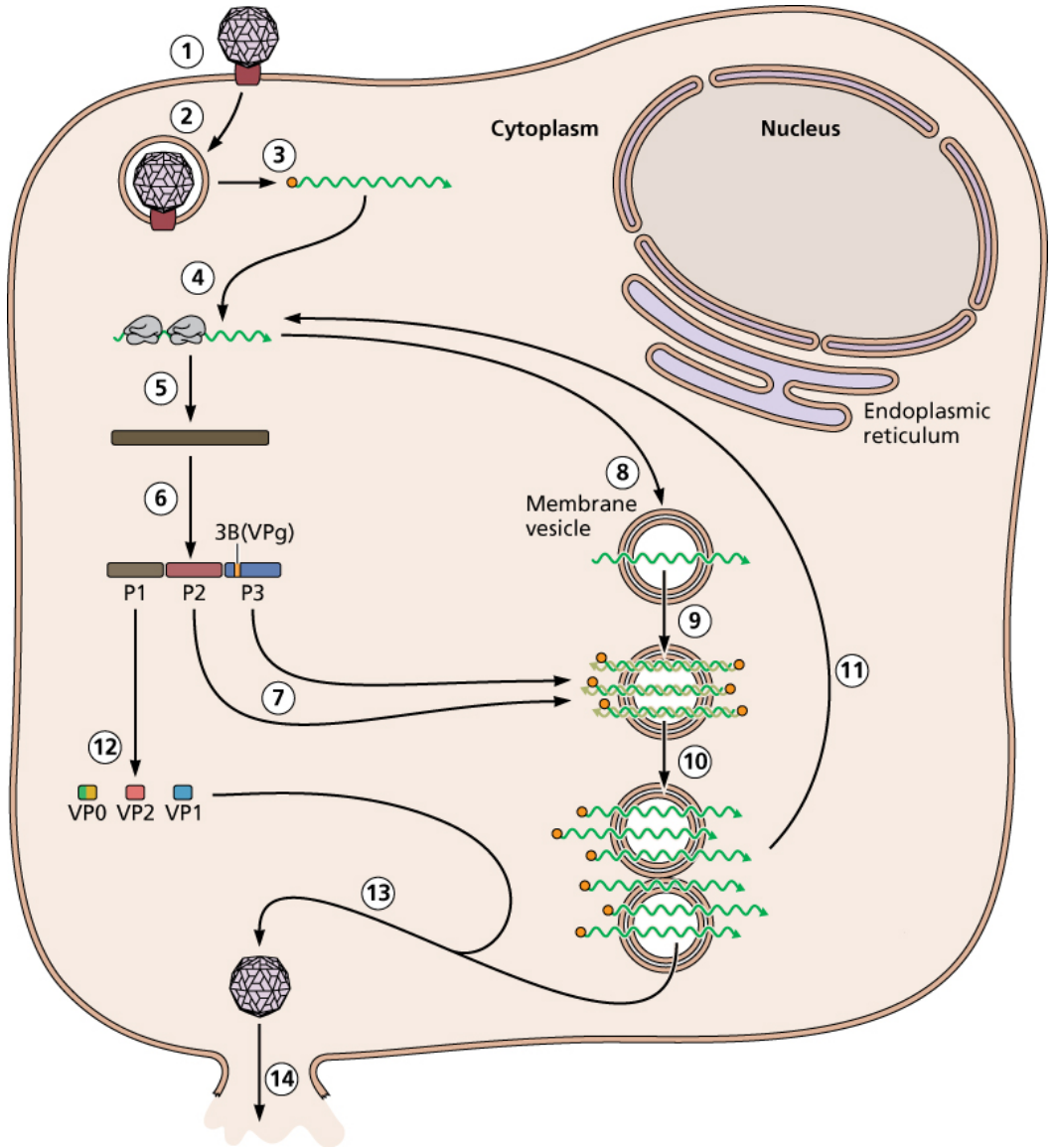


Poliovirus genome structure

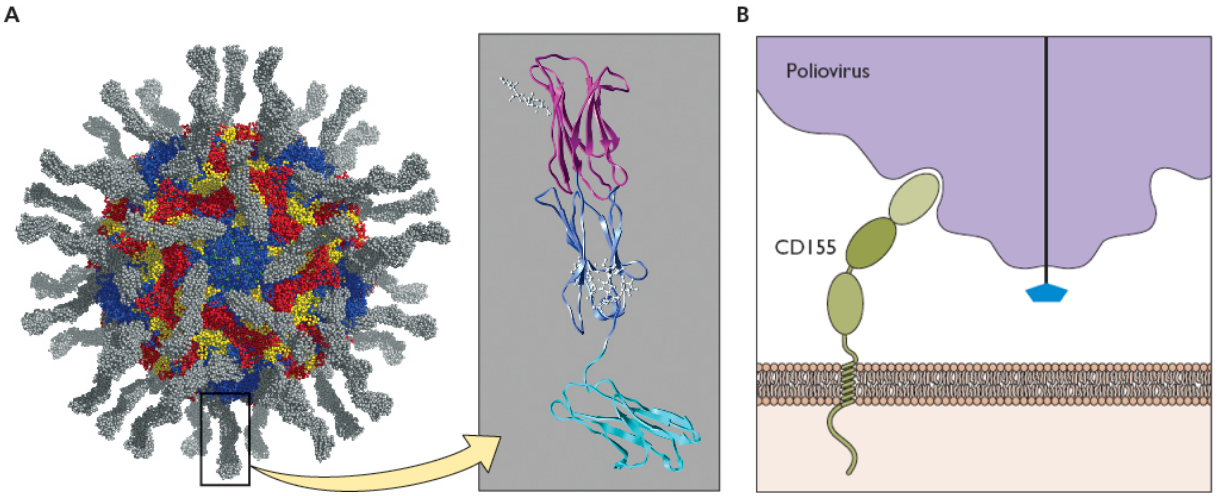


ss (+) RNA viral genomes

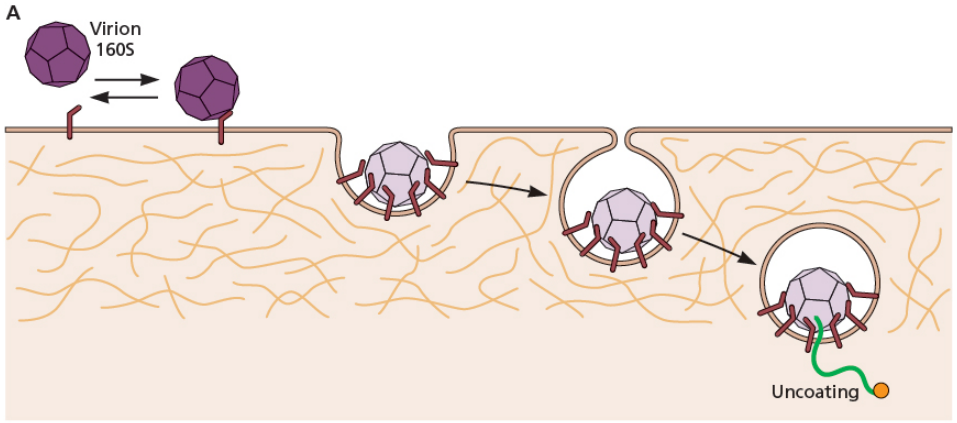




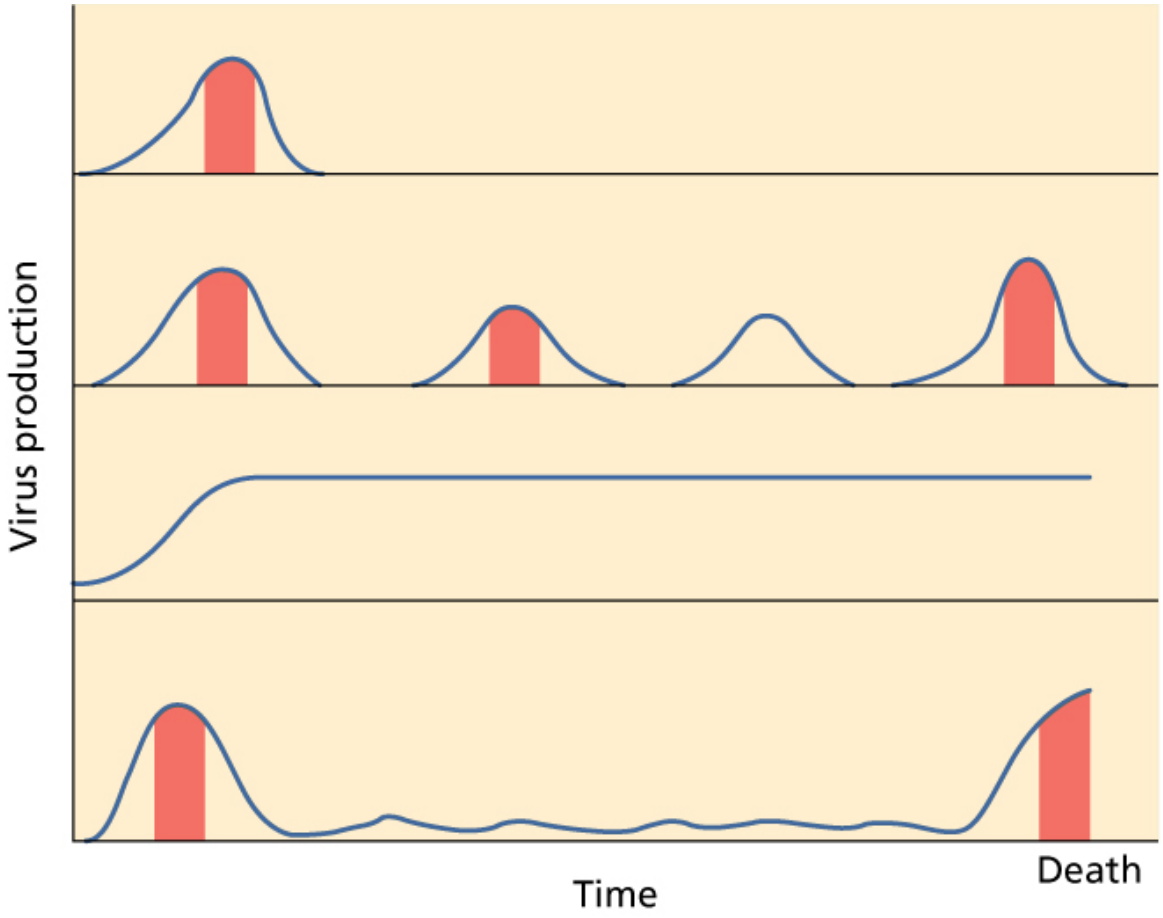
Attachment and entry



Receptor binding in a ‘canyon’



Poliomyelitis is an *acute* infection

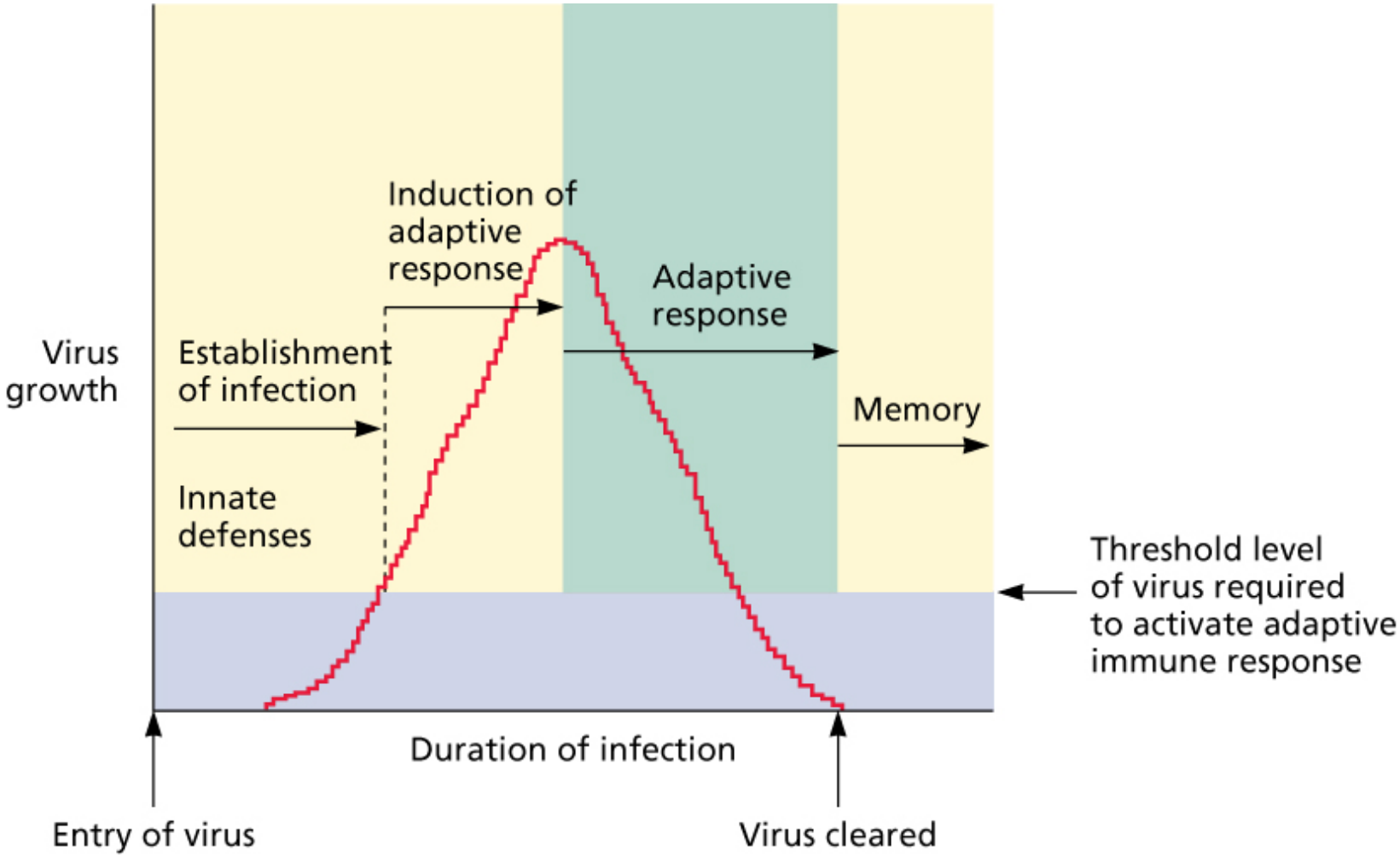


Acute
- Rhinovirus
- Rotavirus
- Influenza virus

Latent
- Herpes simplex virus

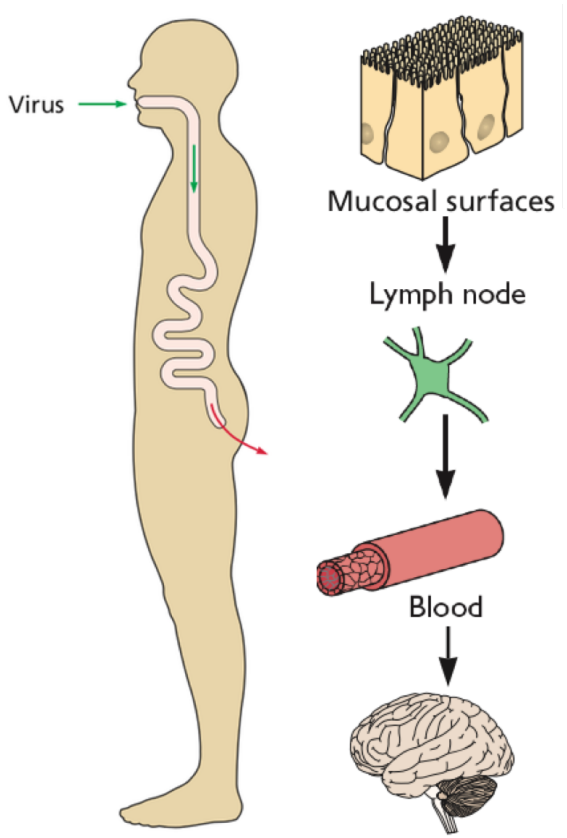
Persistent: asymptomatic
- Lymphocytic choriomeningitis virus
- JC virus

Persistent: pathogenic
- Human immunodeficiency virus
- Human T-lymphotropic virus
- Measles virus (SSPE)



Pathogenesis of poliomyelitis

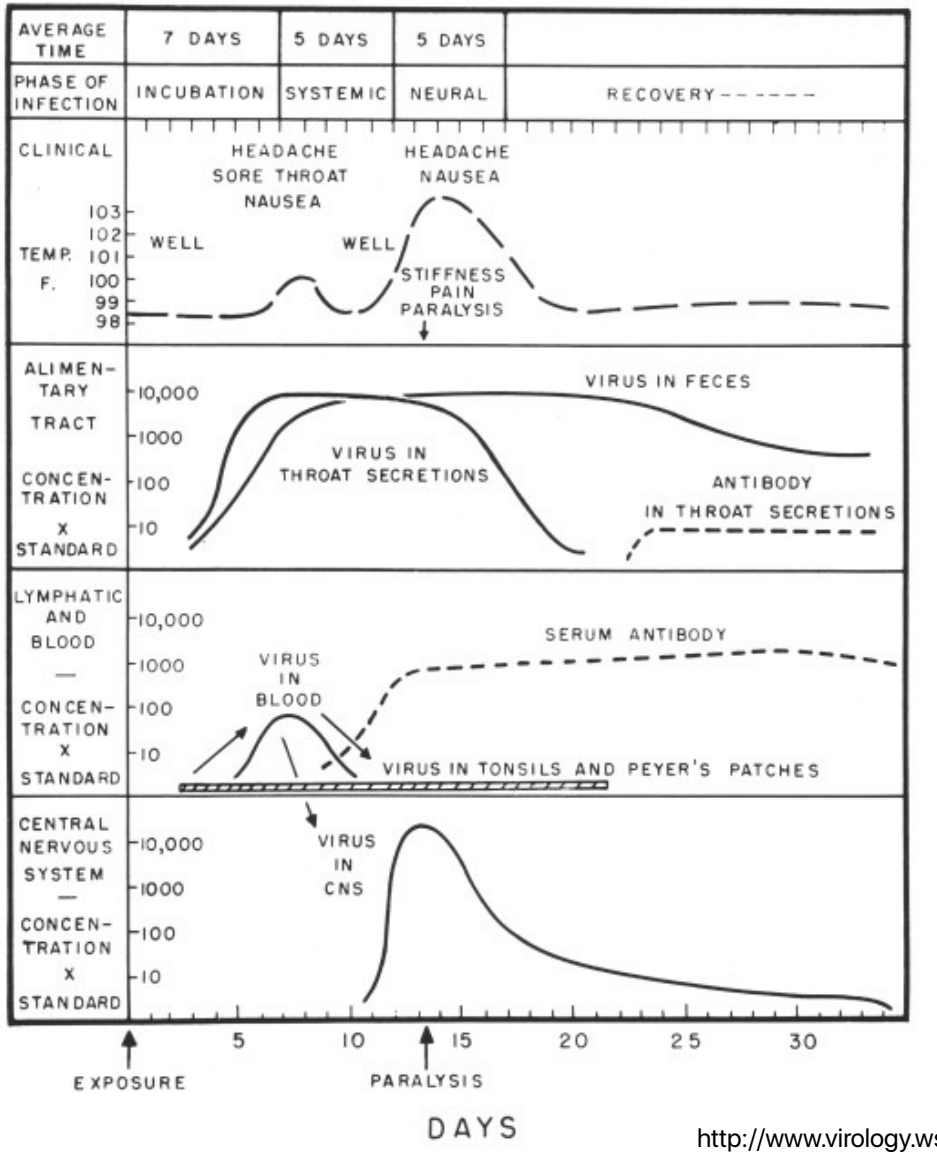
- Humans are only known reservoir
- Spread by fecal-oral transmission
- Peaks during warm months in temperate climates
- Most strains (3 serotypes) only infect primates



~1% of infections

Clinical features of poliomyelitis

- Range from clinically inapparent illness (~90% of infections) to paralytic polio
- Abortive poliomyelitis (~8% of cases)
  - Fever, headache, sore throat, no neurological sequelae
- Nonparalytic poliomyelitis (1-2%)
  - Severe headache, neck stiffness (“aseptic meningitis”)
  - Full recovery after 2-10 days
- Spinal paralytic poliomyelitis (<1%)
  - weakness and flaccid asymmetric lower limb paralysis
  - can involve respiratory muscles
  - recover from paralysis (often incomplete) can occur
  - ~10% fatality rate
- Bulbar paralytic poliomyelitis (<0.1%)
  - Cranial nerve paralysis (mostly CN 9, 10)
  - Vasomotor and respiratory centers involved
  - May be fatal due to respiratory muscle paralysis
  - ~50% fatality rate

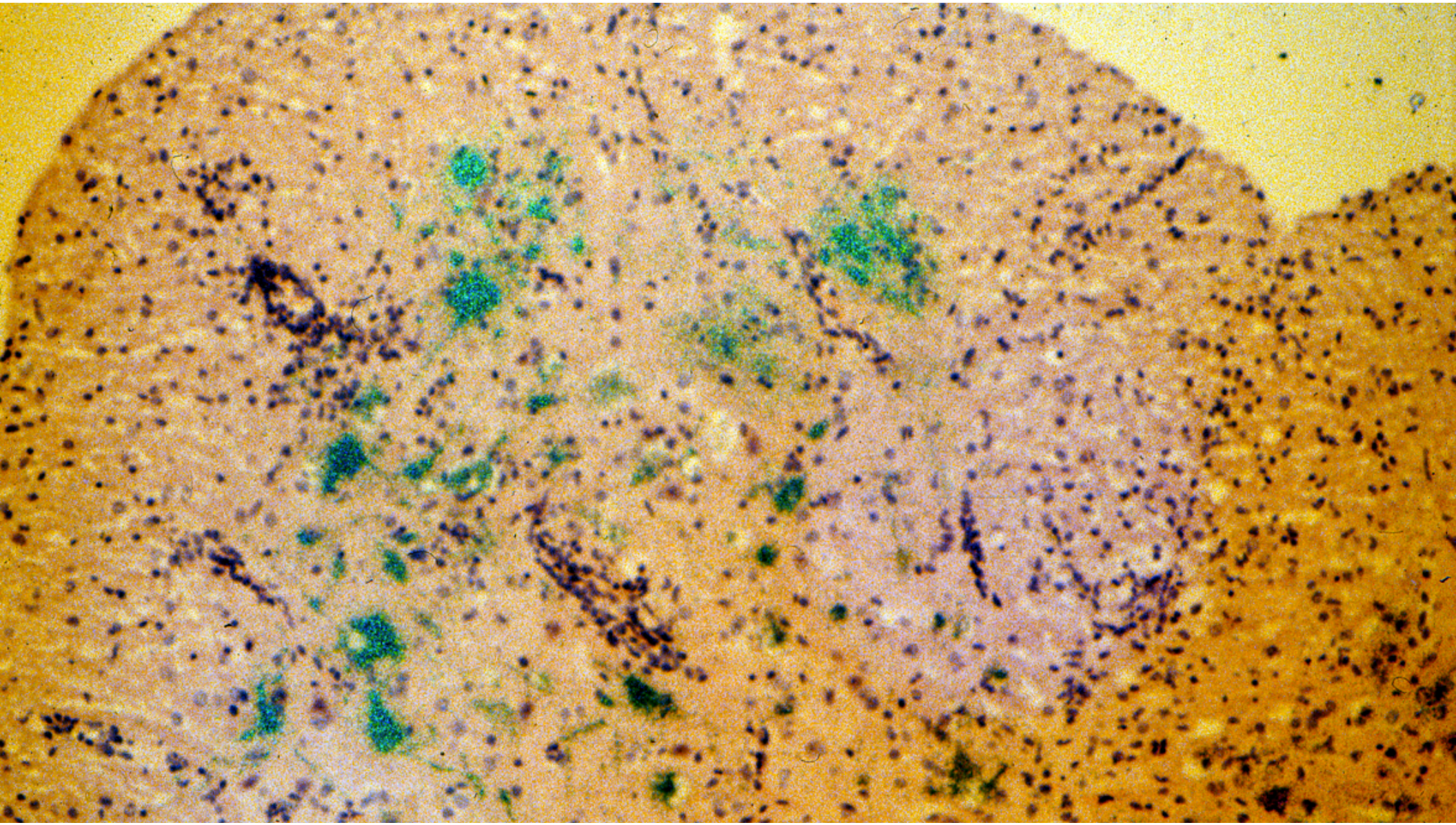


http://www.virology.ws/2009/03/11/chronology-of-an-acute-infection/

Transgenic mice susceptible to all three serotypes of poliovirus

Cathy Mendelsohn
1989

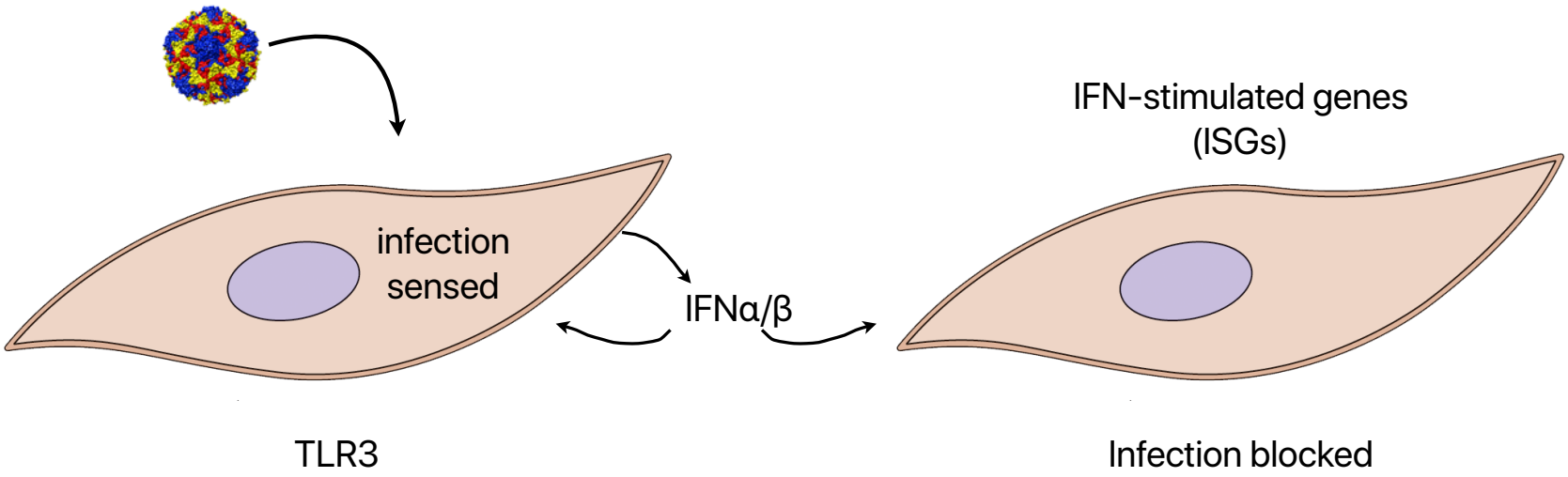
Ruibao Ren
1990

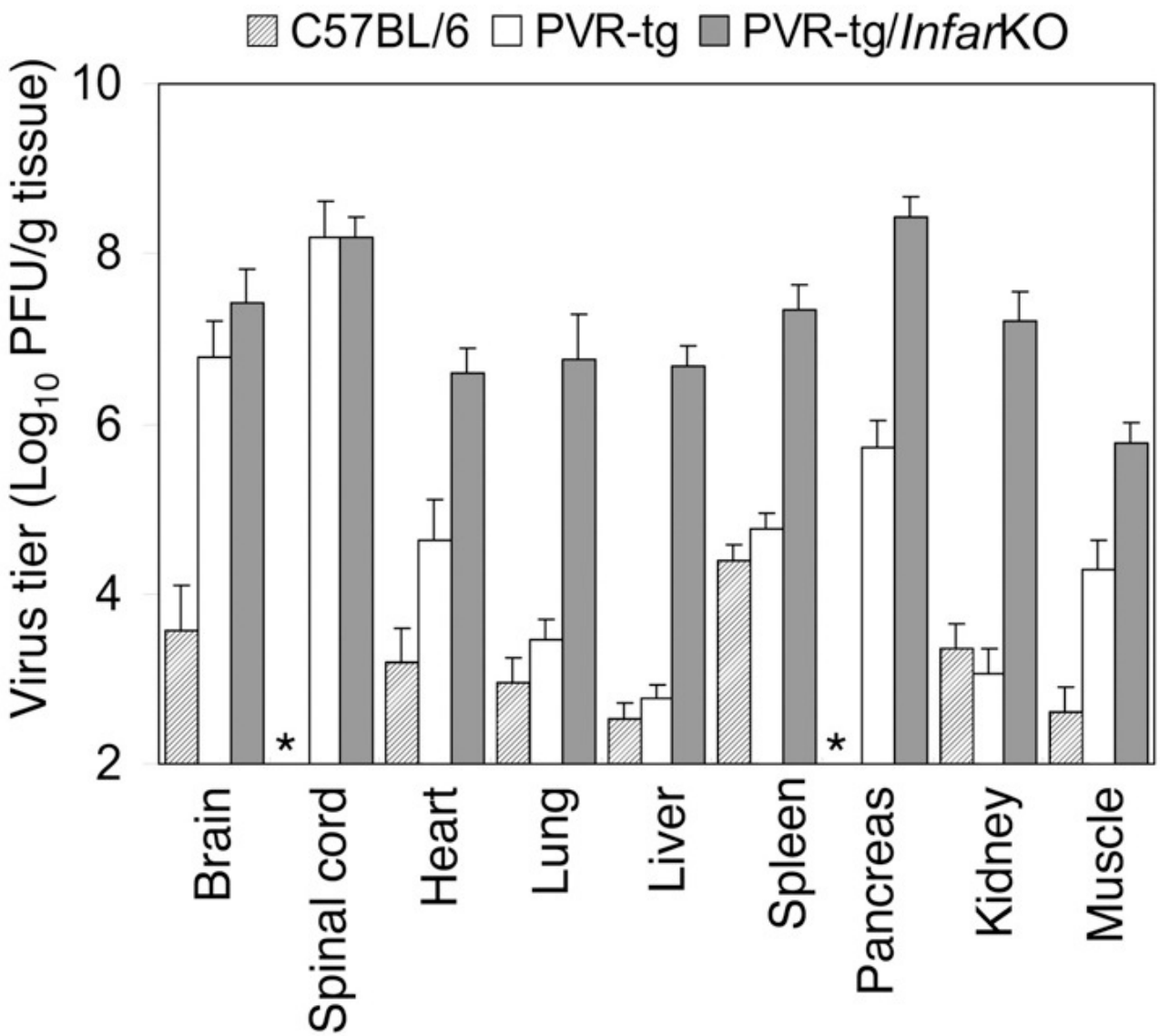


Pathogenesis of poliomyelitis

- What regulates poliovirus tropism?
- Why do only ~1% of infected individuals develop paralytic disease?

Innate immune system: Interferons




C57BL/6
PVR-tg
PVR-tg/*Infar*KO
Virus tier (Log10 PFU/g tissue)
10
8
6
4
2
*
*
Brain
Spinal cord
Heart
Lung
Liver
Spleen
Pancreas
Kidney
Muscle

Genes that influence susceptibility to poliomyelitis

Exome sequencing of genomes from poliomyelitis patients

doi: 10.3389/fmicb.2019.01495

Host Genetics, Innate Immune Responses, and Cellular Death Pathways in Poliomyelitis Patients

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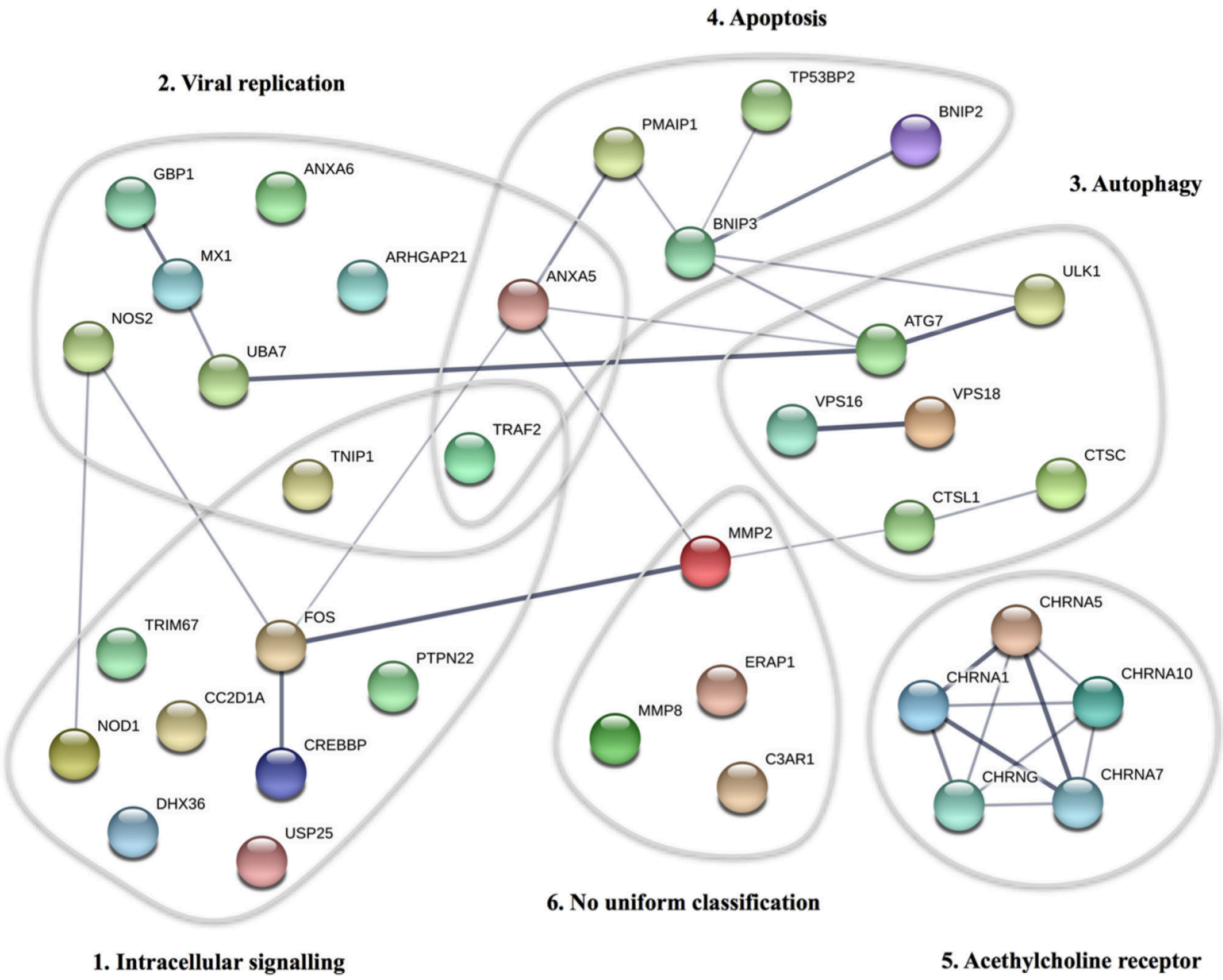
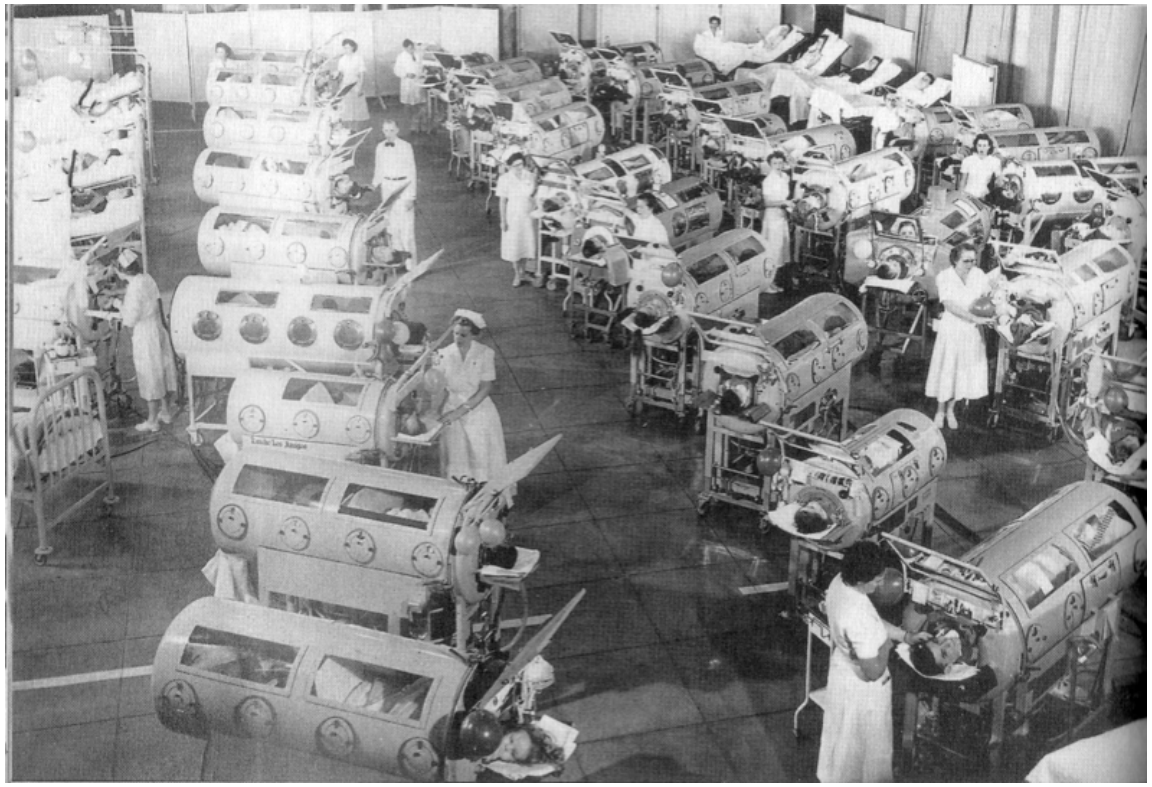


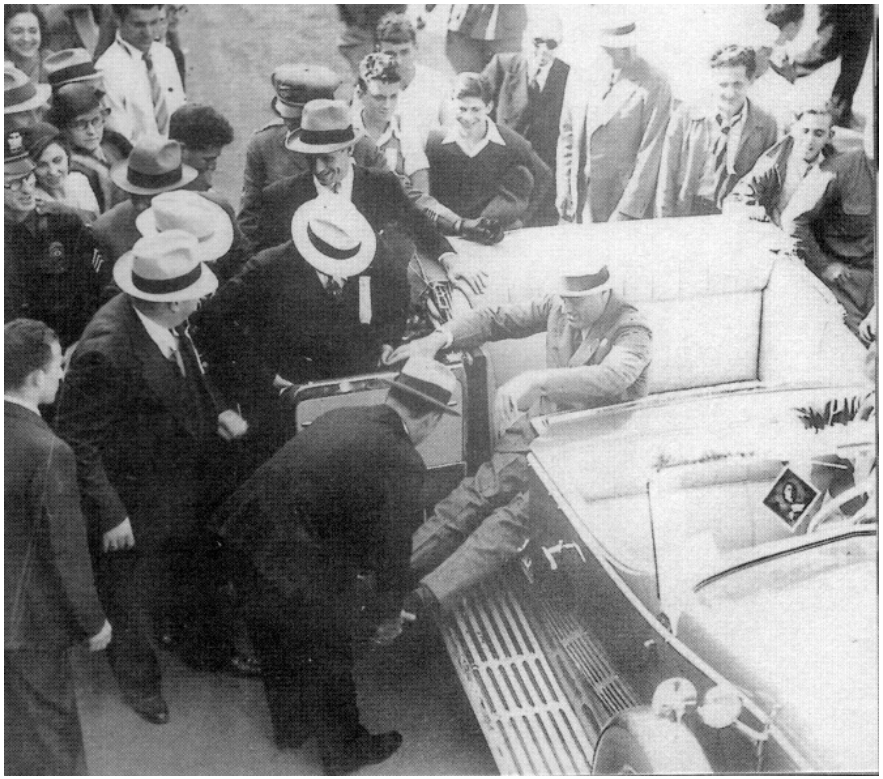
1916 Polio Epidemic, Northeastern US

- 9000 cases in NYC; 27,000 total

- Previous practice of quarantining paralyzed cases recognized as futile

Four conclusions:
1. Polio is exclusively a human infection
2. Infection is far more prevalent than apparent from clinically recognized cases
3. Asymptomatic and mild cases are the most important in spreading the disease
4. An epidemic of 1-3 cases per 1000 immunizes general population, epidemic declines spontaneously





Key milestones in polio research

1931

- Trask & Paul isolate poliovirus from throat washings of non-paralytic cases

1941

- Sabin & Ward isolate poliovirus from the pharynx, ileum and nervous system of fatal polio cases

1947

- Melnick isolates poliovirus from sewage

1954

- Horstmann regularly finds poliovirus in the blood of infected humans

1949

- Enders, Weller, Robbins grow poliovirus in cultures of human cells from non-nervous tissue. Replaces the monkey for detecting and studying poliovirus. Nobel Prize, 1954

1950

- Paul finds evidence, by studying antibodies in the blood of Arctic Eskimos, that a single subclinical infection results in immunity which persists for more than 40 years

1951

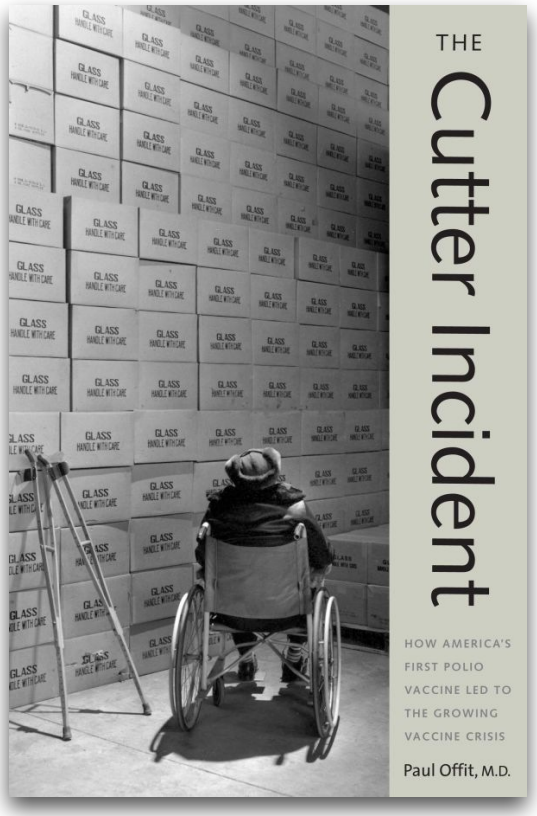
- Results of collaborative typing study sponsored by NFIP: three antigenic types of poliovirus

Inactivated poliovirus vaccine, IPV

- Poliovirus treated with formalin to destroy infectivity
- 1954: NFIP-sponsored clinical trial of Jonas Salk's IPV, 1,800,000 children. >50% protection, results announced 12 April 1955, licensed same day

Cutter Incident: Beginning of product liability

- Large stockpiles of vaccine released after licensure, within 10 days polio appeared in recipients
- 200,000 people infected, 70,000 ill, 260 vaccine-associated cases in 94 immunized children, 166 contacts
- Due to incomplete inactivation of virus in lots produced by Cutter Laboratories
- 1955-1960 polio in US fell from 20,000 cases/yr to 2,500



Attenuation of poliovirus neurovirulence

- Many felt that IPV could not eliminate polio, and that a live vaccine that mimicked the natural infection would provide the most effective and durable immunity
- 1937: Max Theiler develops attenuated yellow fever vaccine after >100 passages in mice (Nobel Prize, 1951 - the only one for a vaccine)
- 1952: Koprowski and Enders showed that passage of poliovirus in cell culture could result in viruses with reduced virulence in animals
- Albert Sabin capitalized on these observations

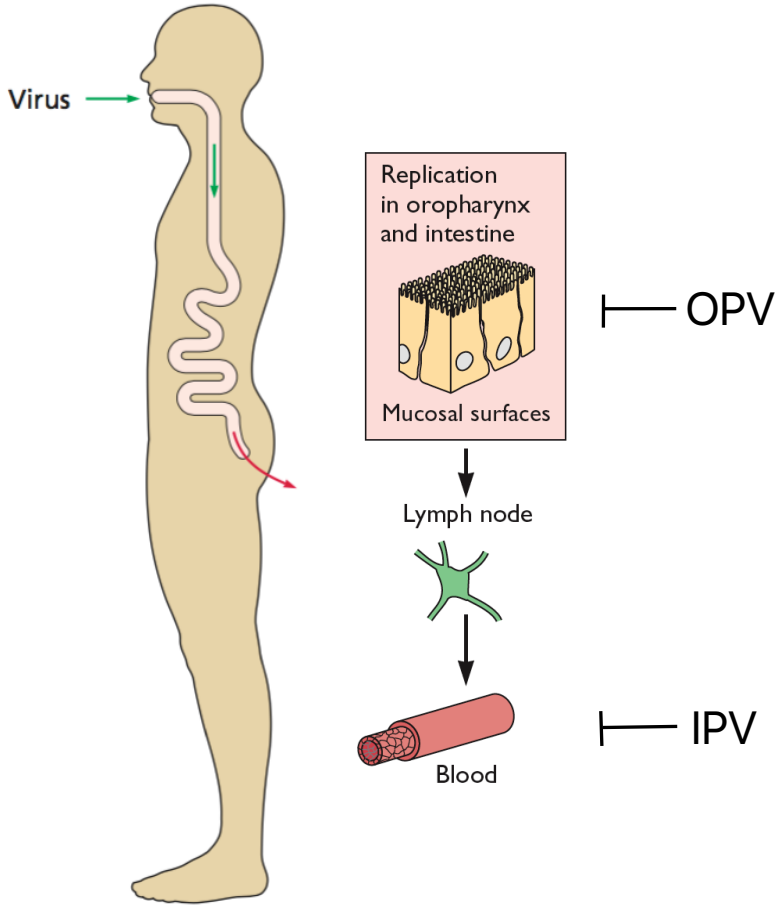
Sabin oral poliovirus vaccine (OPV)

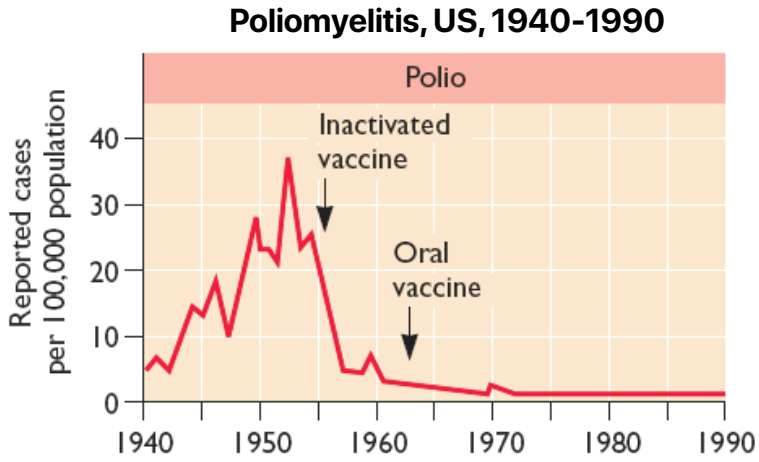
- 1961-62: Sabin's OPV strains are licensed for use in the U.S. after a struggle
- Sabin Sundays: community-wide administration of OPV; but until late 1980s, only 60-70% of children received recommended three doses
- OPV incorporated into the routine vaccination program for young children
- Use of OPV in US from 2,500 cases/yr when only IPV was used, to zero in 1979, last indigenous case

Two poliovirus vaccines

- Inactivated poliovirus vaccine, IPV
  - —must be injected
  - —when properly prepared does not cause disease
  - —does not produce intestinal immunity
  - —used 1955 - 1961 and 2000 - present in U.S.
- Oral poliovirus vaccine, OPV
  - —easy to administer
  - —produces intestinal immunity
  - —mutant viruses empirically derived from virulent strains
  - —usually reverts during intestinal replication
  - —used 1961 - 2000 in U.S.

Two poliovirus vaccines





Poliomyelitis remained a global problem

- Poliovirus vaccines only administered to a small percentage of children in developing countries
- In Brazil Sabin showed that mass immunization campaigns (National Immunization Days) can dramatically reduce the incidence of disease
- WHO established the Expanded Programme on Immunization (EPI) in 1974 to vastly increase use of OPV

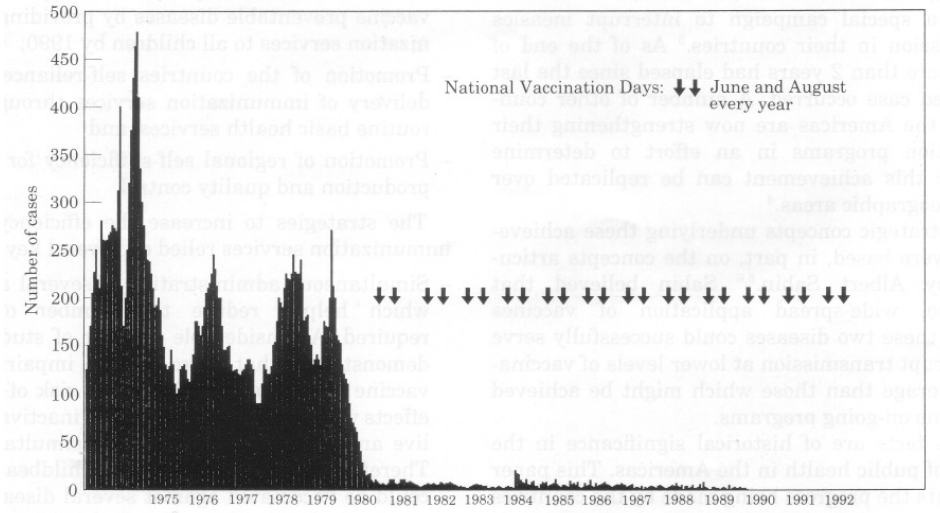
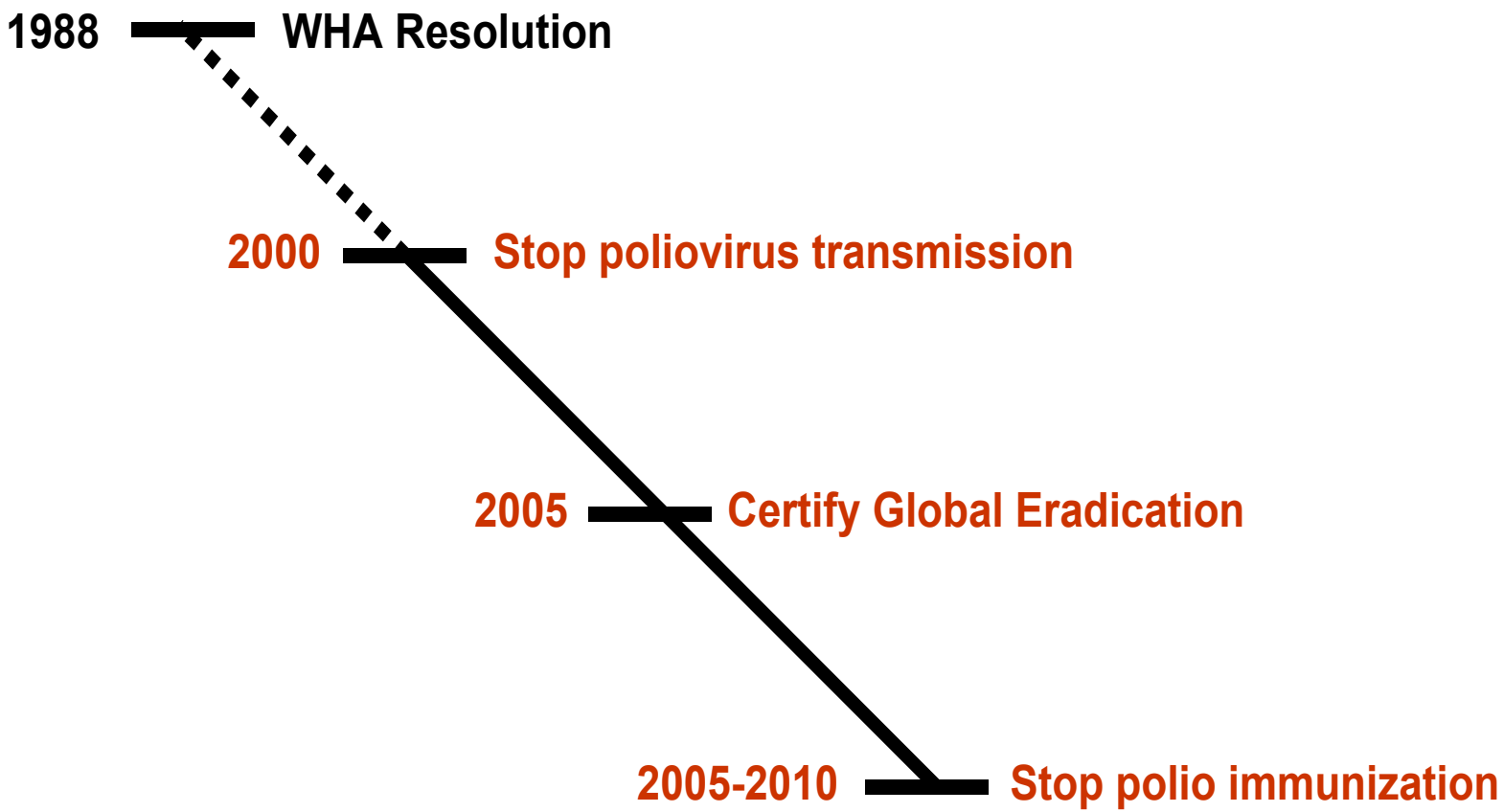
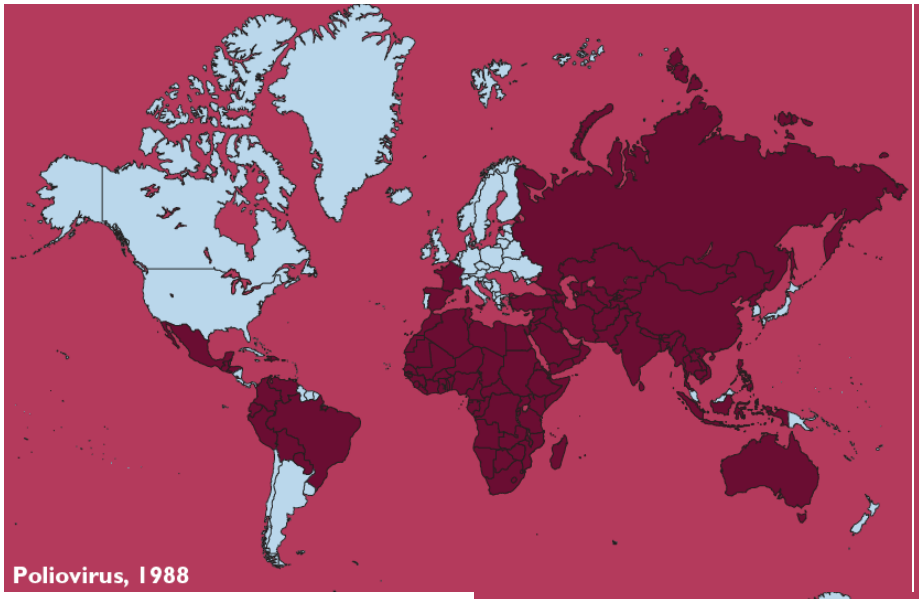
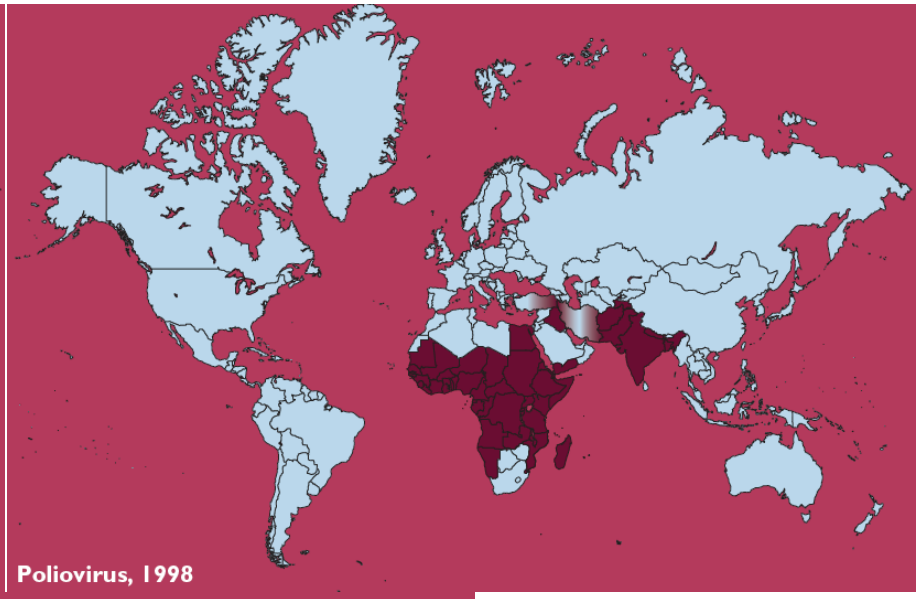


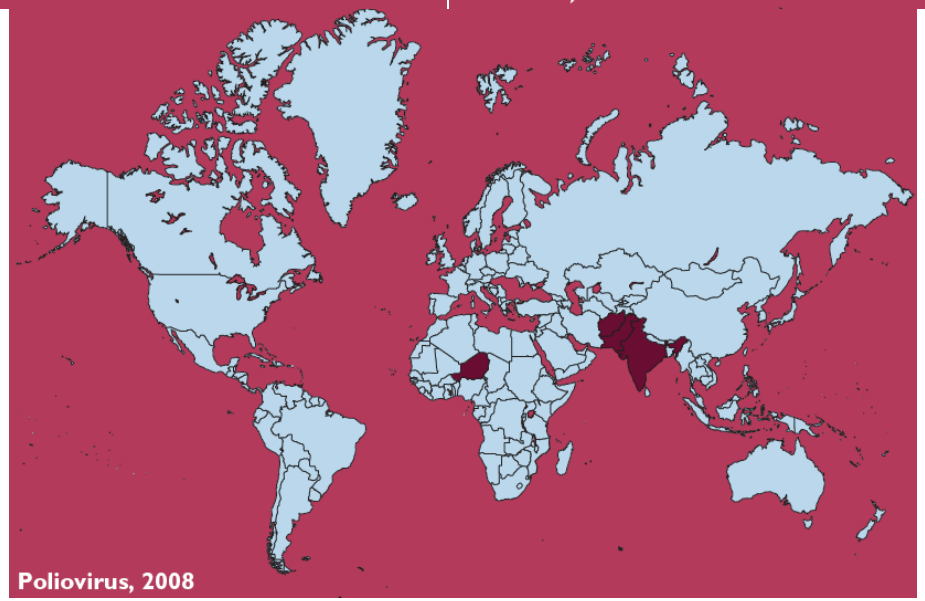
Figure 1. Polio cases by 4-week period Brazil, 1975–1992. Source: DNE-SNABS, MS and PAHO.

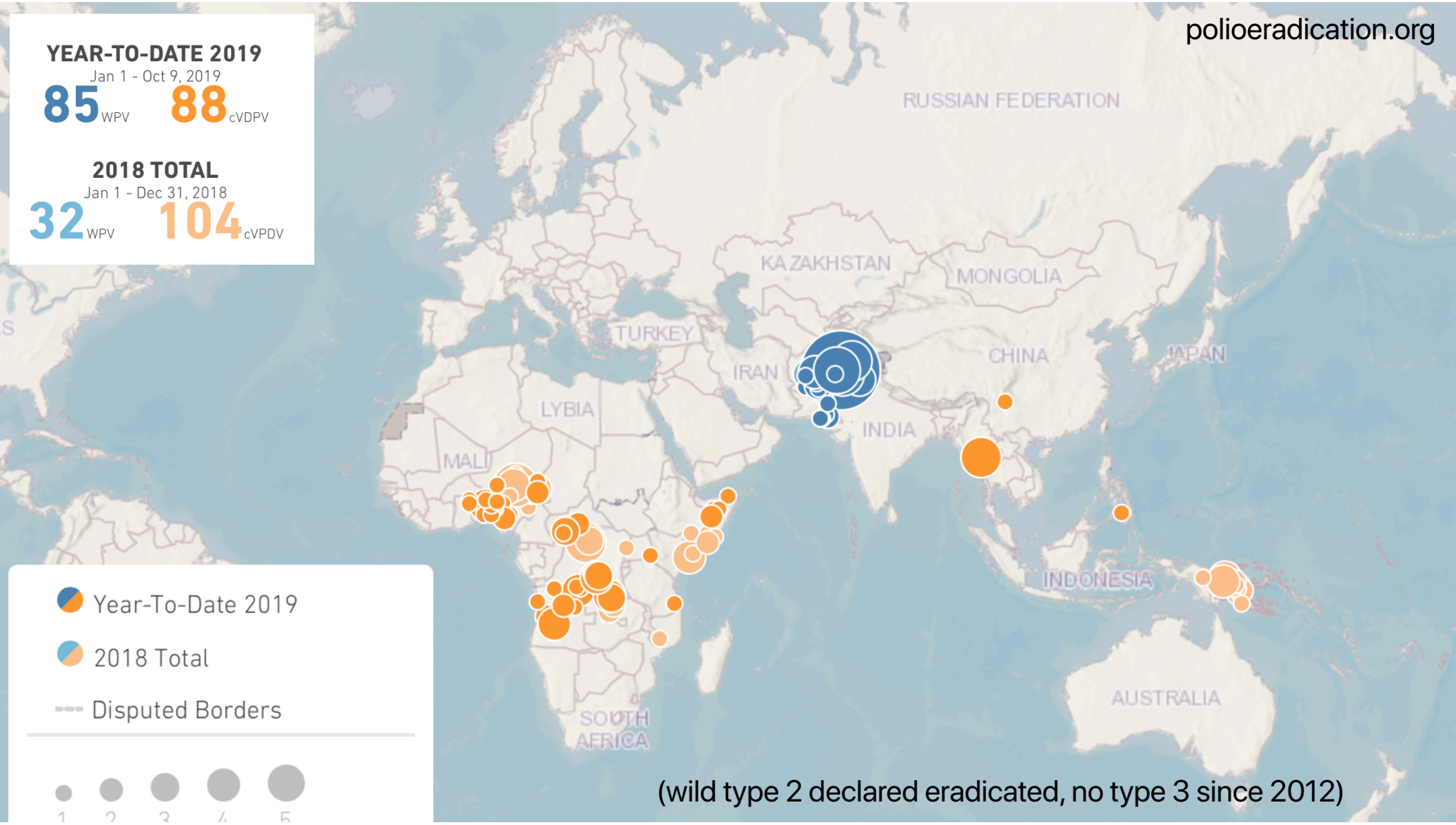
Eradication of poliomyelitis




Poliovirus, 1988

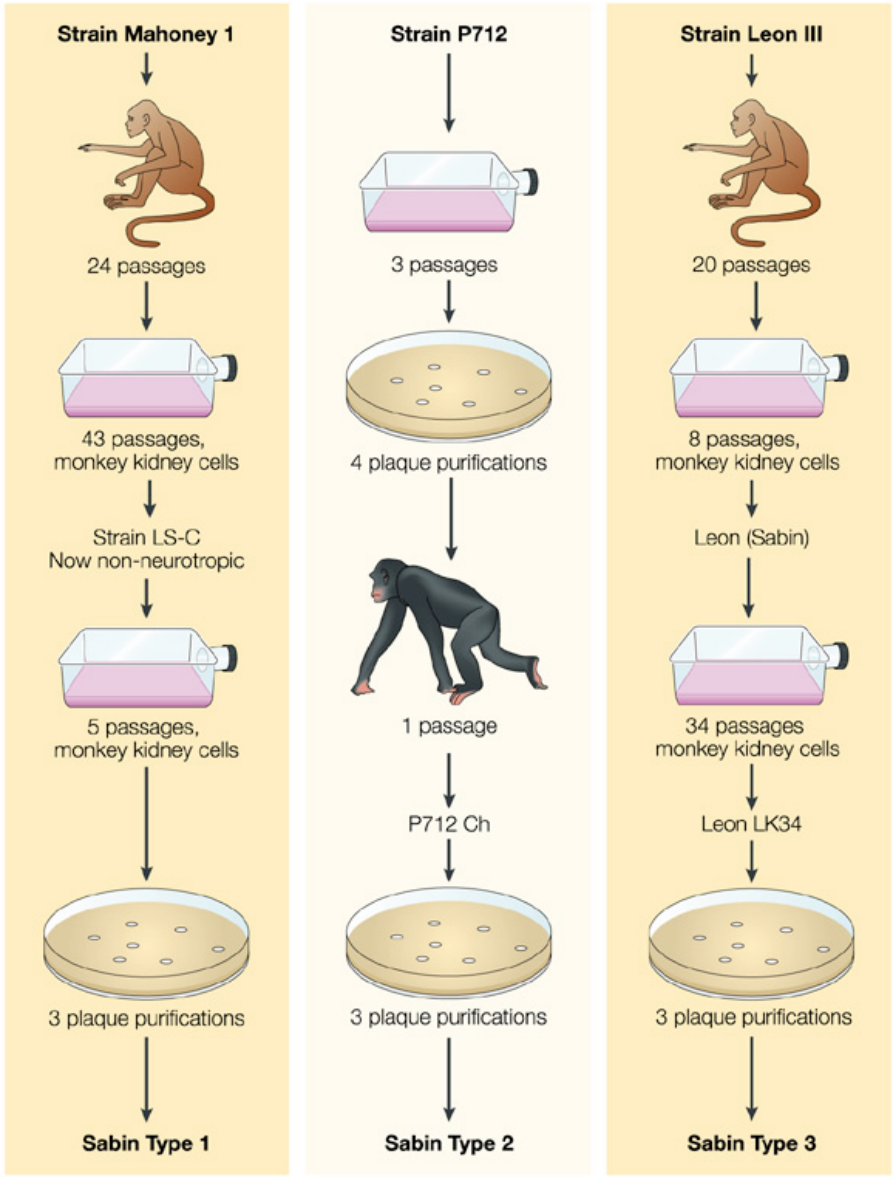

Poliovirus, 1998

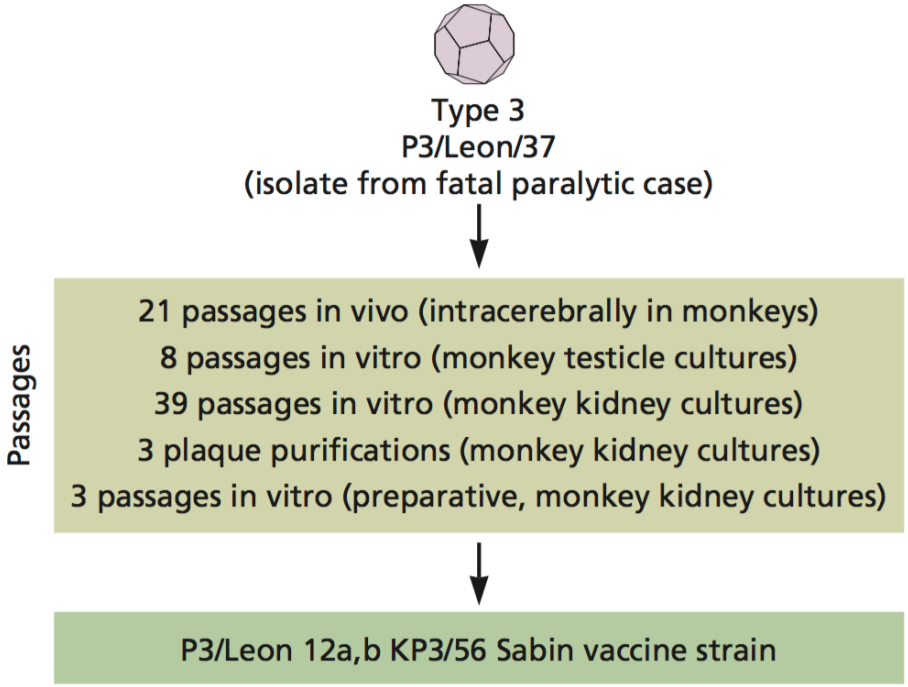

Poliovirus, 2008


YEAR-TO-DATE 2019
Jan 1 - Oct 9, 2019
85 WPV
88 cVDPV
2018 TOTAL
Jan 1 - Dec 31, 2018
32 WPV
104 cVPDV
polioeradication.org
RUSSIAN FEDERATION
KAZAKHSTAN
MONGOLIA
TURKEY
IRAN
CHINA
JAPAN
LYBIA
INDIA
MALI
INDONESIA
AUSTRALIA
SOUTH AFRICA
Year-To-Date 2019
2018 Total
Disputed Borders
1
2
3
4
5
(wild type 2 declared eradicated, no type 3 since 2012)

Polio eradication in India was difficult

- Achieved in 2016 (after 5 years polio-free)
- Considered greatest challenge
- High population density, poor civic infrastructure, poor sanitation, almost nonexistent public health system, rampant malnutrition and diarrhea, difficult-to-reach locales, high population mobility, extremely high force of WPV transmission in few states

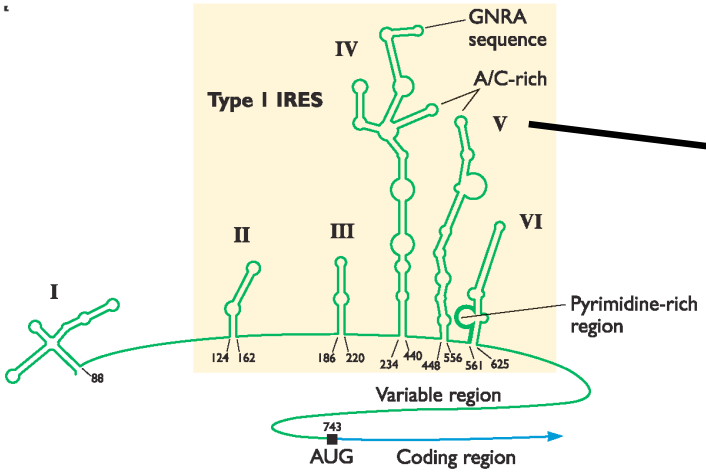


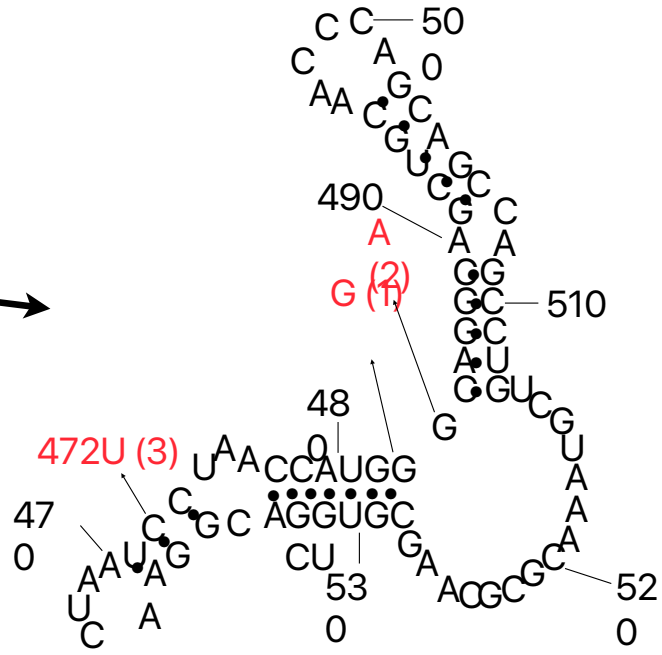


Determinants of attenuation: Sabin OPV

Virus	Mutation (location/nucleotide position)
P1/Sabin	5'-UTR nt 480 VP1 aa 1106 VP1 aa 1134 VP3 aa 3225 VP4 aa 4065
P2/Sabin	5'-UTR nt 481 VP1 aa 1143
P3/Sabin	5'-UTR nt 472 VP3 aa 3091

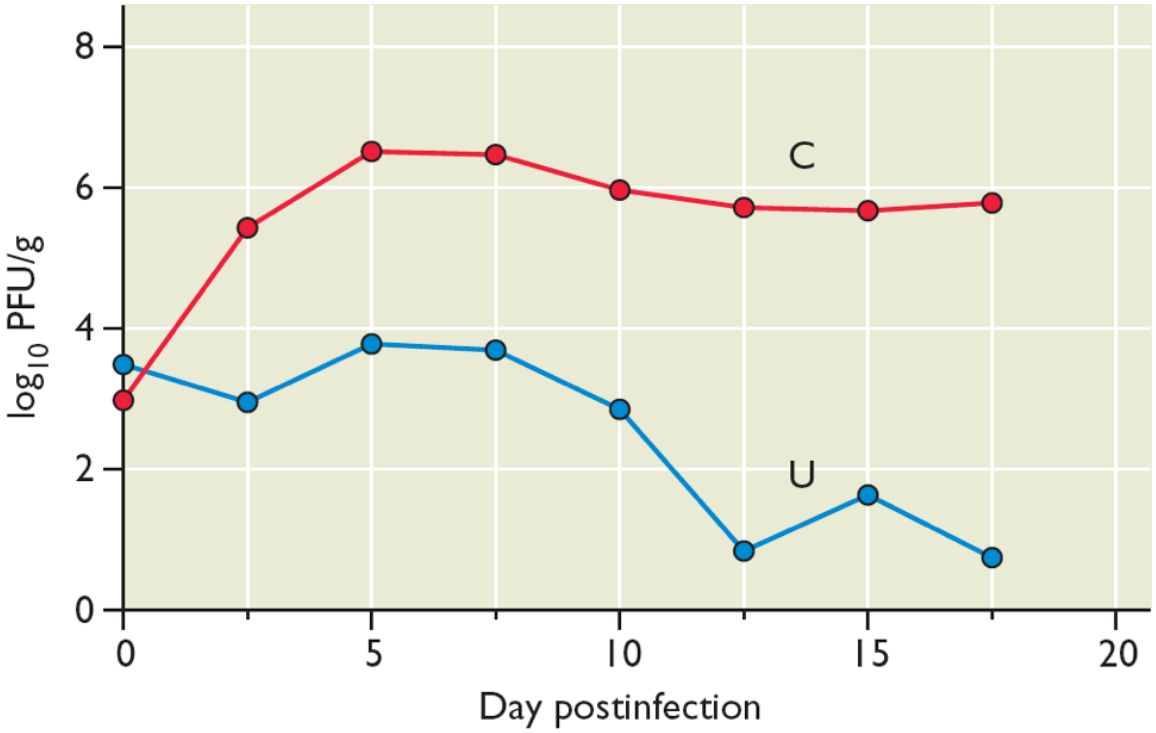
IRES domain V



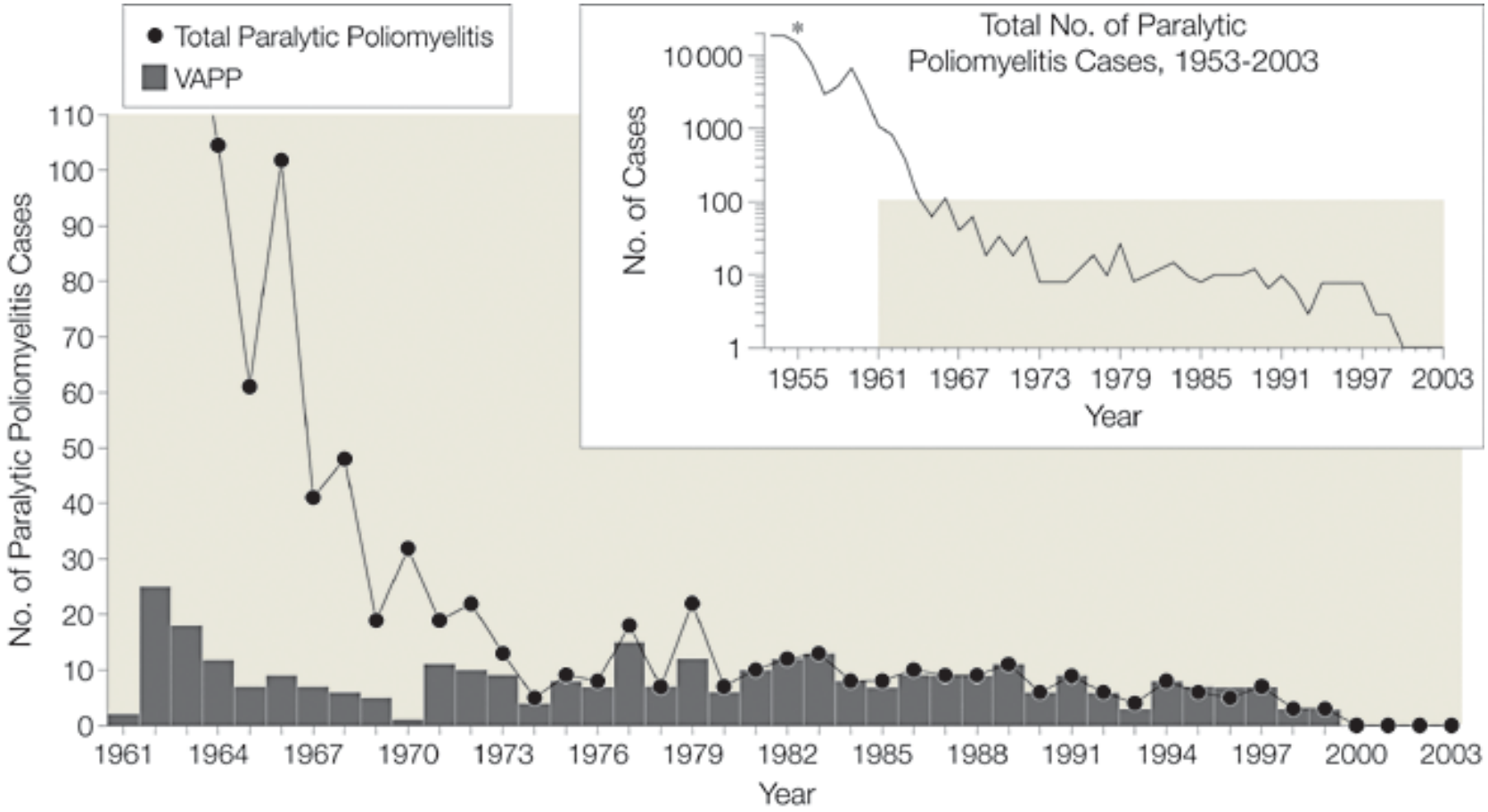


Poliovirus reproduction in mouse brain

Virus	Base at 472	LD_{50}
PRV7.3	U	$>2 \times 10^7$
PRV8.4	C	9×10^3



Reported cases of poliomyelitis, US, 1961-2003



Alexander, L. N. et al. JAMA 2004;292:1696-1701.

Reversion of P3/Sabin

Virus	Base at 472	Time of isolation after vaccination	Histological lesion score
Sabin vaccine	U		0.36
DM1	U	24 h	ND
DM2	U	31 h	1.58
DM3	U/C	35 h	ND
DM4	C	47 h	2.48
DM38	C	18 da	ND
P3/119	C	3-4 weeks	3.34

Evans et al., Nature 314:548 (1985)

Can viral diseases be eradicated?

- Smallpox eradication program was launched in 1967; disease declared eradicated in 1978
- Only major human disease to be eradicated
- For disease eradication, two features are essential
  - Replication must occur in only one host
  - Vaccination must induce lifelong immunity

Polio eradication

- OPV differs from smallpox vaccine in that it can revert to a form that causes disease
- In countries using OPV, the only source of polio eventually is the vaccine
- Therefore, it was decided that OPV use will cease after eradication has been achieved
- Assumptions for cessation of OPV: no non-human reservoirs of poliovirus, time-limited circulation of VDPV

Problems associated with OPV

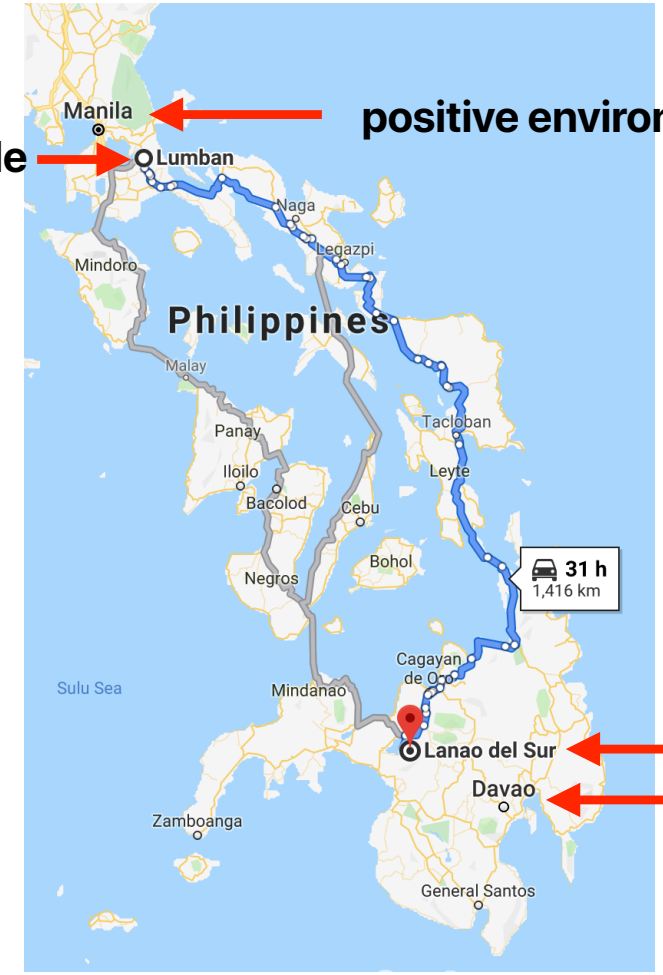
- Outbreaks of polio in Egypt, Dominican Republic/Haiti, Philippines, Madagascar, caused by VDPV
- These VDPV strains regained virulence and spread in human populations
- Long-term persistence and excretion of VDPVs in immunocompromised persons

Country	Number of reported cases	Type	Date of onset of index case	Est. duration of virus circulation	Estimated number of cVDPV infections	References
Hispaniola (pop‡: 16.4 million)	21 VC & 21 PC *	1	July 2000	~2 years	100,000–200,000	[12,48,49]
Madura, Indonesia (pop: 3.5 million)	46 VC and 10 PC	1	June 2005	~2 years	100,000+	[11]
Egypt (pop: 55.8 million)	30 VC	2	1988	~10 years	Several million	[1]
Philippines (pop: 75.7 million)	3 VC	1	March 2001	~3 years	1,000–10,000	[9,62]
Madagascar (pop: 16 million)	4 VC	2	March 2002	~2.5 years	10,000–50,000	[10]
China (pop: 1.3 billion)	3 VC	1	May 2004	~1 year	1,000–10,000	[8]
Madagascar (pop: 16 million)	5VC	2	April 2005	~1.5 years	10,000–50,000	[13]
Cambodia (pop: 14 million)	2 VC	3	Nov 2005	~2 years	1,000–10,000	[7,14,63]

*VC (virologically-confirmed), PC (polio-compatible)
‡approximate population size at the time of the outbreak
doi:10.1371/journal.pone.0003433.t001

Polio returns to Philippines after 19 years

- Vaccine-derived type 2 PV
- Coverage dropped from 95% to 66%
- Decline blamed on Dengvaxia controversy



OPV transmission

- The recent polio outbreaks demonstrate that neurovirulent revertants of OPV can circulate for years (even in immune populations) and cause poliomyelitis
- These outbreaks mimic the situation that will occur when OPV usage is halted: circulation of neurovirulent revertants when vaccination coverage drops
- In light of this information, we cannot stop vaccinating

Polio in Nigeria

- Rumors of contaminated OPV in mid-2003 led to official suspension of immunization
- Increased wild type poliovirus transmission in Nigeria, spread to 18 countries that had been polio free for 1 or more yr, including 3 outside Africa
- In July 2004 immunization resumed
- Polio still endemic in Nigeria - 62 cases in 2011, 122 in 2012, 53 in 2014

Poliovirus type 2 in Nigeria

- Last case of poliovirus type 2 in 1999
- When Nigeria resumed immunization in 2004, monovalent type 1 and 3 were used
- Outbreak caused by vaccine-derived type 2 polio in 2005

Poliovirus returns to Nigeria

- No reported polio cases from July 2014
- July 2016, 3 confirmed polio cases in Borno State
- Two AFP, one asymptomatic
- Related to poliovirus from Borno State in 2011
- VDPV2 also found in this area, circulating for 2 yr

As long as there is wild poliovirus, all countries must maintain high immunization coverage

IPV Introduction, OPV Withdrawal and Routine Immunization Strengthening

© UNICEF Pakistan/2011/Asad Zaidi— in Karachi, Pakistan.

This site provides information on objective 2 of the Polio Eradication and Endgame Strategic Plan 2013-2018. Objective 2 seeks to hasten the interruption of all poliovirus transmission and, where possible, contribute to strengthening immunization services for the delivery of other lifesaving vaccines.

The Endgame Plan was developed in response to the World Health Assembly (WHA) in May 2012, which declared the completion of poliovirus eradication to be a "programmatic emergency for global public health". Under objective 2, at least one dose of inactivated poliomyelitis vaccine (IPV) will be introduced into routine immunization programmes globally, after which trivalent oral polio vaccines (OPV) will be replaced with bivalent OPV in all OPV-using countries – setting the stage for eventually ending bOPV use.

- IPV introduced into high-risk countries
- April 17 2016 - Global synchronized switch from trivalent to bivalent OPV
- mOPV2 stockpiled in case of VDPV outbreak (problematic!)
- Might be necessary to switch to non-revertible OPV

WHO poliovirus vaccine recommendations

- As long as poliovirus circulates, all children worldwide should be vaccinated against poliovirus
- For countries using OPV only, at least one dose of IPV should be added to schedule (3 bOPV + 1 IPV)
- When VAPP is a concern: IPV-OPV schedule
- IPV only with high coverage, low importation risk

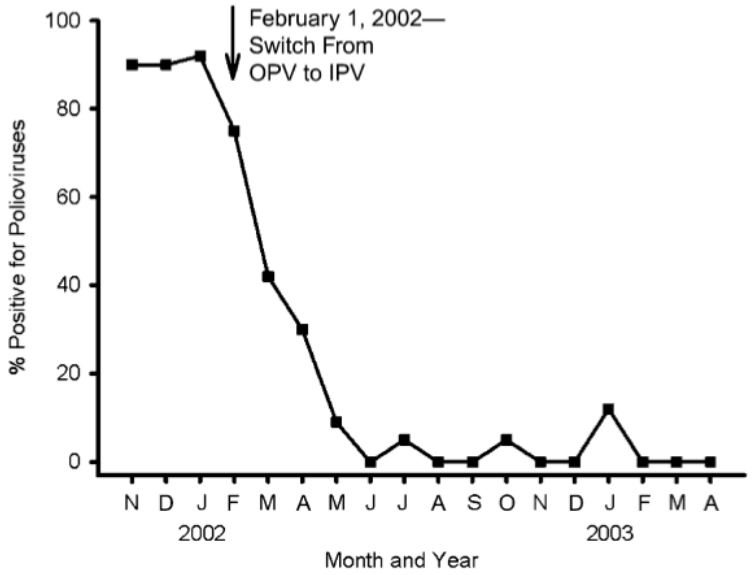
Weekly Epidemiological Record 28 February 2014, v. 89

Poliovirus vaccines in use globally

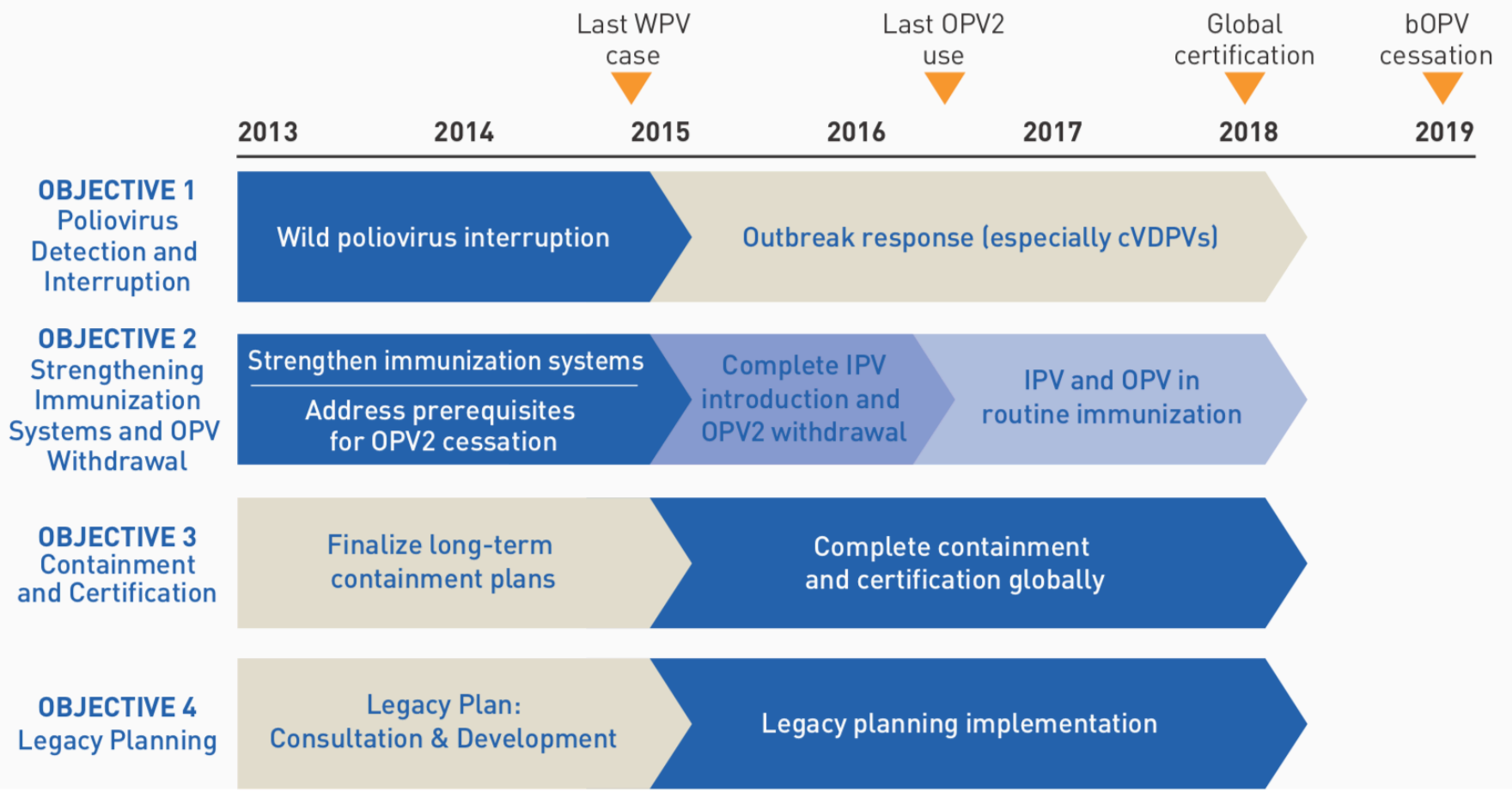
- bOPV (1, 3)
- mOPV1, mOPV3 (mOPV2 stockpiled for outbreaks)
  - Stronger immunity vs OPV; less transmission
- IPV

Polio surveillance

- Acute flaccid paralysis (AFP) surveillance
  - Finding and reporting children with AFP
  - Transporting stool samples for analysis
  - Isolating and identifying poliovirus
  - Determine origin of virus strain
- Environmental surveillance
  - Testing sewage or other environmental samples for poliovirus
  - Limitations shown by recent Nigerian experience



Polio eradication and endgame timeline



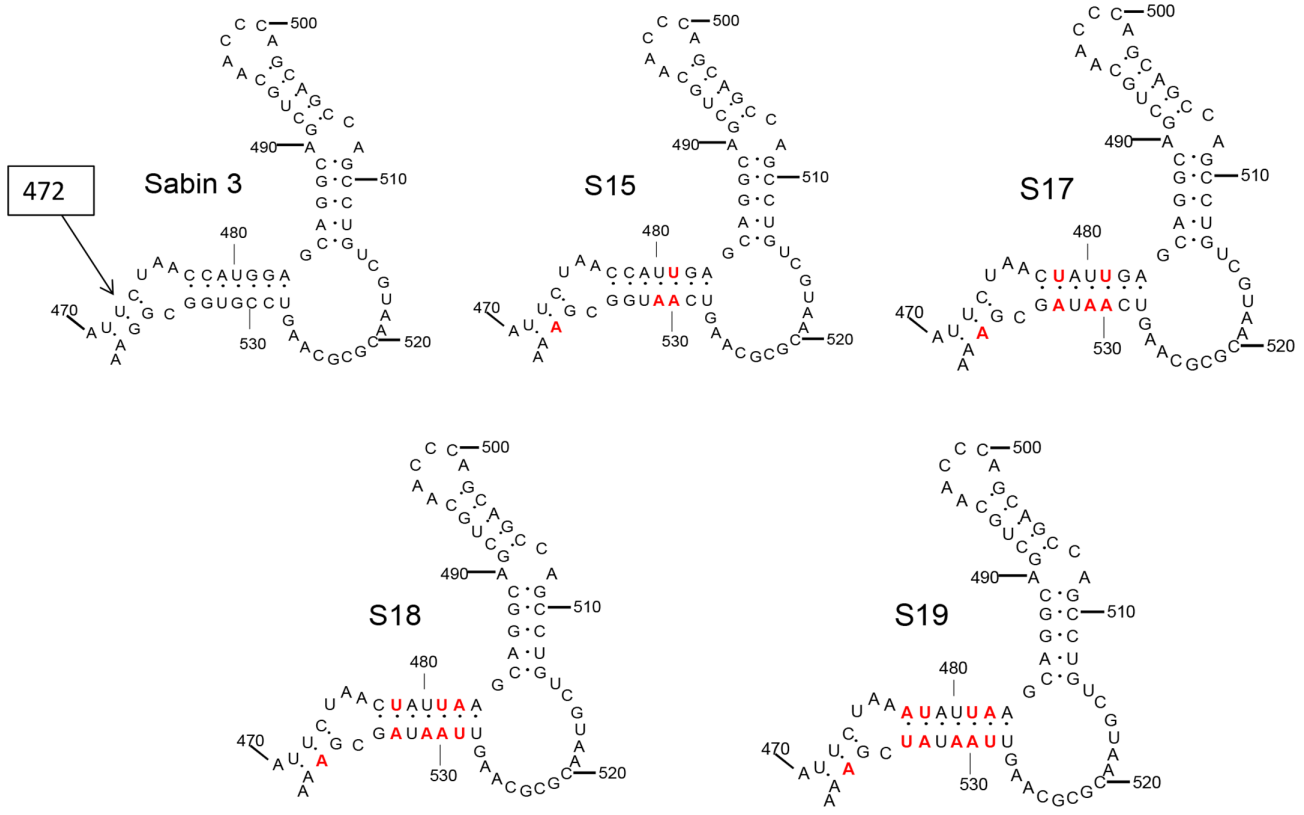
Post-eradication issues

- Synthesis of infectious virus from genome sequence
- Infectious virus in clinical samples
- Need to stockpile vaccines: which one?
- Development of antivirals for immunodeficient shedders

Which vaccine should be used/stockpiled?

- IPV: noninfectious, no reintroduction of virus into the environment
- However, IPV is produced from virulent strains
- Poliovirus has escaped from vaccine-manufacturing plants at least twice
- Sabin IPV - in use China, Japan
- IPV is not as good as OPV in stopping outbreaks

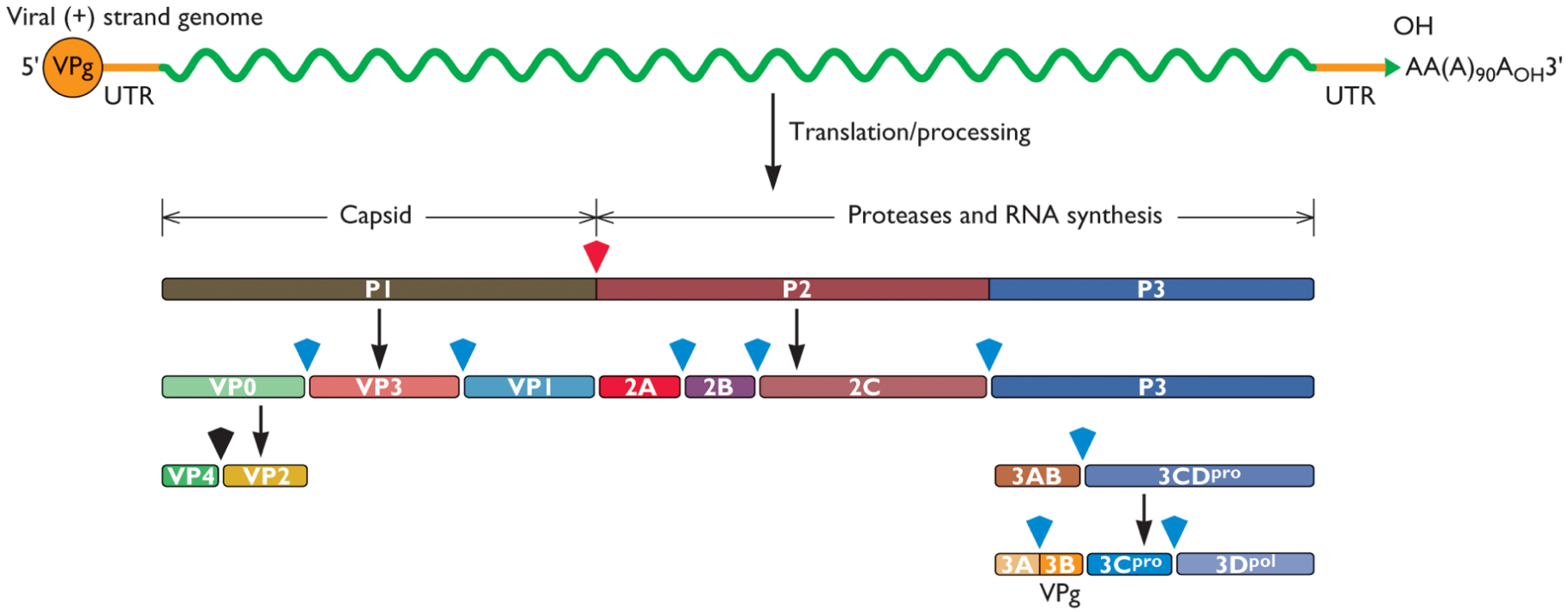
New IPV strains for low-containment production (or non-revertible OPV)



http://dx.doi.org/10.1371/journal.ppat.1005316

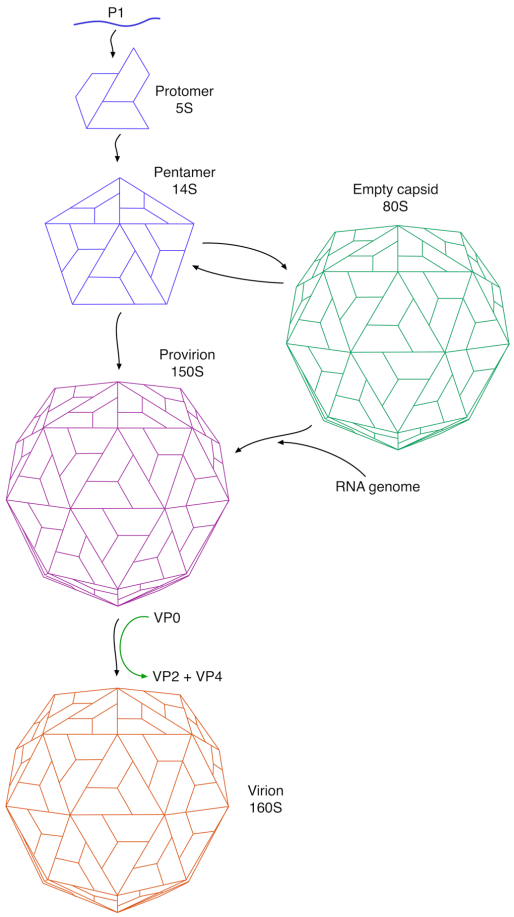
Virus Attenuation by Genome-Scale Changes in Codon Pair Bias

J. Robert Coleman,[1] Dimitris Papamichail,[2]* Steven Skiena,[2] Bruce Futcher,[1]
Eckard Wimmer,[1]† Steffen Mueller[1]



Science June 27 2008

Empty capsid vaccines

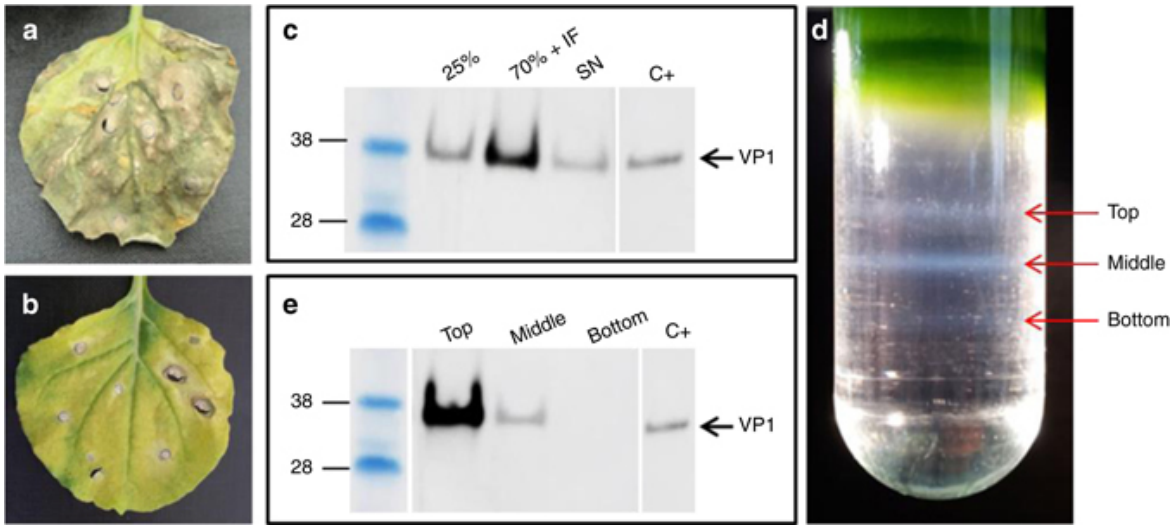


Plant-made polio type 3 stabilized VLPs–a candidate synthetic polio vaccine

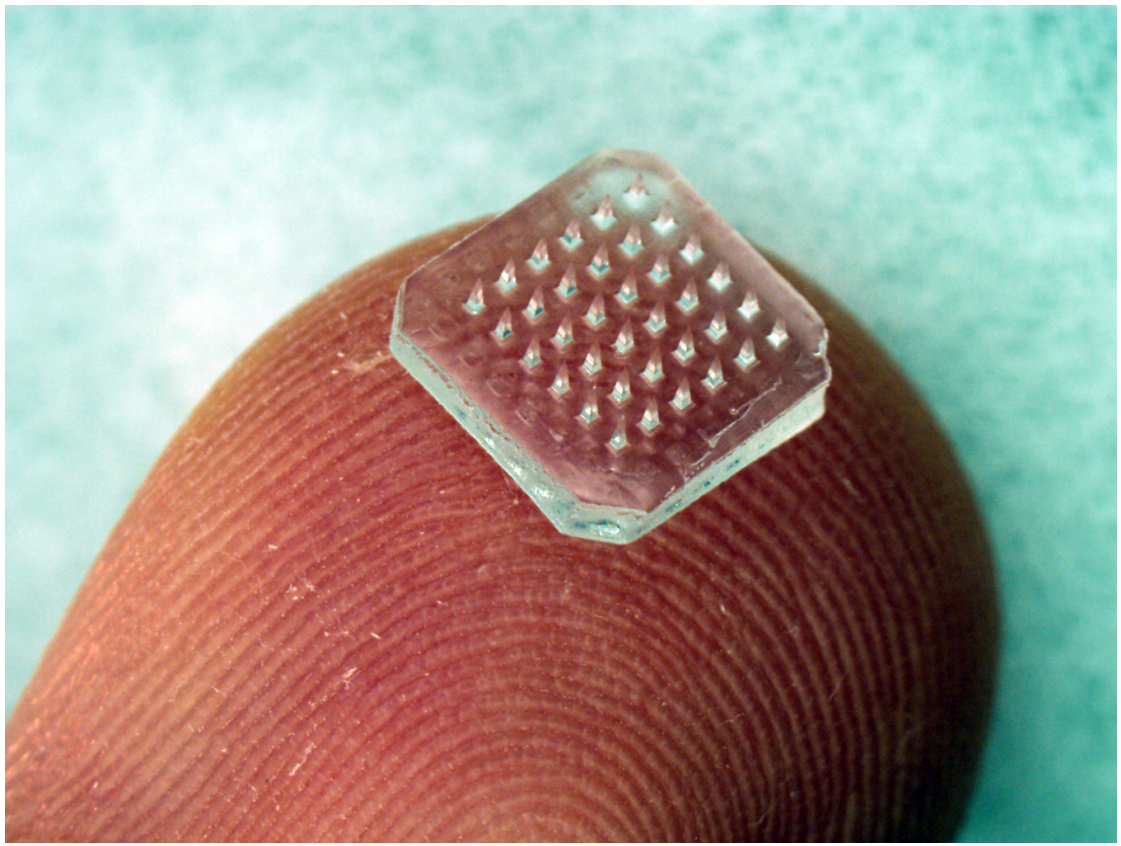
Johanna Marsian, Helen Fox, Mohammad W. Bahar, Abhay Kotecha, Elizabeth E. Fry, David I. Stuart, Andrew J. Macadam, David J. Rowlands & George P. Lomonossoff

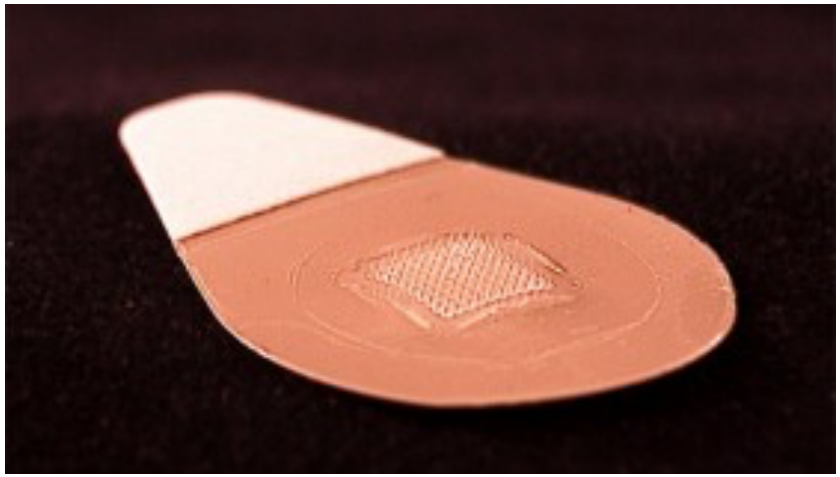
Nature Communications **8**, Article number: 245 (2017)
doi:10.1038/s41467-017-00090-w

Received: 24 November 2016
Accepted: 31 May 2017
Published online: 15 August 2017



Microneedle vaccine patch





Welcome to Poliopolis – An nOPV2 Clinical Trial

Welcome to Poliopolis! You'll spend the next 28 days in a container village to help us test a new polio vaccine. Poliopolis is equipped with all the amenities to make your stay comfortable: air-conditioned private rooms with workstations and sinks, a lounge area with a flat screen TV and foosball table, a fitness room with a variety of exercise equipment, and a bright, sunny dining area. Enjoy your stay!

Sounds like a scene from a science fiction story, right? But this is a real polio vaccine trial that took place in a parking lot at the University of Antwerp, Belgium in mid-2017. The study, funded by the Bill and Melinda Gates Foundation, evaluated two novel oral polio vaccine candidates. These vaccine candidates were developed by scientists from CDC's polio laboratory, the National Institute for Biological Standards and Control, United Kingdom, and University of California, San Francisco, with support from the U.S. Food and Drug Administration.

Poliopolis is a 66-unit container village built by the University of Antwerp, Belgium, to house a polio vaccine clinical trial. Photo credit: Ananda Bandyopadhyay, Bill and

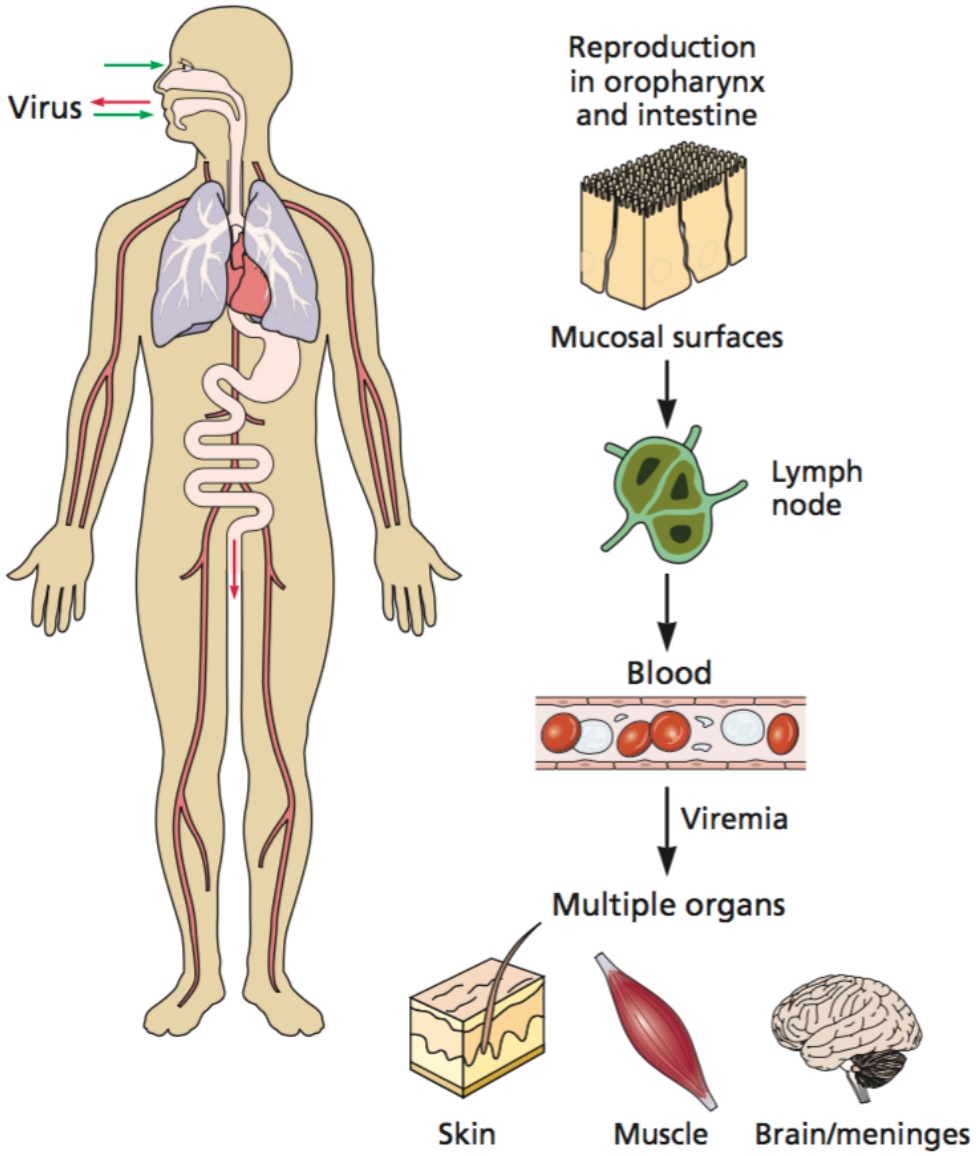
Poliovirus antiviral initiative

- Two antivirals recommended for post-poliovirus era
- For immunodeficient shedders
- For persons exposed to poliovirus (e.g. laboratory)
- For cVDPV outbreaks (with IPV)

Non-polio enteroviruses

- Common childhood infections
- Usually no GI symptoms
- Worldwide distribution, summer peaks in temperate climates
- Diagnosed clinically or viral culture or PCR
- In a poliovirus-free world, could a new poliovirus emerge from non-polio enteroviruses?

Species: *Enterovirus A*
Species: *Enterovirus B*
Species: *Enterovirus C*
Species: *Enterovirus D*
Species: *Enterovirus E*
Species: *Enterovirus F*
Species: *Enterovirus G*
Species: *Enterovirus H*
Species: *Enterovirus I*
Species: *Enterovirus J*
Species: *Enterovirus K*
Species: *Enterovirus L*
Species: *Rhinovirus A*
Species: *Rhinovirus B*
Species: *Rhinovirus C*



States and CDC probe reports of rare poliolike symptoms in kids

Filed Under: **Enterovirus, Non-Polio**

Lisa Schnirring I News Editor I CIDRAP News I Oct 08, 2018

Health officials in Minnesota and Colorado are among the states investigating acute flaccid myelitis (AFM) cases in children, raising concerns about another possible uptick in the rare condition, similar to steep rises seen in 2014 and 2016.

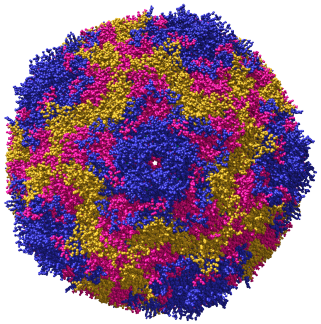
Wavebreakmedia/ iStock

The hallmark of AFM is a sudden onset of limb weakness associated with spinal cord inflammation. In 2014, a large outbreak coincided with a national outbreak of severe respiratory illness causes by enterovirus D68 (EV-D68), but intensive investigations have not consistently found a specific pathogen in spinal fluid samples.

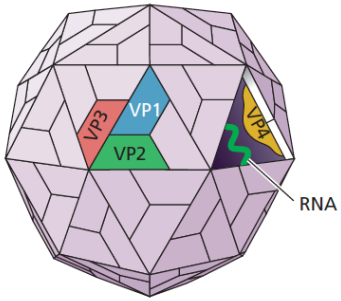
The US Centers for Disease Control and Prevention (CDC) said as of Sep 30, there have been 38 cases reported from 16 states. In 2017 the CDC recorded only 33 cases, and in 2015 it confirmed only 22 cases. However, during the two seasons when cases spiked—2014 and 2016—there were 120 and 149 cases, respectively.

Minnesota reports 6 recent cases

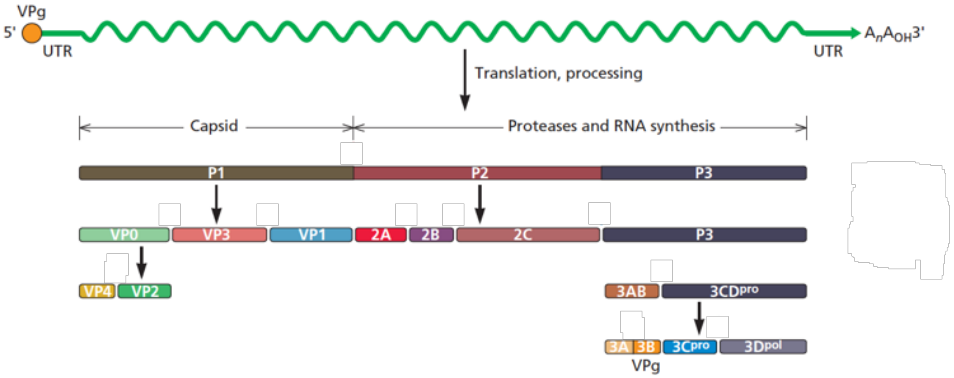
In an Oct 5 statement, the Minnesota Department of Health (MDH) said it is investigating six AFM cases that have occurred in children since the middle of September. Health officials are collecting information about the cases from health providers and are in contact with the CDC, the MDH said.

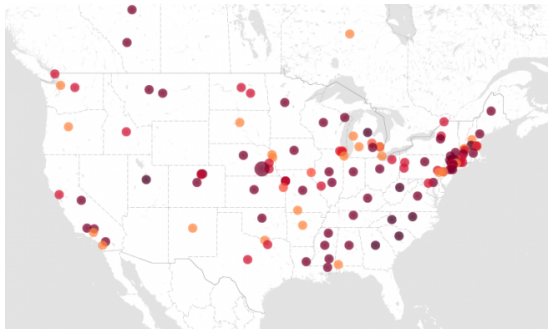


Enterovirus D68 (EV-D68)



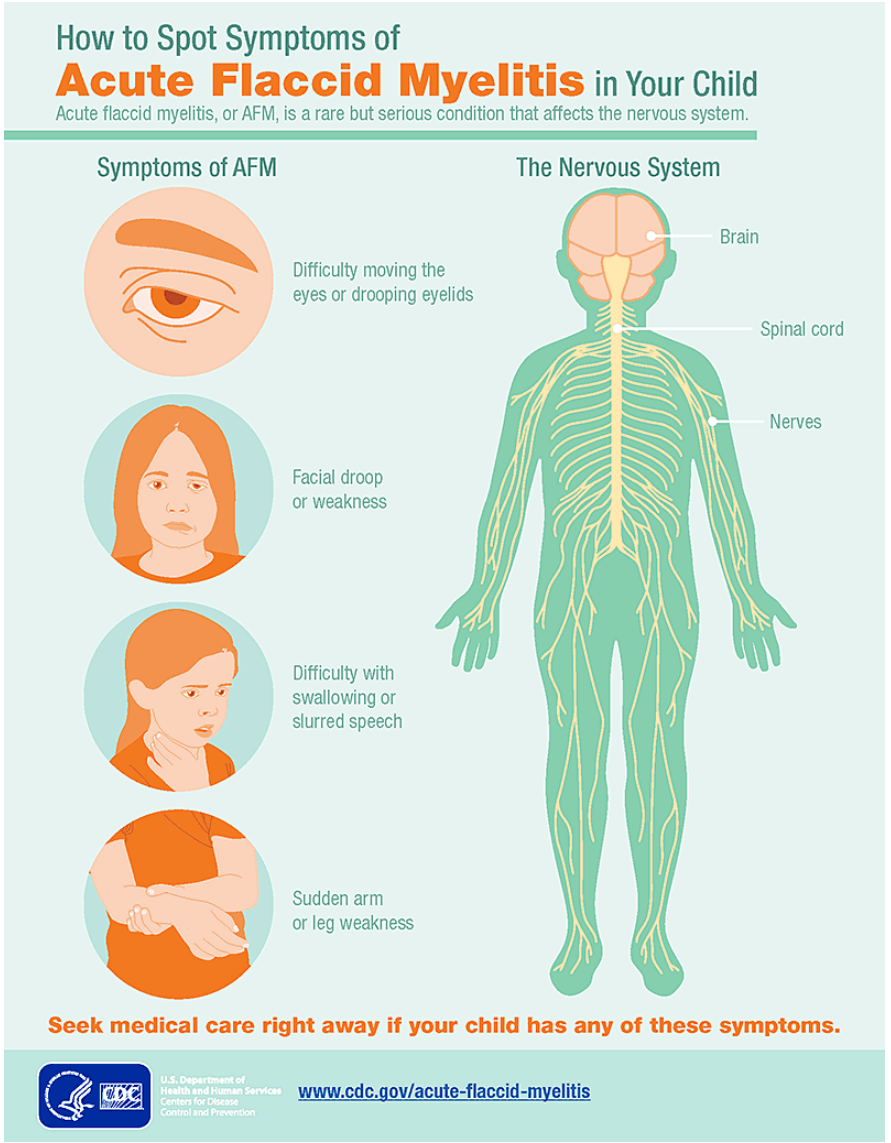
- Isolated from children with pneumonia 1962
- Infection results in “common cold-like” symptoms
- Few infections until 2014
- Associated with respiratory induced acute flaccid paralysis/myelitis



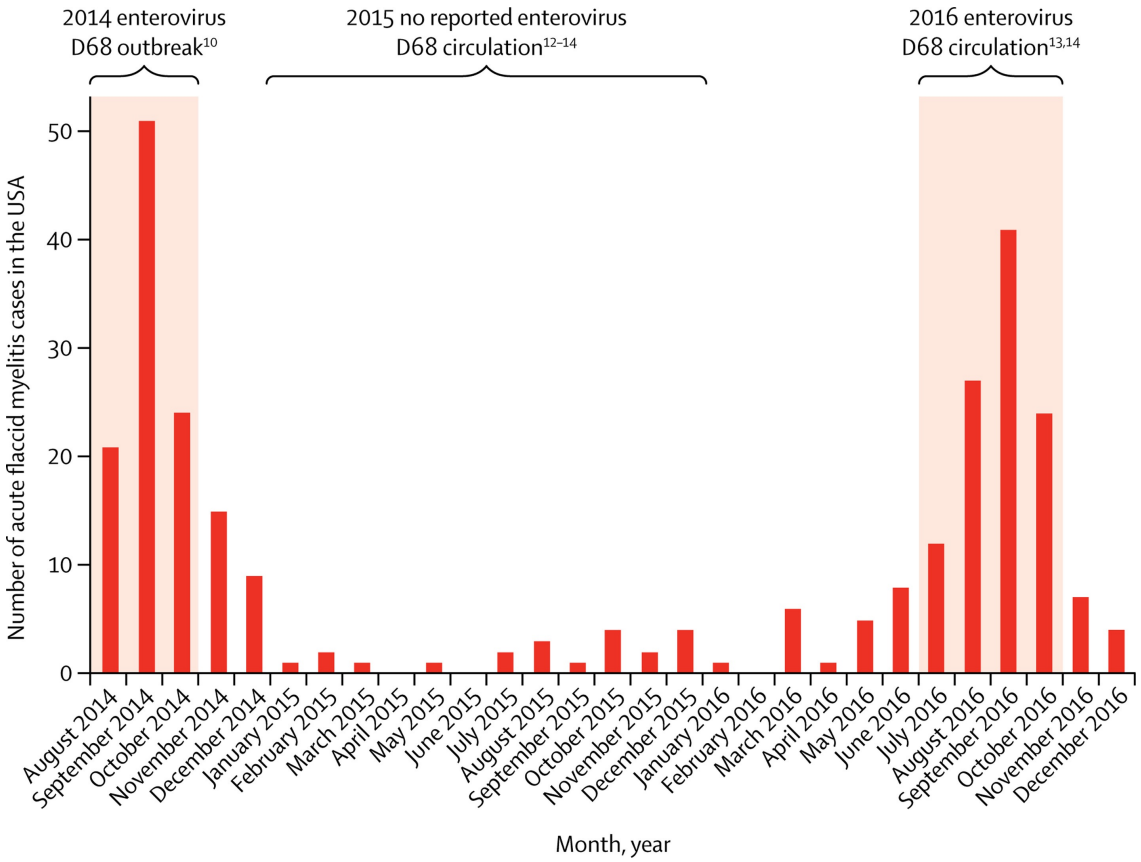


Acute flaccid paralysis

- Sudden onset of paralysis/weakness in any part of the body in a child younger than 15 years of age
- Definition was designed for poliomyelitis surveillance purposes
- Acute flaccid myelitis (AFM) is a subset of AFP, injury to spinal cord presumed present, no age limitation
- May have a wide range of etiologies, including infectious and non-infectious (e.g. neurotoxins)



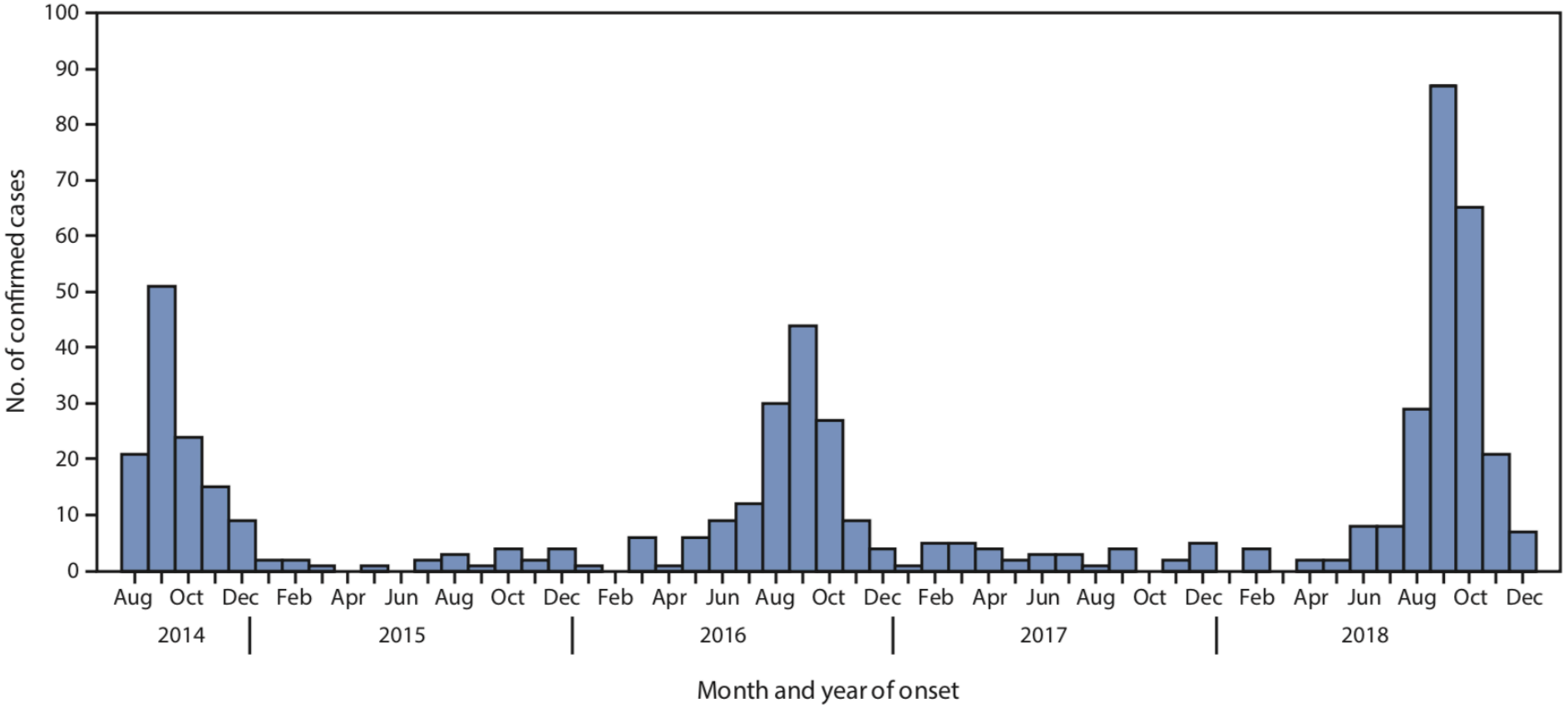
Association between EV-D68 infection and acute flaccid myelitis



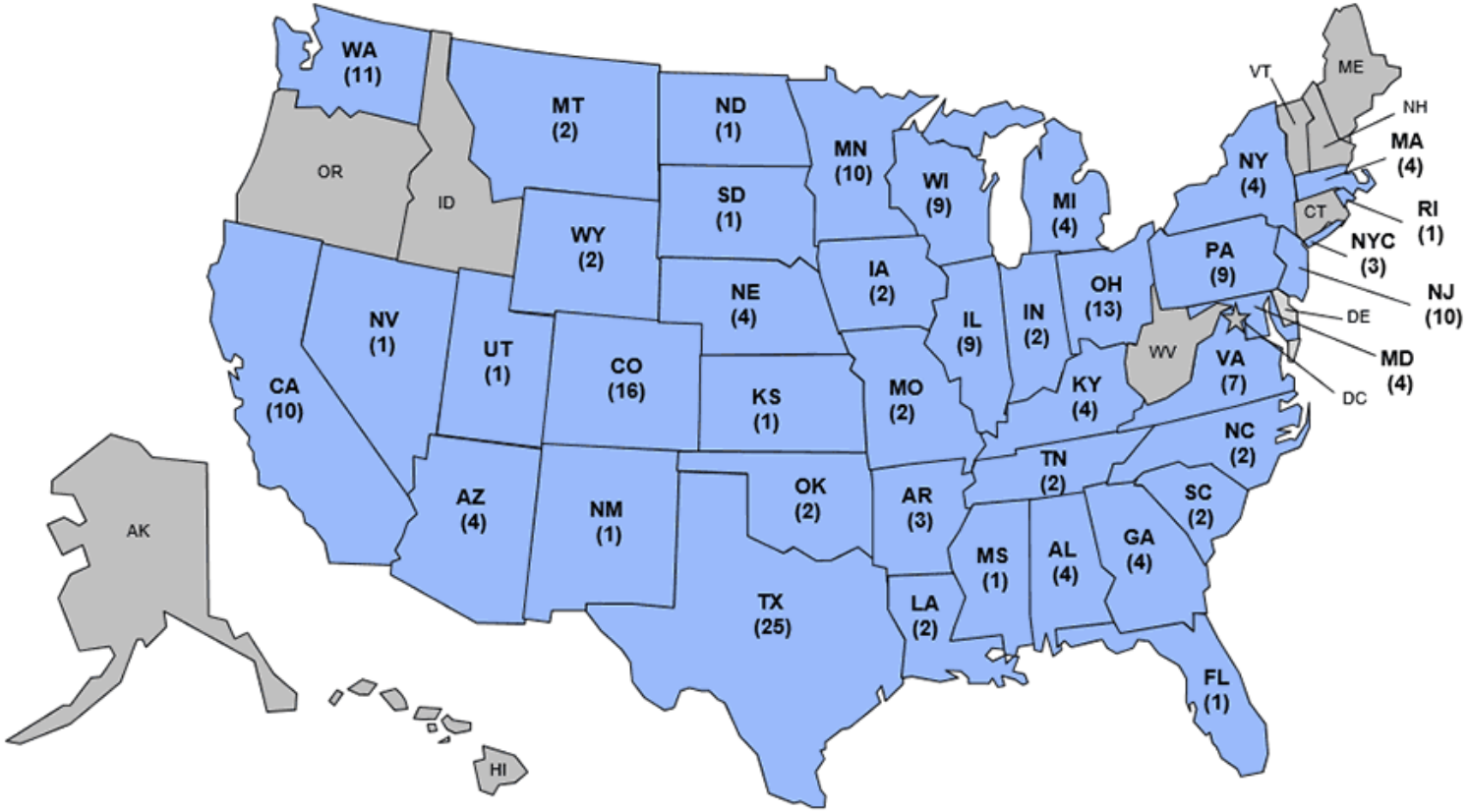
Messacar, *et al.*, Lancet Infect Dis, **2018**: AOP

Confirmed US AFM cases reported to CDC

N = 559 — United States, August 1, 2014–December 31, 2018



2018 confirmed cases of acute flaccid myelitis (AFM) by state (N=233)*



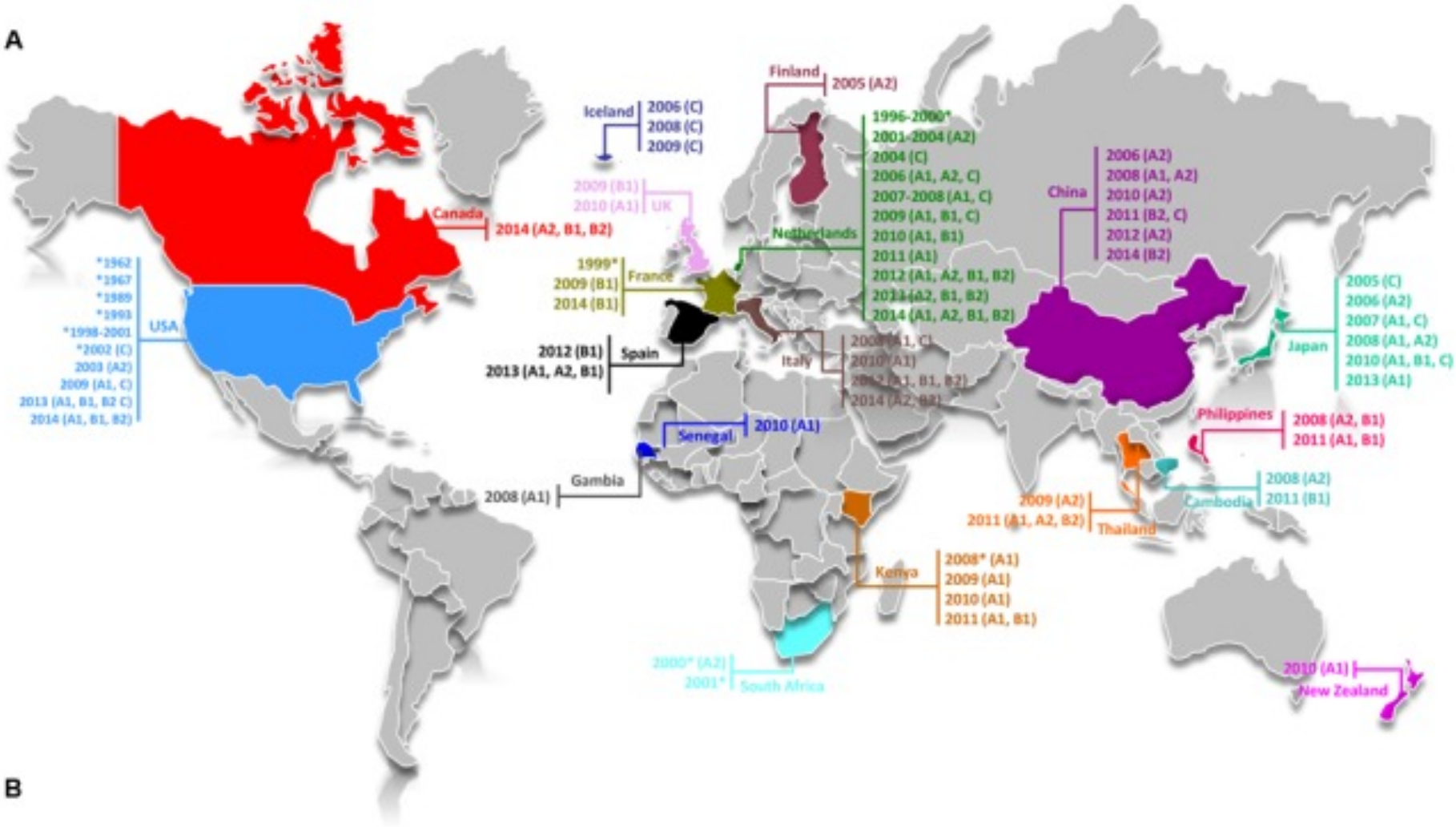
*Confirmed AFM cases as of January 18, 2019. Patients under investigation are still being classified, and the case counts are subject to change. One of the confirmed cases is a foreign resident (based on the country of usual residence) and therefore not included in the state map.

Laboratory results from specimens collected from patients with confirmed acute flaccid myelitis (N = 233) — United States, 2018

Specimen source	No. with specimens available (% of 233)	No. (%) positive	Positive test results (No.)
CSF	74 (32)	2/74 (3)	EV-A71 (1) EV-D68 (1)
Respiratory	123 (53)	54/123 (44)	EV-D68 (30) EV-A71 (10) Other/Untyped EV/RV (14)
Stool	100 (43)	13/100 (13)	EV-D68 (1) EV-A71 (2) Echovirus 11 (1) Coxsackievirus (3) Parechovirus (4) Other/Untyped EV/RV (2)

Abbreviations: EV = enterovirus; RV = rhinovirus.

Global distribution of EV-D68 as of 2014

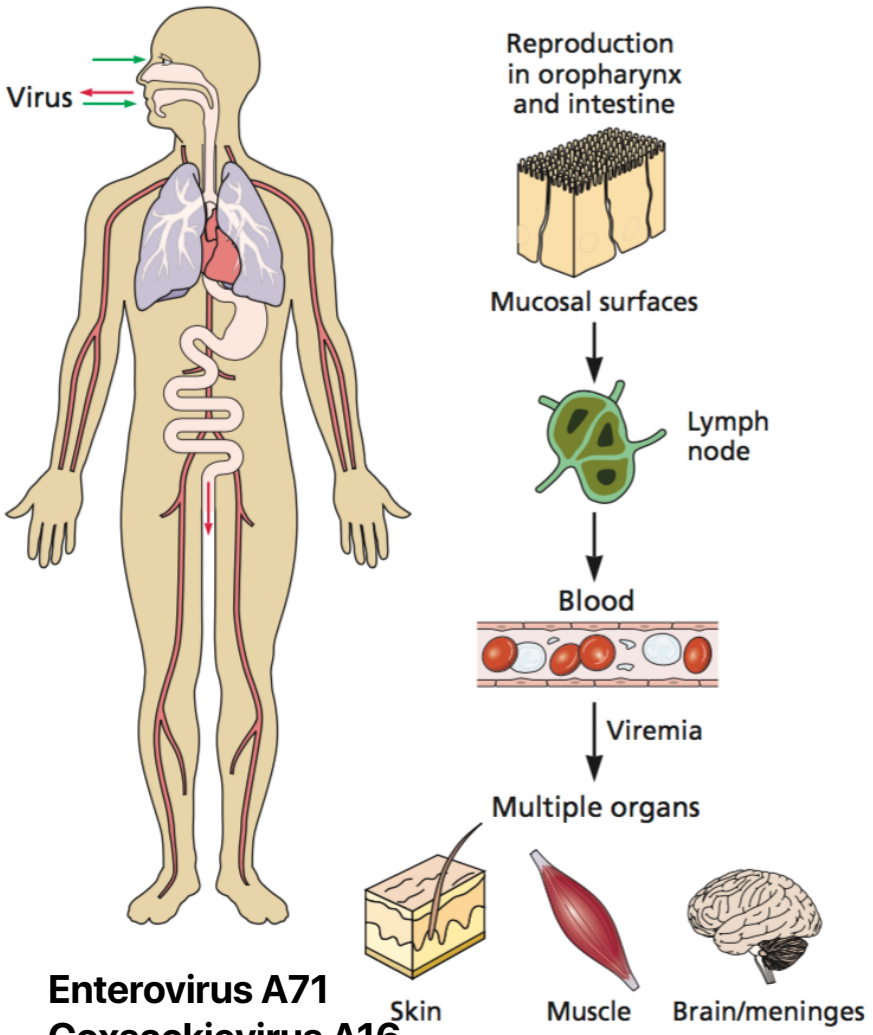


Picornaviridae

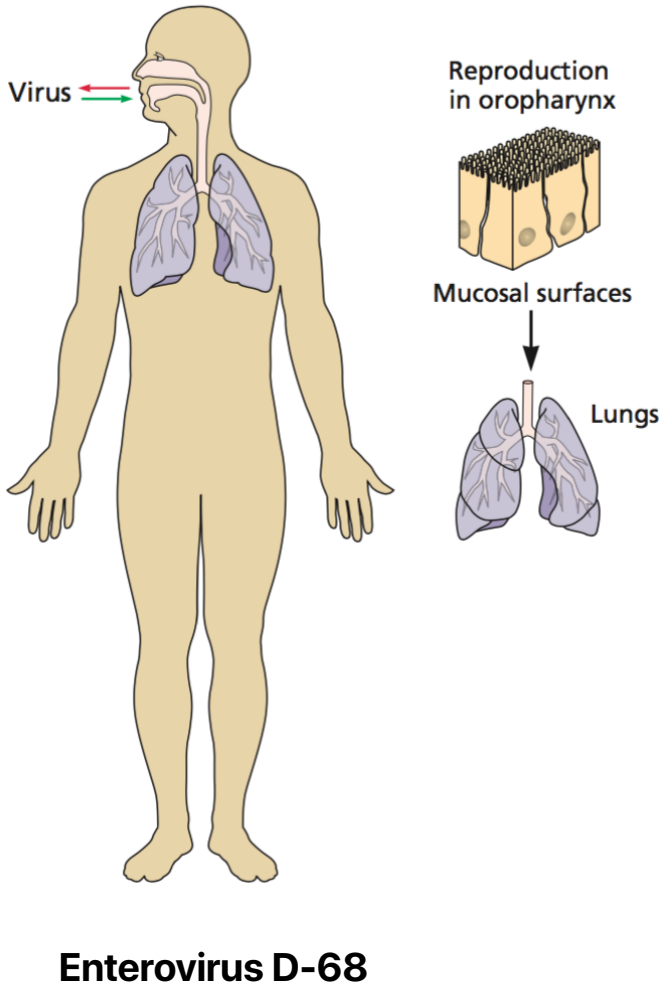
- **Genus:** *Aalivirus*
- **Genus:** *Ampivirus*
- **Genus:** *Aphthovirus*
- **Genus:** *Aquamavirus*
- **Genus:** *Avihepatovirus*
- **Genus:** *Avisivirus*
- **Genus:** *Bopivirus*
- **Genus:** *Cardiovirus*
- **Genus:** *Cosavirus*
- **Genus:** *Crohivirus*
- **Genus:** *Dicipivirus*
- **Genus:** *Enterovirus*
- **Genus:** *Erbovirus*
- **Genus:** *Gallivirus*
- **Genus:** *Harkavirus*
- **Genus:** *Hepatovirus*
- **Genus:** *Hunnivirus*
- **Genus:** *Kobuvirus*
- **Genus:** *Kunsagivirus*
- **Genus:** *Limnipivirus*
- **Genus:** *Megrivirus*
- **Genus:** *Mischivirus*
- **Genus:** *Mosavirus*
- **Genus:** *Orivirus*
- **Genus:** *Oscivirus*
- **Genus:** *Parechovirus*
- **Genus:** *Pasivirus*
- **Genus:** *Passerivirus*
- **Genus:** *Potamipivirus*
- **Genus:** *Rabovirus*
- **Genus:** *Rosavirus*
- **Genus:** *Sakobuvirus*
- **Genus:** *Salivirus*
- **Genus:** *Sapelovirus*
- **Genus:** *Senecavirus*
- **Genus:** *Shanbavirus*
- **Genus:** *Sicinivirus*
- **Genus:** *Teschovirus*
- **Genus:** *Torchivirus*
- **Genus:** *Tremovirus*

40 genera

- **Species:** *Enterovirus A* ⇨ **Enterovirus A71, Coxsackievirus A16**
- **Species:** *Enterovirus B* ⇨ Coxsackievirus B, Echovirus 1
- **Species:** *Enterovirus C* ⇨ Poliovirus 1, 2, 3
- **Species:** *Enterovirus D* ⇨ **Enterovirus D-68**
- **Species:** *Enterovirus E*
- **Species:** *Enterovirus F*
- **Species:** *Enterovirus G*
- **Species:** *Enterovirus H*
- **Species:** *Enterovirus I*
- **Species:** *Enterovirus J*
- **Species:** *Enterovirus K*
- **Species:** *Enterovirus L*
- **Species:** *Rhinovirus A*
- **Species:** *Rhinovirus B*
- **Species:** *Rhinovirus C*

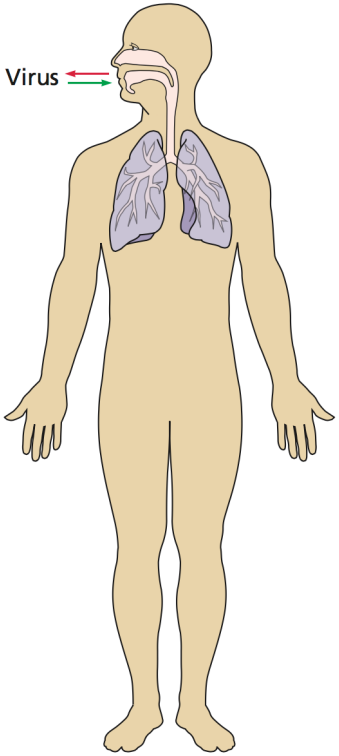


Enterovirus A71
Coxsackievirus A16
Poliovirus 1, 2, 3



Enterovirus D-68

EV-D68 pathogenesis



- Virus infection of nasopharyngeal cavity
- Infection results in respiratory disease
- No virus isolated from blood or stool of patients
- Virus in CSF in just two cases, often pleocytosis
- Motor cortex lesions similar to those of poliovirus
- Cannot be distinguished from RV by RT-PCR
- Is the virus neurotropic?

Acute Flaccid Paralysis and Enteroviral Infections

Ari Bitnun[1] · E. Ann Yeh[2]

Published online: 29 June 2018

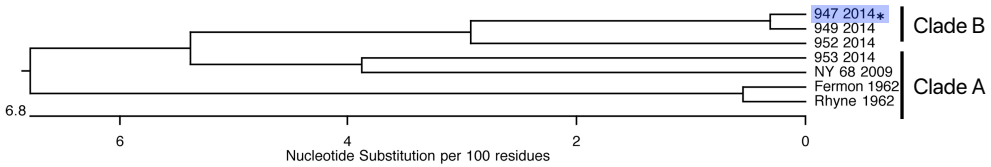
Abstract

Purpose of Review The focus of this review is on enterovirus (EV)-associated acute flaccid paralysis (AFP) due to spinal cord anterior horn cell disease. Emphasis is placed on the epidemiology, pathogenesis, diagnosis, treatment, and outcome of AFP caused by polioviruses, vaccine-derived polioviruses, EV-D68, and EV-A71.

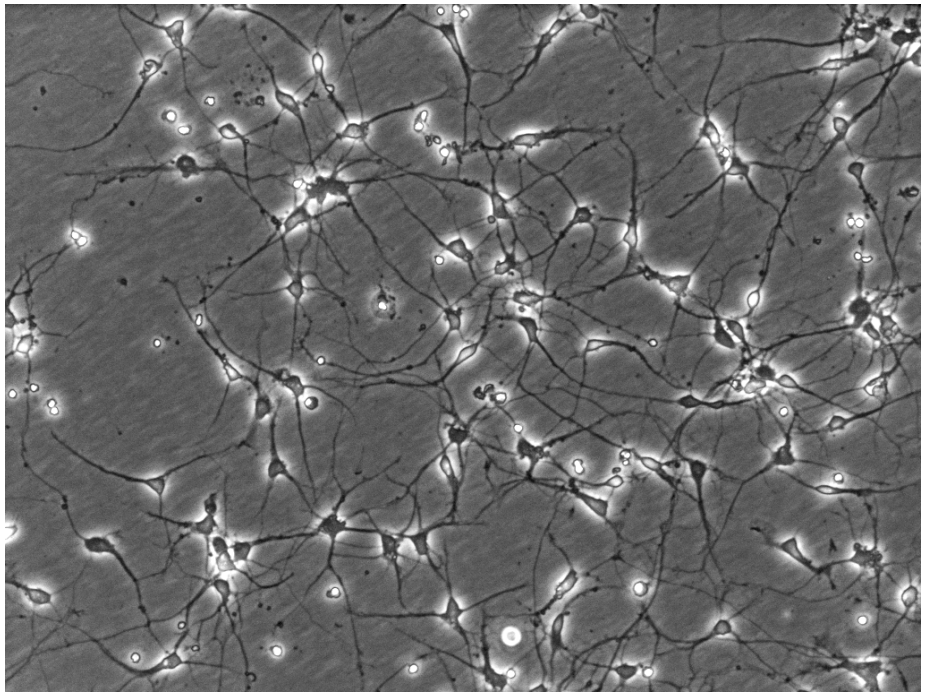
Recent Findings Since the launch of The Global Polio Eradication Initiative in 1988, the worldwide incidence of polio has been reduced by 99.9%, with small numbers of poliomyelitis cases being reported only in Afghanistan, Pakistan, and Nigeria. With the planned phaseout of oral polio vaccine, vaccine-associated poliomyelitis is also expected to be eliminated. In their place, other EVs, chiefly EV-D68 and EV-A71, have emerged as the principal causes of AFP. There is evidence that the emergence of EV-D68 as a cause of severe respiratory disease and AFP was due to recent genetic virus evolution. Antiviral medications targeting EV-D68, EV-A71, and other EVs will likely be available in the near future. An effective EV-A71 vaccine has been developed, and preliminary investigations suggest an EV-D68 vaccine could be on the horizon.

Summary The eradication of poliomyelitis and vaccine-associated poliomyelitis is near, after which other EVs, presently EV-D68 and EV-A71, will be the principle viral causes of AFP. Moving forward, it is essential that EV outbreaks, in particular those associated with neurologic complications, be investigated carefully and the causal strains identified, so that treatment and prevention efforts can be rapidly developed and implemented.

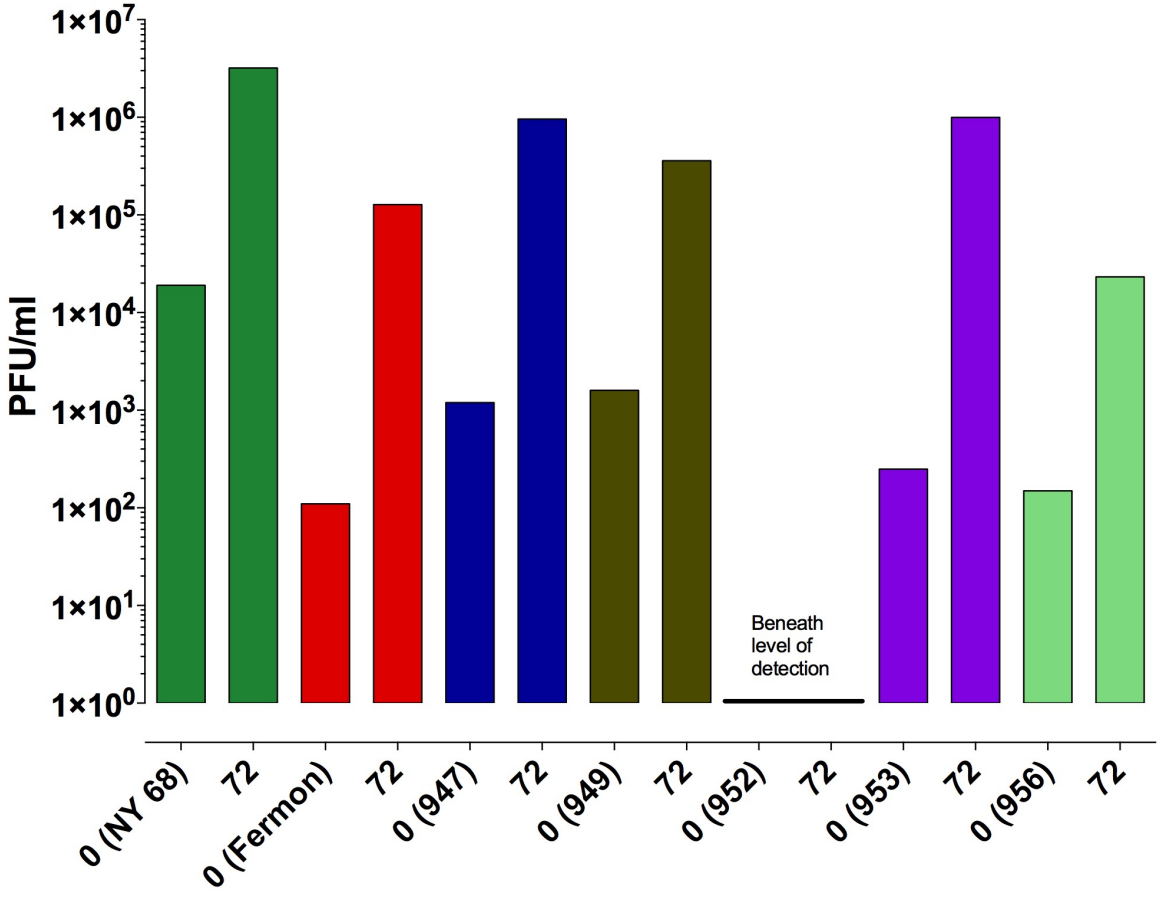
Is EV-D68 neurotropic?



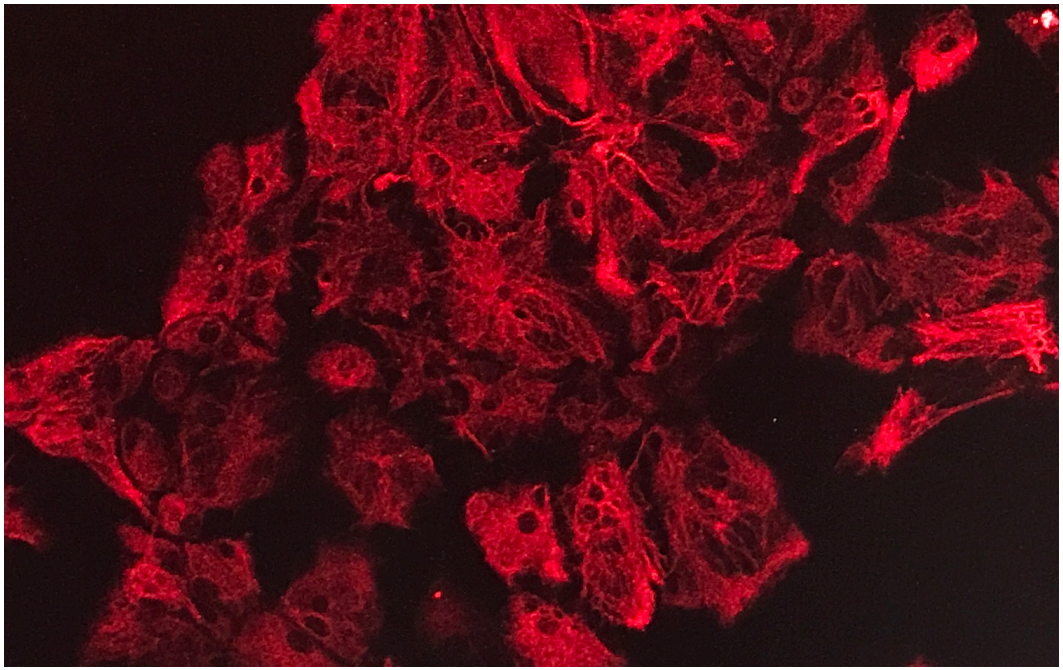
**subclade B1, clinically associated with the development of EV-D68 associated acute flaccid paralysis*

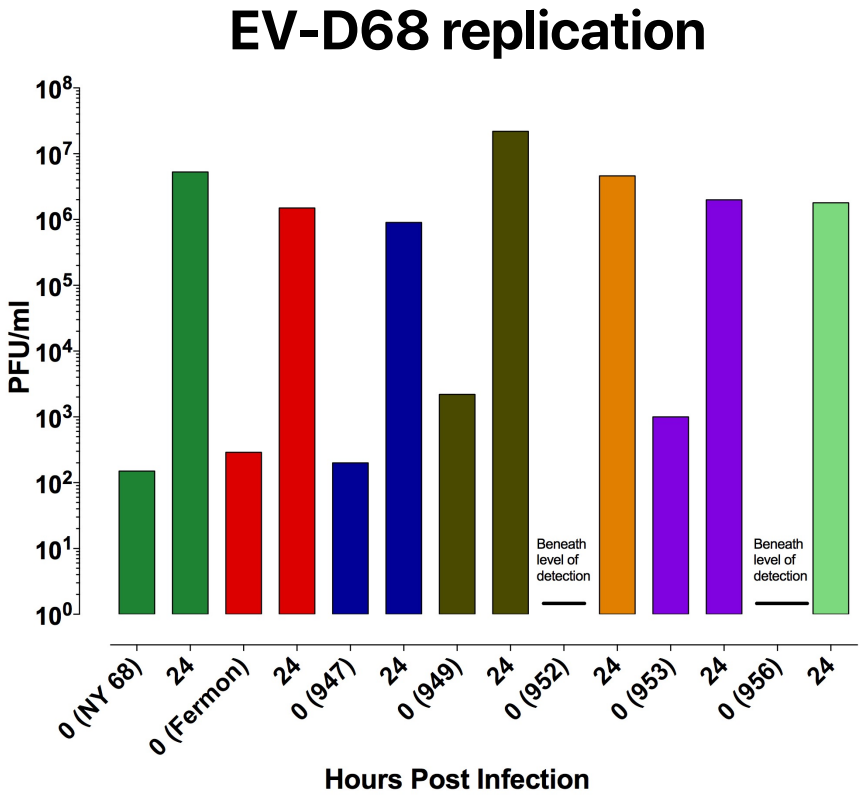


EV-D68 replication in iCell Neurons (human)

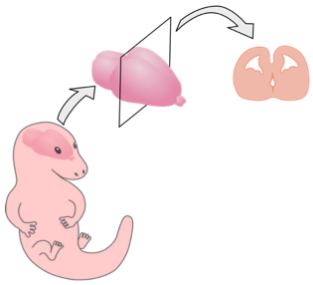


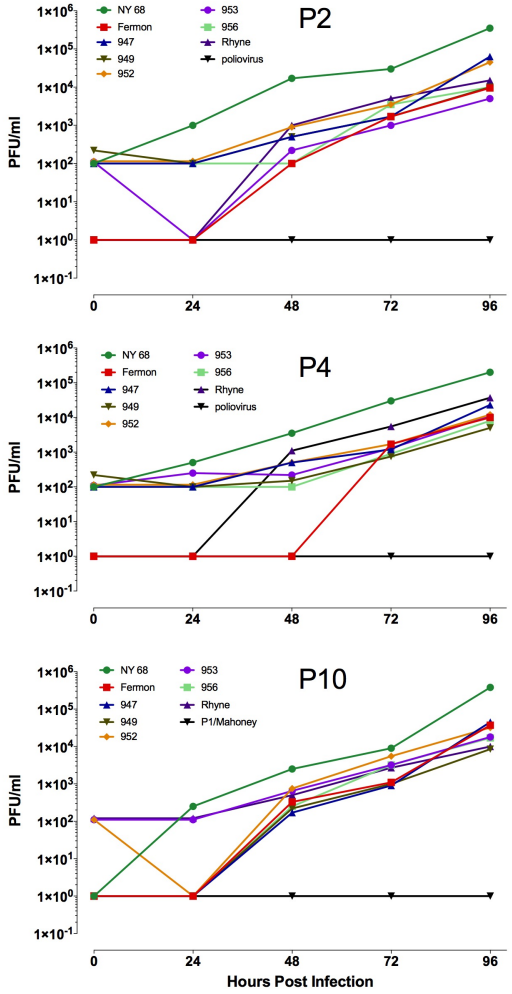
GFAP positive iAstrocytes (human)

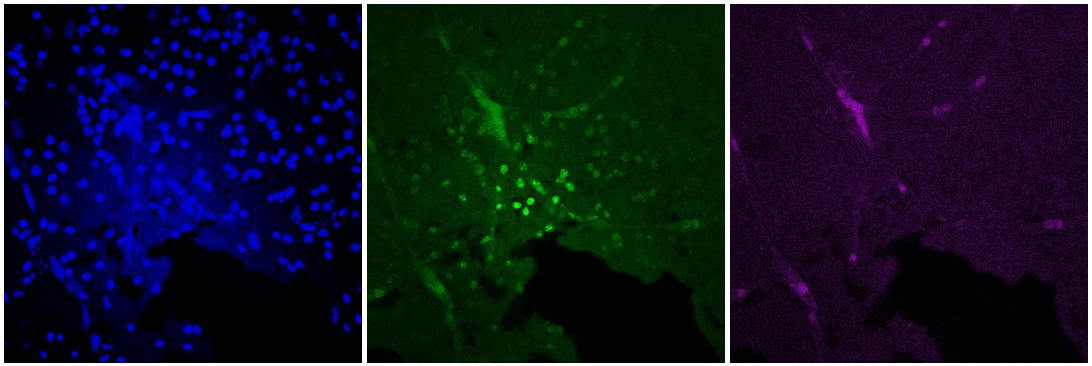




EV D-68 replication in mouse postnatal brain slices

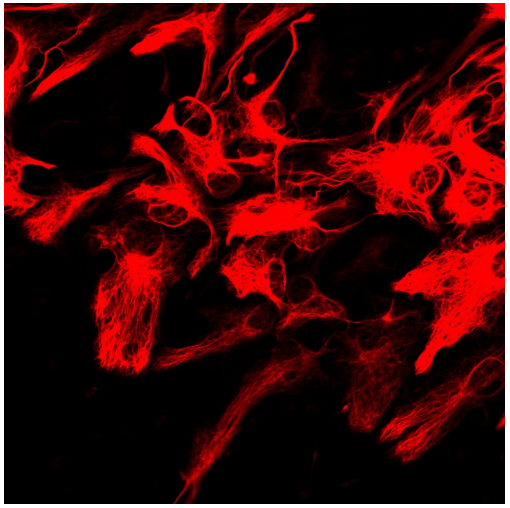




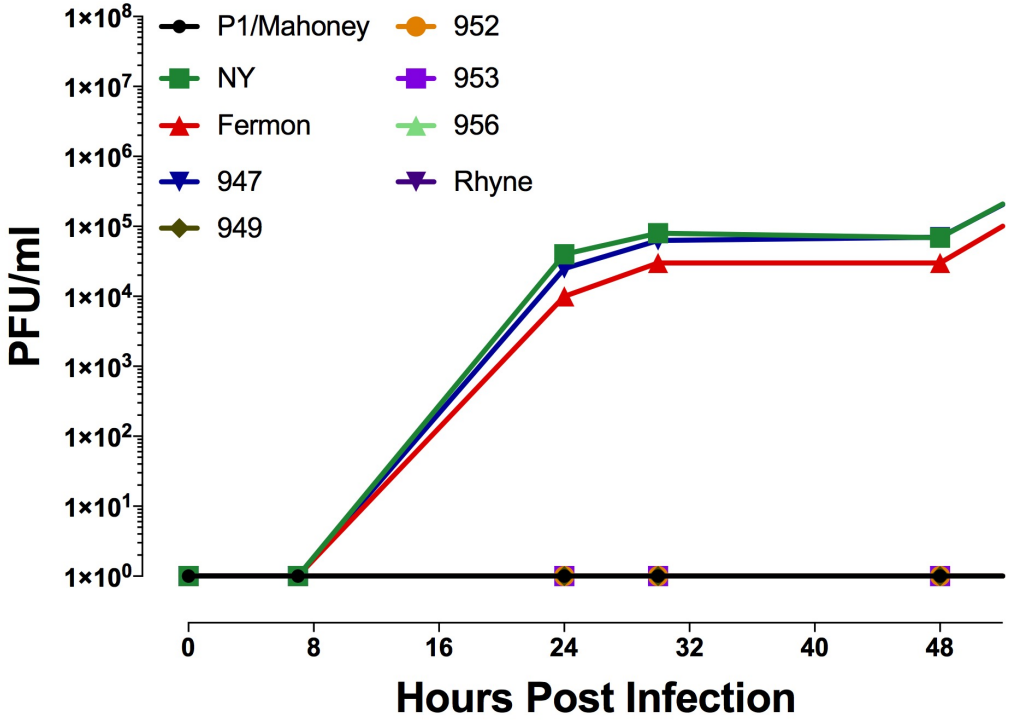


DAPI Anti-enterovirus Nissl

EV-D68 replication in isolated glial fibrillary acidic protein (GFAP) positive mouse astrocytes

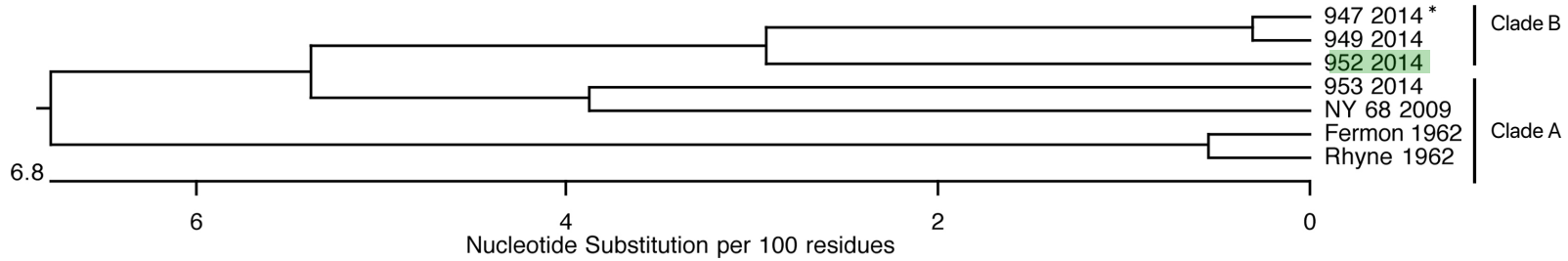


from P1-P3 mice



7 of 7 EVD68 isolates are neurotropic

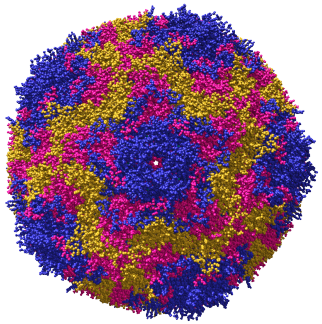
EV-D68 neurotropism is not a recently acquired phenotype (why would it be?)

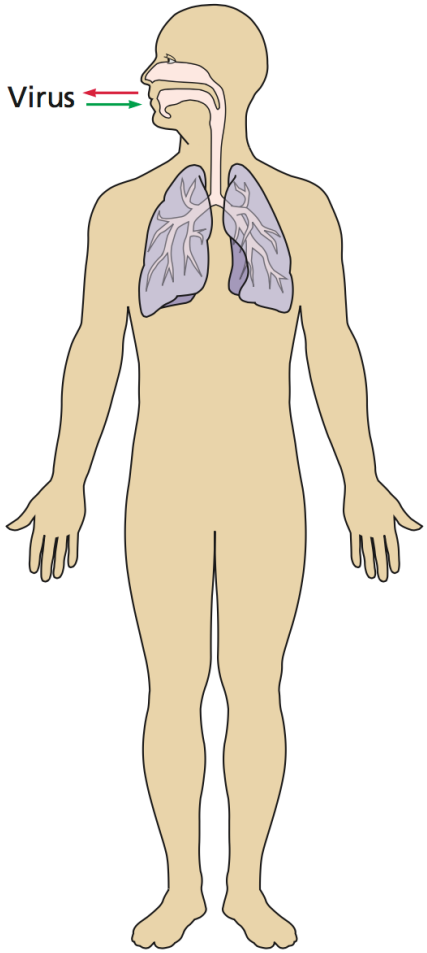


**subclade B1, clinically associated with the development of EV-D68 associated acute flaccid paralysis*

952 isolate only infects astrocytes, not neurons

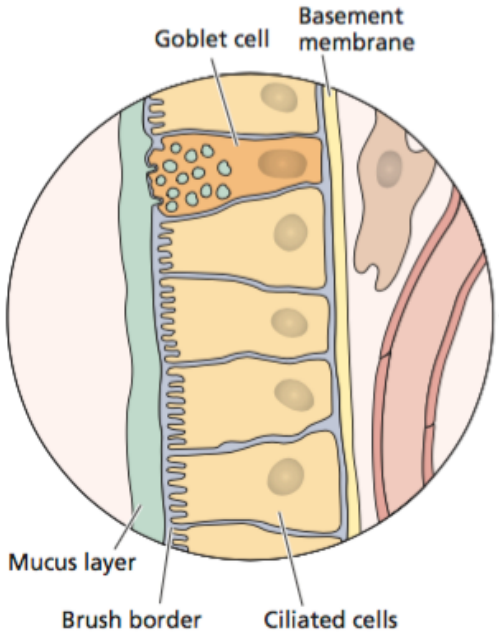
How does EV-D68 travel from respiratory tract to CNS?

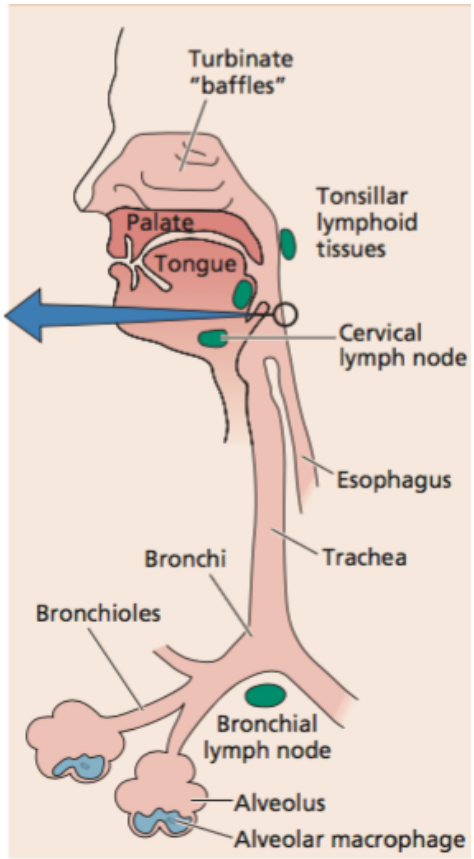


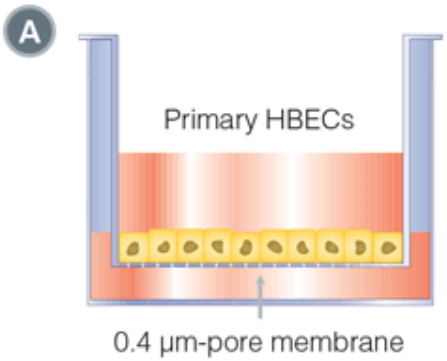


Virus not detected in blood, feces, or CSF
Are we missing a transient viremia?

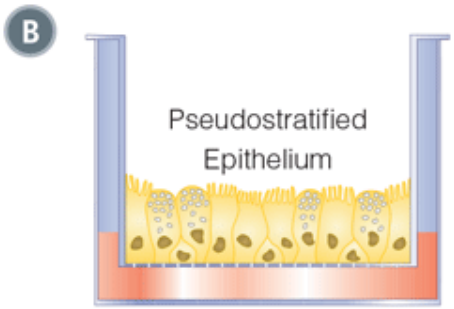
Airway epithelial liquid interface cultures



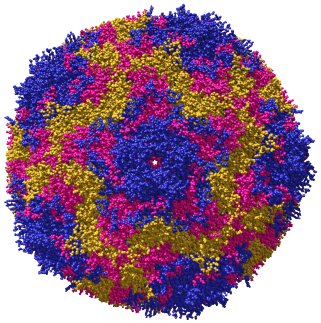




Isolated cells



Differentiated cells

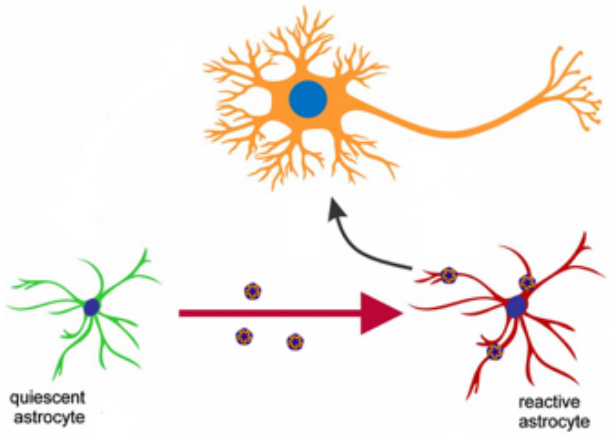


Summary and Hypothesis

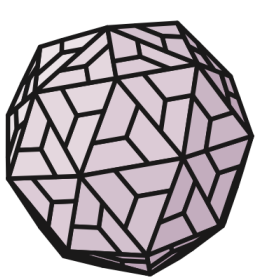
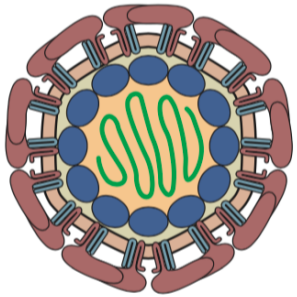
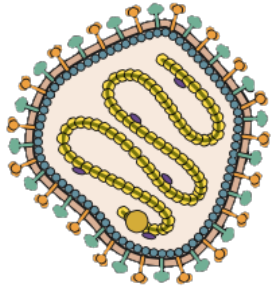
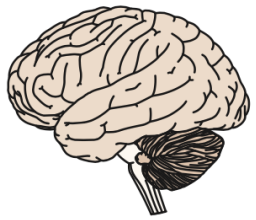
- Established neuronal and lung culture systems to study EV-D68 pathogenesis
- 7/7 isolates of EV-D68 are neurotropic
- Neurotropism of EV-D68 not a recently acquired phenotype
- Selection for better respiratory transmission => 2014 outbreak
- More infections => rare AFM becomes evident
- Surveillance: EV-D68 scores as HRV in RT-PCR

Future Directions

- Which cell types does EV-D68 infect in the respiratory tract?
- How does virus spread to CNS?
- How do neurotoxic astrocytes cause neuronal death during EV-D68 infection?
- Do inborn errors in innate immune system identified in humans influence replication?
- Higher replication => CNS invasion?

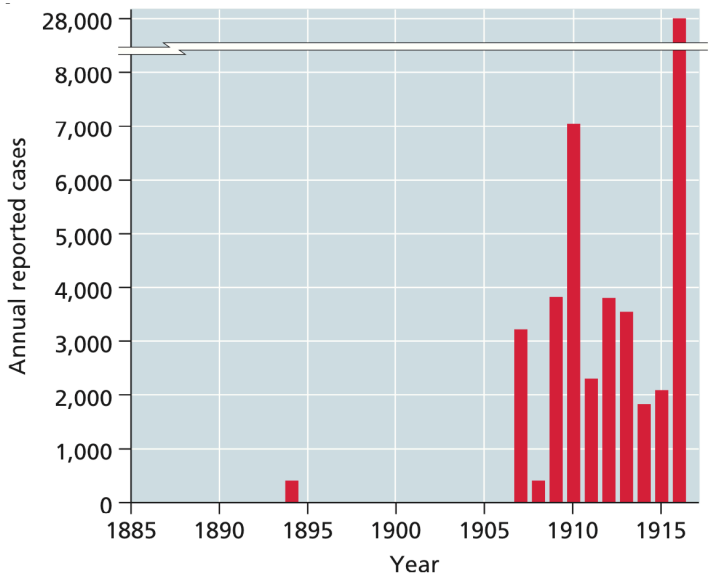


Viruses and the CNS

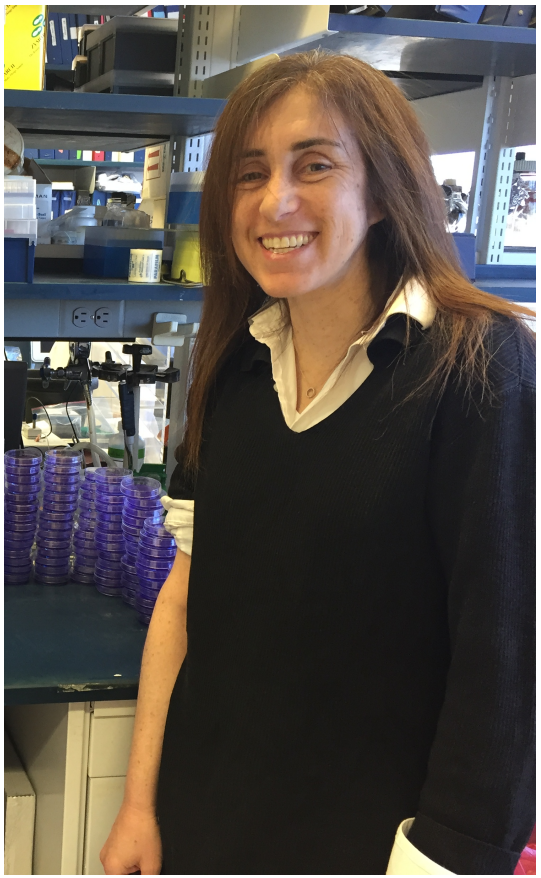





- Many viruses invade CNS (poliovirus, Zika virus, EV-D68, West Nile virus, measles virus)
- Replication in CNS not a recently acquired property for ZIKV, EV-D68
- These viruses are most efficiently transmitted to new hosts by shedding (gut, respiratory tract) or by mosquitoes
- CNS invasion is a rare accidental event, a viral dead end - in humans

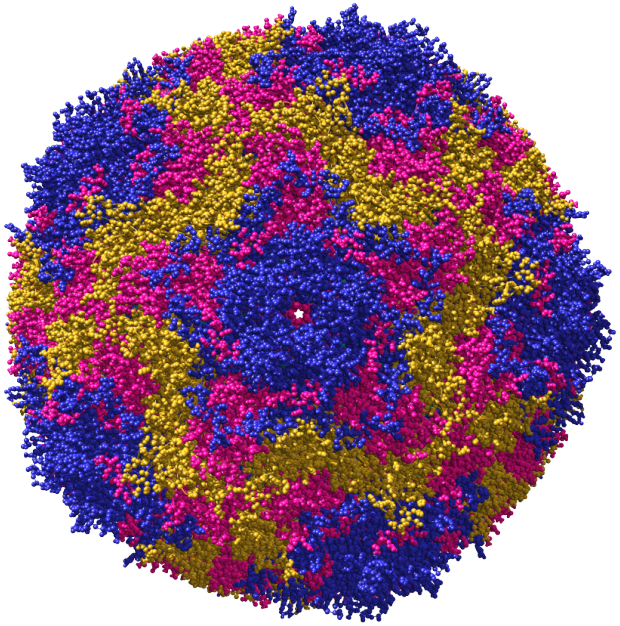
It is not selected during viral evolution!



Had there been genome sequencing in 1908, would the emergence of epidemic polio been blamed on mutation?



Amy Rosenfeld



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Virology Lectures
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