

## Gastrointestinal Viruses: Rotavirus and the Enteroviruses

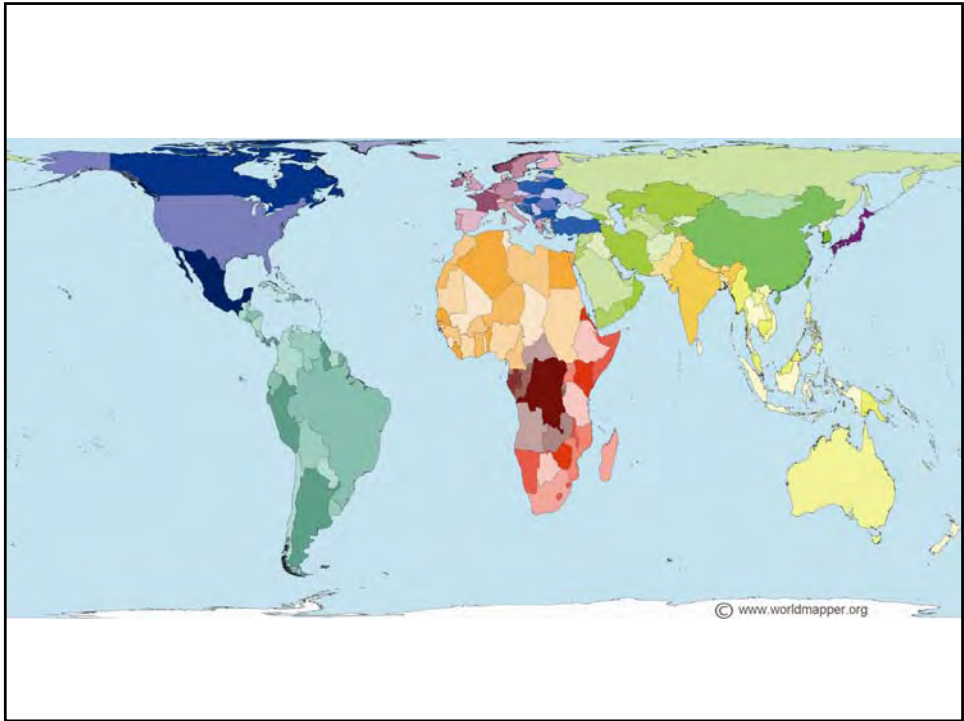
Adam J. Ratner, M.D., M.P.H.  
Assistant Professor of Pediatrics and Microbiology  
Columbia University



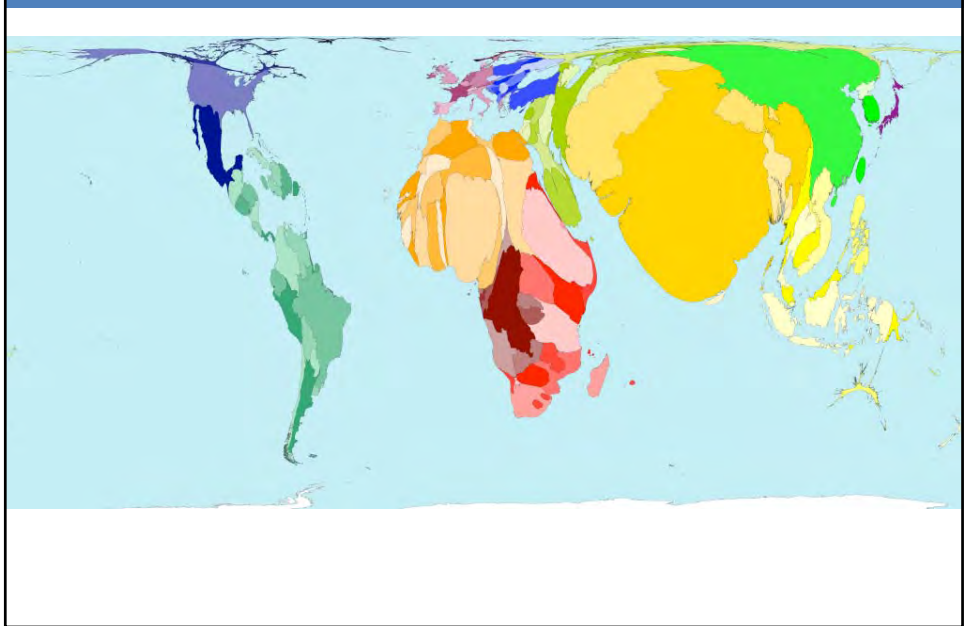
### Gastrointestinal Viruses

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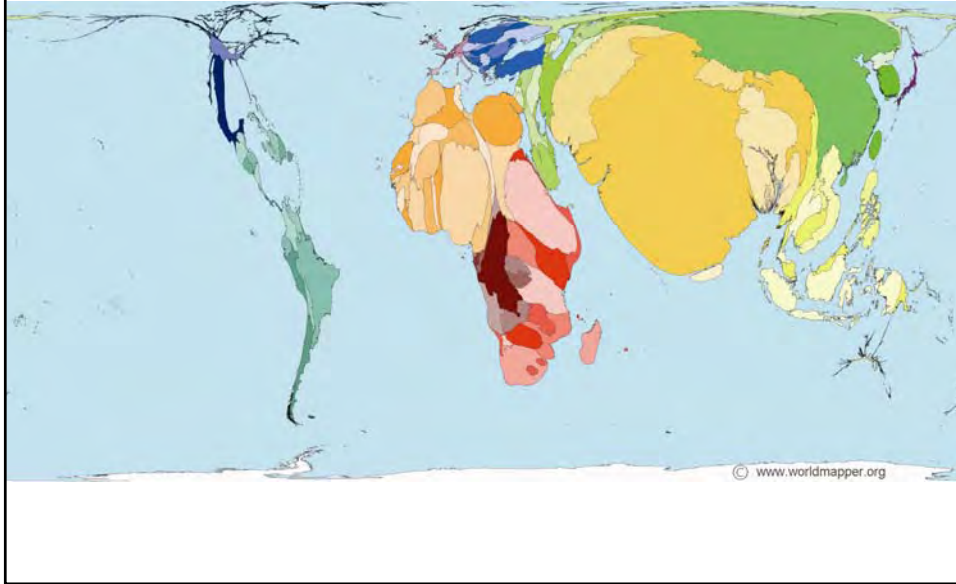
- Viral diarrheal illness
  - tremendous cause of morbidity/mortality worldwide
  - rotavirus, calicivirus (norovirus), astrovirus, adenovirus 40/41
- Viruses that replicate in the gastrointestinal tract but generally don't cause diarrhea
- One from each category:
  - Rotavirus – most important cause of childhood diarrhea worldwide
  - Enteroviruses – replicate in GI tract, cause a wide spectrum of disease



### Childhood diarrheal disease

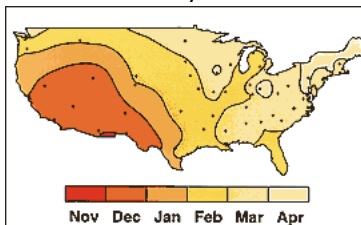


## Poverty



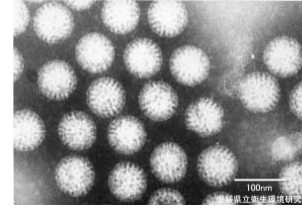
## Rotavirus

- Ubiquitous viral diarrheal illness – essentially all children infected by age 5
- Most common cause of viral gastroenteritis in childhood
- High mortality rates in developing world (>600,000 global deaths/yr)  
~5% of all-cause mortality in under 5 year-olds  
death is due to dehydration – not overwhelming viral replication
- In U.S., tremendous numbers of hospital admissions, doctor visits  
1 in 72 children hospitalized, 1 in 19 seen by physician
- Seasonality – peak in winter – later as you move East in U.S.

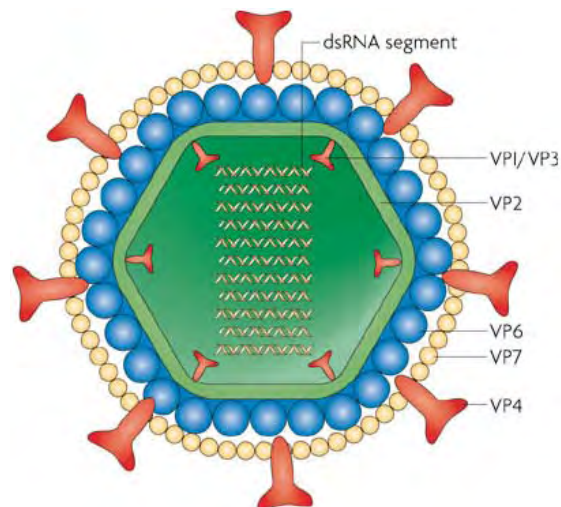


## Rotavirus: pathogenesis

- Member of *Reoviridae*
  - Large, non-enveloped dsRNA virus (rota = wheel)
  - 11 segments of dsRNA
    - structural proteins (VP1-VP4, VP6, VP7)
    - non-structural (NS) proteins
  - reassortment can occur
  - RNA-dependent RNA polymerase used in replication
- Classified by group (A-F, based on VP6 protein)
  - only A, B, C cause disease in humans
  - group A also classified by serotype (based on VP7 (G) and VP4 (P) proteins)
    - specific groups/serotypes important for vaccine design
    - G1-G4, P1 most common

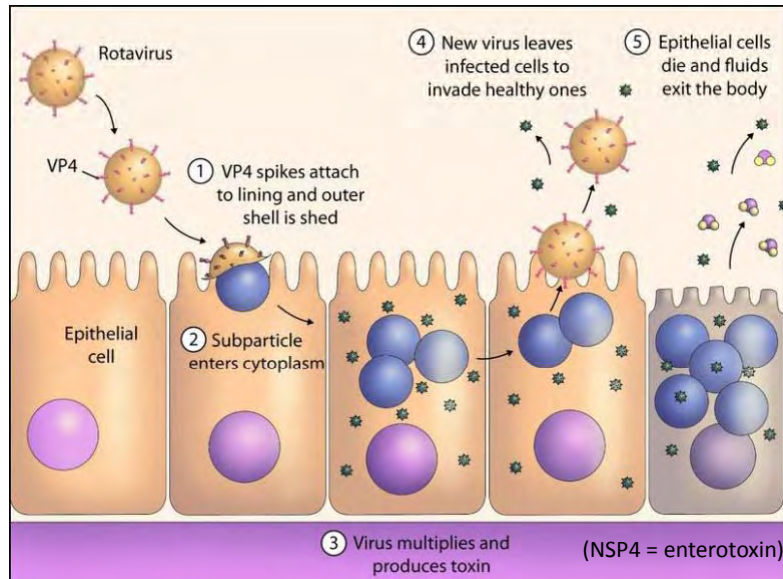


## Rotavirus: pathogenesis



Nature Reviews | Microbiology

## Rotavirus: pathogenesis



## Rotavirus: clinical syndrome

- Fecal-oral spread – highly infectious (1 pfu = disease), survives on fomites
- Enters and replicates in mature villus cells of duodenum/jejunum
- Fever, nausea/vomiting following 1-3 day incubation period lasts 2-4 days
- Diarrhea – watery, generally not bloody; lasts 5-8 days
  - loss of brush-border enzymes
  - enterotoxin-mediated epithelial cell lysis
  - activation of enteric nervous system
- Dehydration, electrolyte abnormalities, transient hepatitis
- Extraintestinal complications occur exceedingly rarely, if ever
- Asymptomatic cases may occur, especially in adults

## Rotavirus: treatment

- Rehydration (oral or IV) may be life-saving
- Early reintroduction of feeding promotes enterocyte renewal  
avoid foods/drinks high in simple sugars due to osmotic load
- Probiotic therapies – unproven
- No benefit of antimotility agents



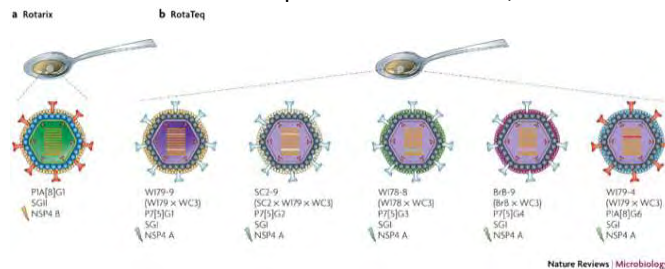
WHO

## Rotavirus: diagnosis

- Clinical diagnosis
- ELISA detection of rotavirus antigen in whole stool  
widely used in hospital, office settings (>90% sensitive, specific)
- PCR – gold standard for sensitivity, specificity but not widely available
- Stool electron microscopy – not used clinically
- Serology – epidemiological tool
- Pyrosequencing – pathogen discovery

## Rotavirus: prevention

- Breastfeeding infants provides some IgA-mediated protection
- Handwashing, cleaning of fomites, keep symptomatic kids home
- Contact isolation in hospital
- Vaccination (oral, live attenuated vaccines)
  - 2 currently licensed vaccines for children at 2, 4, 6 months of age
    - RotaTeq, pentavalent bovine reassortant
    - RotaRix, monovalent human
  - Prior U.S. vaccine (RotaShield) removed from market based on possible increase in cases of intussusception – was effective, unclear if risk was real.

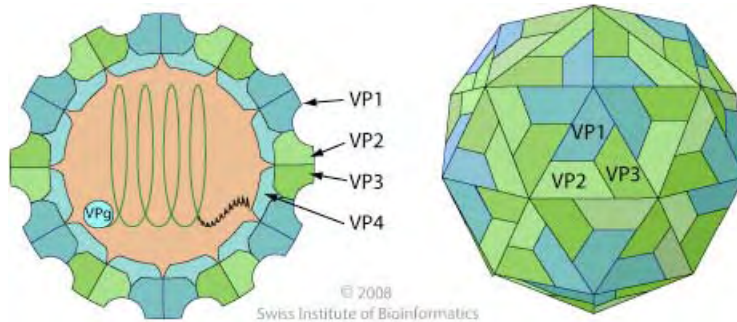


## Enteroviruses

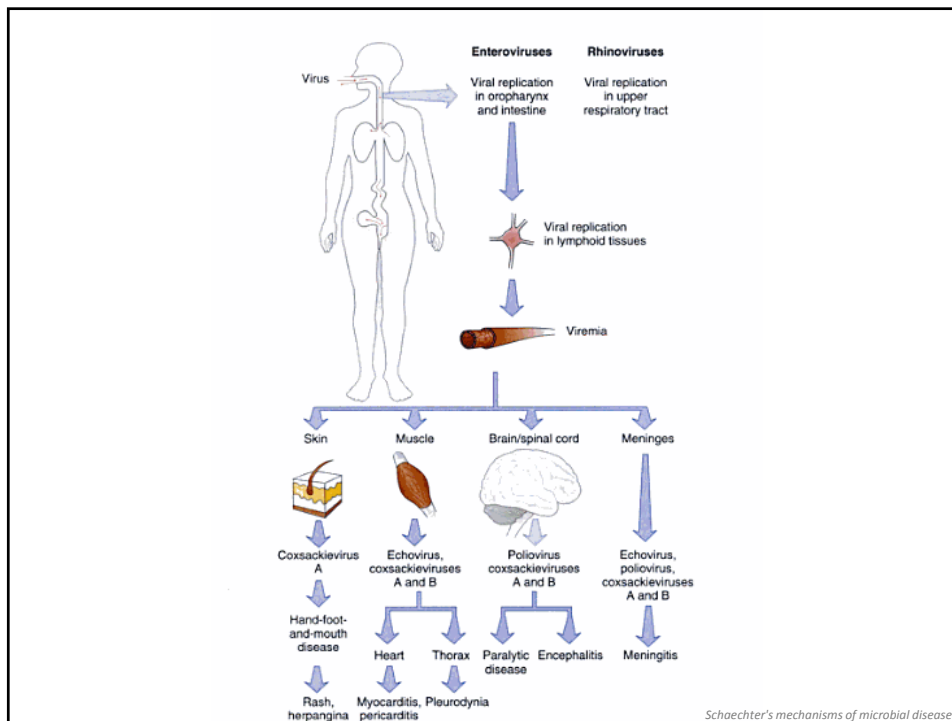
- Members of *Picornaviridae*
- 4 subgroups (polioviruses, coxsackieviruses, echoviruses, enteroviruses)
- More than 70 subtypes
- Non-enveloped viruses with positive-sense ssRNA genomes
  - capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)
- Acid-stable, enter through GI tract, fecal-oral transmission
- Replication in oropharynx, intestine, submucosal lymphoid tissues, regional lymph nodes
- Viremic stage
- Cause a wide variety of clinical syndromes

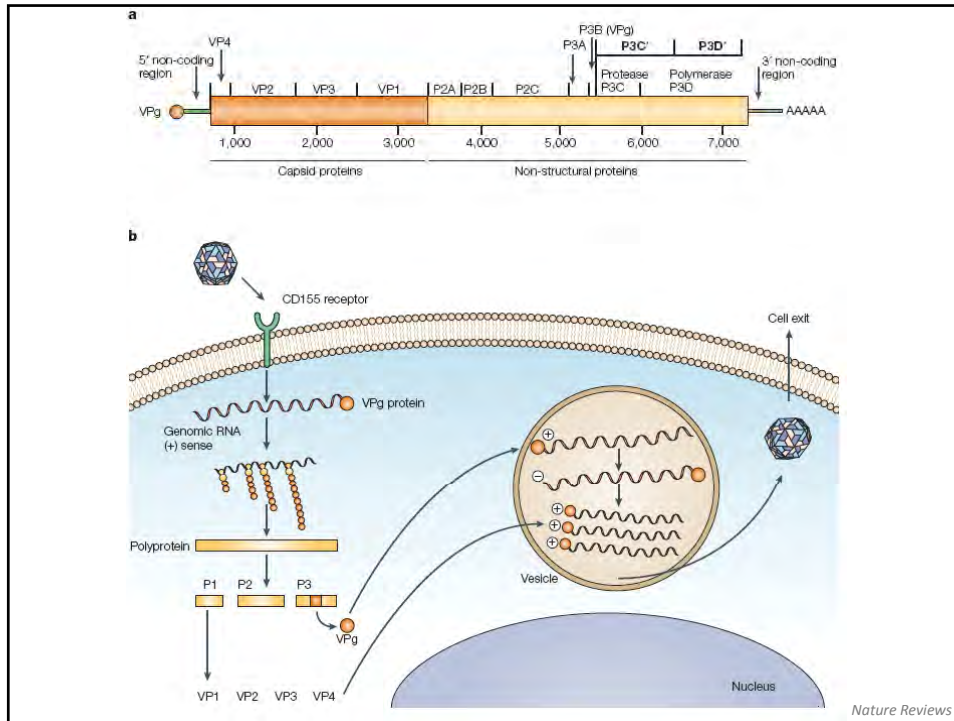
# Enteroviruses

- Non-enveloped viruses with positive-sense ssRNA genomes  
capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)



ExPASy





## Poliovirus

- Cause of poliomyelitis, three serotypes
- Human-specific
- Fecal-oral spread, environmental reservoir
- Predilection for spread to CNS following viremia
  - replicates within neurons: especially anterior horn cells of spinal cord
  - necrosis of neurons
  - both motor and autonomic

**TABLE 236-1. Pathogenesis of Poliovirus Infection**

Site of Virus Replication	Time (Days)	Clinical Illness
Pharynx and intestine	0-1	Asymptomatic
Regional lymph nodes	1-3	Asymptomatic
Blood (minor viremia), muscle, fat, liver, spleen, bone marrow	3-7	Minor illness
Blood (major viremia), central nervous system	7-21	Major illness

Long, PPPID

## Polio: clinical features

- Incubation period = 6-20 days
- Diagnosis: viral isolation from throat (early) or stool (3-6 weeks); serology
- May range from clinically inapparent illness (~90% of infections) to paralytic polio
- Abortive poliomyelitis (~8% of cases)
  - Mild viral syndrome
  - Fever, headache, sore throat
  - No neurological sequelae
- Nonparalytic poliomyelitis (1-2% of cases)
  - As above but with signs of meningeal infection
  - Severe headache, neck stiffness (“aseptic meningitis”)
  - Full recovery after 2-10 days

## Polio: clinical features

- Spinal paralytic poliomyelitis (<1% of cases)
  - biphasic illness
    - first phase mimics abortive polio
    - followed 2-5 days later by headache, fever, vomiting, myalgia
  - weakness and flaccid paralysis
  - asymmetric paralysis: generally lower limbs, proximal muscles
  - can involve respiratory muscles
  - recover from paralysis (often incomplete) can occur
  - ~10% fatality rate
- Bulbar paralytic poliomyelitis (<0.1% of cases)
  - Cranial nerve paralysis (mostly CN 9, 10)
  - Vasomotor and respiratory centers involved
  - May be fatal due to respiratory muscle paralysis
  - ~50% fatality rate



## Polio: Epidemiology

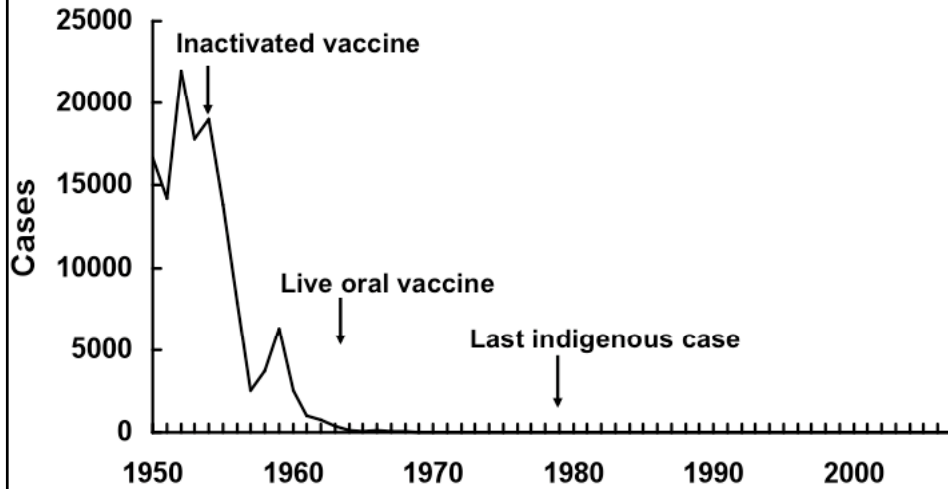
- Used to be world-wide disease, yearly peaks in summer months
  - U.S. outbreak in 1950s
    - Improved sanitation had increased age at first exposure
    - More paralytic cases (>13,000/yr in U.S.)
  - Polio vaccine introduced 1955
  - Transmission interrupted in U.S. in 1979
  - Last case in Western hemisphere 1991
  - 2008: 1655 cases world wide
    - India, Nigeria, Afganistan, Pakistan are the only countries in which transmission has never been interrupted.
- Almost there.

## Polio vaccines

- Inactivated polio vaccine (IPV, Salk vaccine)
  - Contains all three serotypes
  - Formalin-inactivated
  - Injected subcutaneously or intramuscular
  - >95% immune after primary 3-dose series (2, 4, 6 months)  
booster dose given at 4-6 yrs
  - Duration of immunity unknown
- Oral polio vaccine (OPV, Sabin)
  - Contains all three serotypes (10:1:3 ratio)
  - Vaccine virus excreted in stool (herd immunity)
  - Immunity probably life-long
  - Very rare cases of vaccine-associated paralytic polio (VAPP)
  - Still used in most of the world
  - Not currently recommended in U.S. because risk of VAPP greatly exceeds risk of wild-type polio

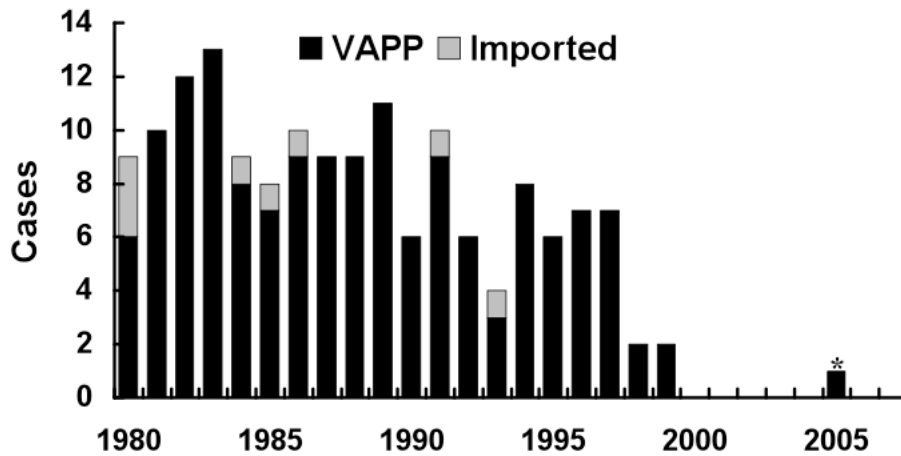


### Polio in the U.S. (1950-2008)



CDC

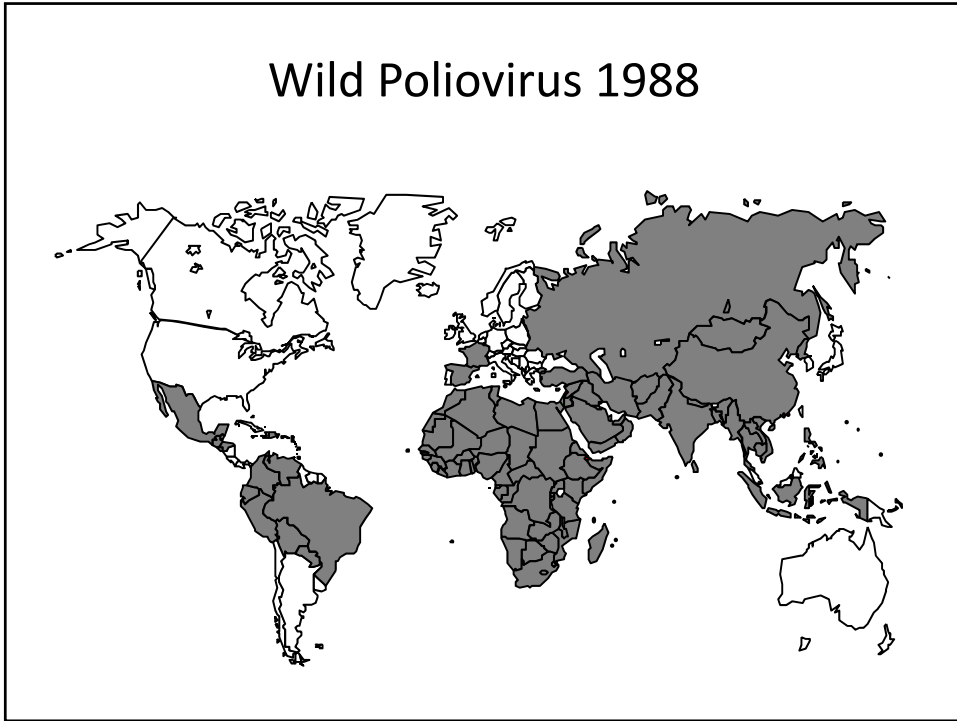
### Polio in the U.S. (1980-2008)



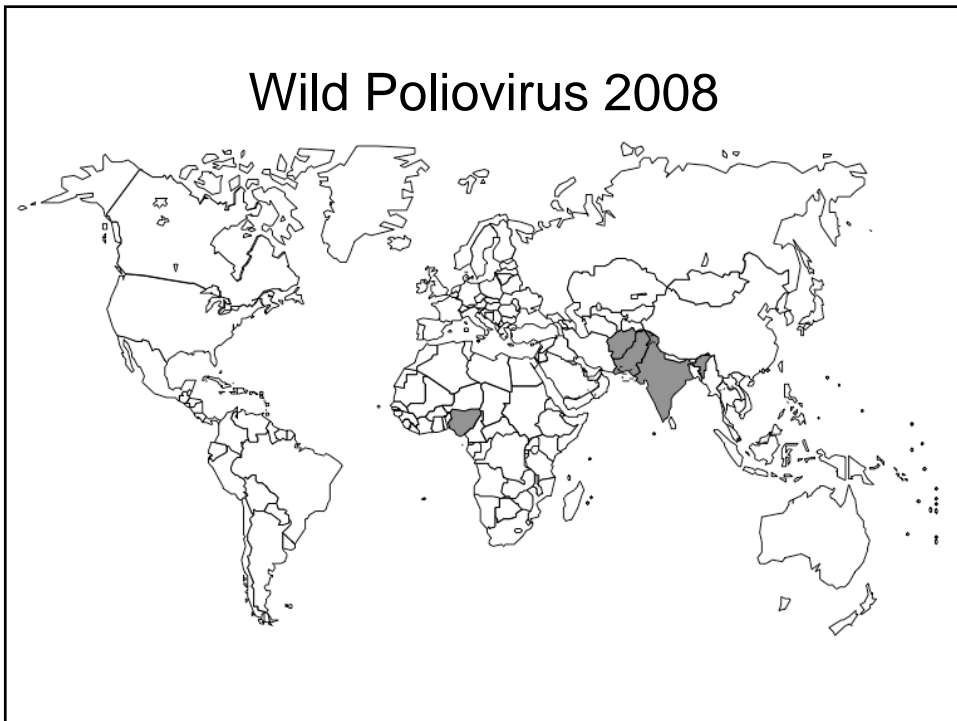
\*Vaccine-acquired paralytic polio (VAPP) in a U.S. resident acquired outside the U.S.

CDC

## Wild Poliovirus 1988



## Wild Poliovirus 2008



## Other enteroviral infections

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- Generally not associated with symptomatic gastrointestinal disease
- World-wide distribution, summer peaks
- Common causative agents of disease in children
- Diagnosis either clinical or by viral culture or PCR
- Serology less reliable (many distinct serotypes)

## Other enteroviral infections

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- Non-specific febrile illnesses (often with rash)
- Aseptic meningitis, encephalitis
  - recurrent enteroviral meningitis seen in patients lacking functional B lymphocytes
  - rarely, polio-like syndromes may occur
- Myocarditis
  - mainly coxsackie A, B and echovirus 16
- Acute hemorrhagic conjunctivitis (enterovirus 70, highly contagious)
- Hand/foot/mouth disease (coxsackie A16, enterovirus 71)
- Enterovirus infections of newborn
  - can be overwhelming disease, sepsis-like syndrome, hepatic necrosis
  - perinatal acquisition

## Enteroviral meningitis

- Most common cause of aseptic meningitis
- Common in infants under 3 months, especially in summer
  - Can also occur in older kids, adults
- 90% caused by coxsackie B or echoviruses
- Febrile prodrome
- Most cases uncomplicated, recover in less than 1 week
- Adults may have more prolonged course
  - higher rate of complications (seizures, obtundation)
- CSF profile with 10-500 WBC, lymphocyte predominance
- Diagnosis by PCR or viral culture of CSF

## Myopericarditis

- Group B coxsackieviruses account for majority of cases
- Viral replication in myocardium
- Preceding upper respiratory illness
- Male predominance (2:1)
- Local necrosis and inflammatory infiltrate
- Detectable by PCR or immunofluorescence of cardiac biopsy
- Some benefit to intravenous immune globulin

## Acute hemorrhagic conjunctivitis

- highly contagious
- person-to-person transmission via fingers, fomites
- enterovirus 70, coxsackie A24
- symptoms peak on first day of illness
- generally no long-term ophthalmic complications



## Hand, foot, and mouth disease

