

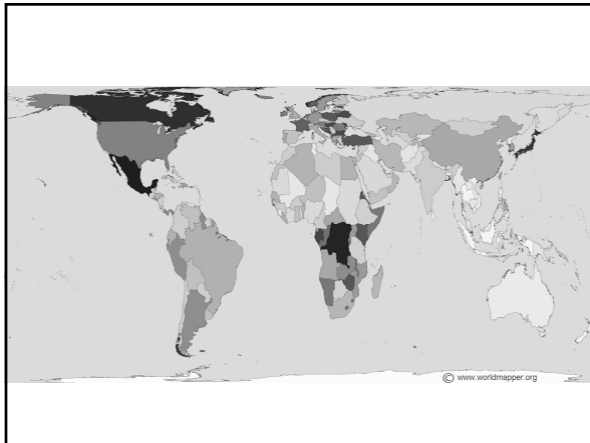
Gastrointestinal Viruses: Rotavirus and the Enteroviruses

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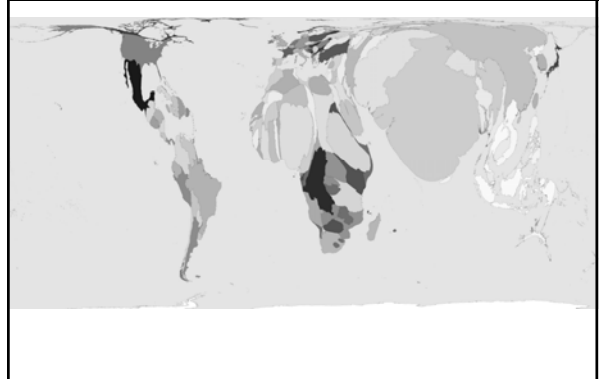


Gastrointestinal Viruses

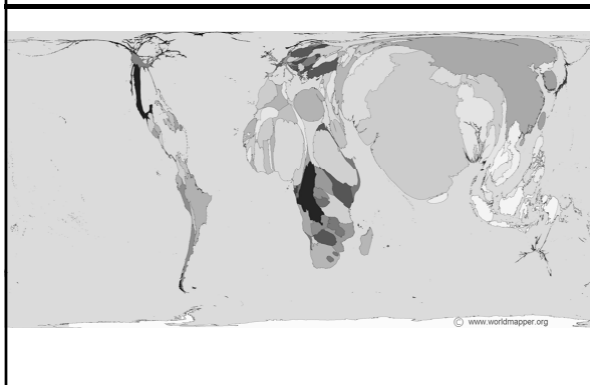
- Viral diarrheal illness
 - tremendous cause of morbidity/mortality worldwide
 - rotavirus, calicivirus (norovirus), astrovirus, adenovirus 40/41
- Viruses that replicate in the gastrointestinal tract but generally don't cause diarrhea
- One from each category:
 - Rotavirus – most important cause of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



Childhood diarrheal disease

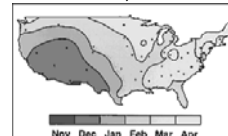


Poverty



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.



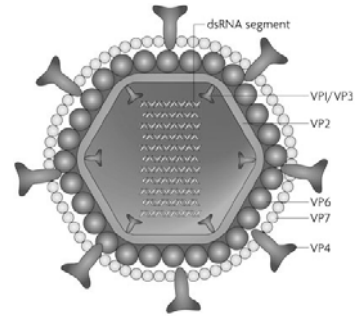
Rotavirus: pathogenesis

- 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



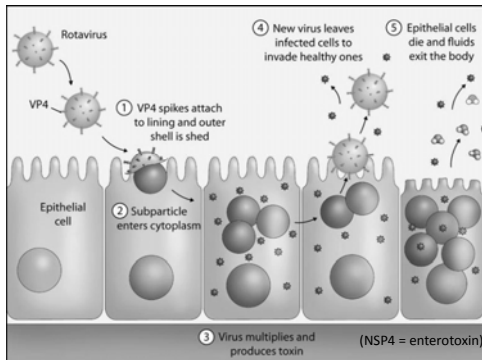
- Classified by group (A-F, based on VP6 protein)
 - only A, B, C cause disease in humans
 - group A also classified by serotype (based on VP7 (G) and VP4 (P) proteins)
 - specific groups/serotypes important for vaccine design
 - G1-G4, P1 most common

Rotavirus: pathogenesis



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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

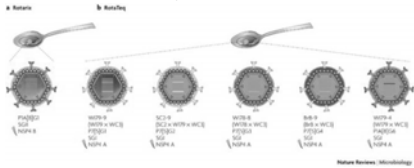


Rotavirus: diagnosis

- 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.

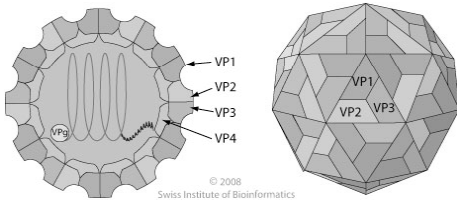


Enteroviruses

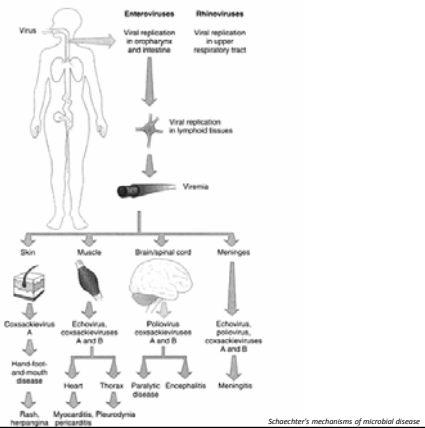
- Members of *Picornaviridae*
- 4 subgroups (polioviruses, coxsackieviruses, echoviruses, enteroviruses)
- More than 70 subtypes
- Non-enveloped viruses with positive-sense ssRNA genomes
capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)
- Acid-stable, enter through GI tract, fecal-oral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

Enteroviruses

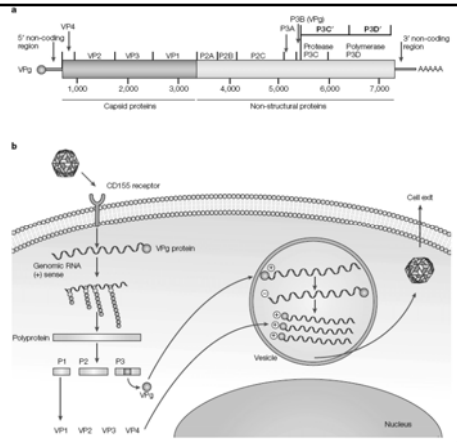
- Non-enveloped viruses with positive-sense ssRNA genomes
capsids: icosahedral symmetry, 60 copies of each of 4 proteins (VP1-4)



ExPASy



Schaechter's mechanisms of microbial disease



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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 230-1. 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

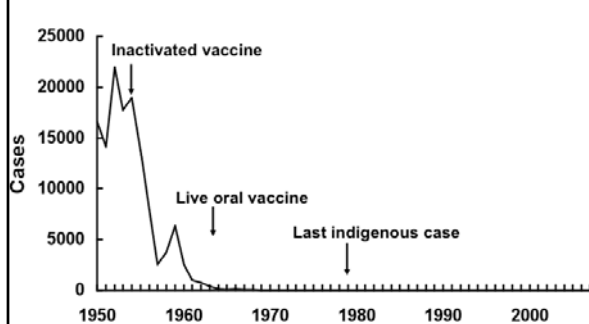
- Used to be world-wide disease, yearly peaks in summer months
 - U.S. outbreak in 1950s
 - Improved sanitation had increased age at first exposure
 - More paralytic cases (>13,000/yr in U.S.)
 - Polio vaccine introduced 1955
 - Transmission interrupted in U.S. in 1979
 - Last case in Western hemisphere 1991
 - 2008: 1655 cases world wide
 - India, Nigeria, Afghanistan, 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

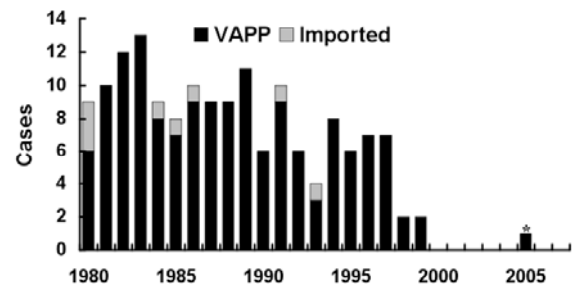


Polio in the U.S. (1950-2008)



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

- 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

- 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

