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Acute Gastrointestinal Infections

Watery Diarrhea- Viral Pathogens

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Learning Objectives

- List the main viruses that cause acute gastroenteritis
- Describe the viral structure and genomic organization, and link these to clinical features, diagnostic methods, and epidemiology
- Explain the most salient features of their pathogenesis
- Recognize mechanisms of protective immunity and whether vaccines are available

Major Human Pathogens

Gram positive Bacteria

Cocci
Staphylococcus
Streptococcus
Enterococcus

Rods
Listeria
Bacillus
Clostridium
Corynebacterium
Gardnerella
Propionibacterium

Branching
Actinomyces
Nocardia

No cell wall
Pleomorphic
Mycoplasma

Acid Fast Bacilli
Mycobacterium tuberculosis
Mycobacterium leprae
Non-tuberculous *Mycobacteria*

Viruses

RNA

Rhinovirus
Coxsackie
Enteroviruses
Poliovirus
Rotavirus
Norovirus
Hepatitis A
Hepatitis C
HIV
HTLV-1
Measles
Mumps
Rubella
Influenza A, B
Parainfluenza
RSV
Human metapneumovirus
Coronavirus (MERS, SARS)
Ebola
Rabies

Vector borne
West Nile
Dengue
Chickengunya
Yellow Fever

DNA

Adenovirus
Herpes simplex
Varicella zoster
Cytomegalovirus
Epstein Barr virus
HHV6, HHV7, HHV8
Smallpox
Molluscum contagiosum
Hepatitis B
Parvovirus
Human papillomavirus
BK polyomavirus

Fungi

Yeast
Candida
Cryptococcus
Pneumocystis
Malassezia
Microsporidia

Mold
Aspergillus
Mucor
Rhizopus
Fusarium

Dimorphic
Coccidioides
Histoplasmosis
Blastomyces
Paracoccidioides
Sporothrix

Dermatophytes
Microsporum, Epidermophytum Trichophytum

Protozoa

GI/GU
Entamoeba
Giardia
Cryptosporidium
Trichomonas

Blood
Plasmodium
Babesia

Tissue
Trypanosoma
Leishmania
Toxoplasma
Naegleria

Gram negative Bacteria

Rods

Enteric flora
E. coli
Klebsiella
Proteus
Serratia
Enterobacter

Respiratory Pathogens
Haemophilus
Bordatella
Legionella

Spiral
Campylobacter
Helicobacter

Opportunistic
Pseudomonas

Enteric pathogens
Shigella
Salmonella
Yersinia

Anaerobic
Bacteroides
Prevotella
Fusobacterium

Comma
Vibrio

Diplococci
Neisseria
Moraxella

Zoonotic
Brucella
Francisella
Campylobacter
Pasteurella
Bartonella
Yersinia
Coxiella
Chlamydophila psittaci
Rickettsia
Ehrlichia
Anaplasma
Borrelia
Leptospira

Spirochaetes
Treponema
Borrelia
Leptospira

Intracellular
Chlamydia
Chlamydophila
Rickettsia
Coxiella
Legionella
Ehrlichia
Anaplasma
Bartonella
Brucella
Francisella
Shigella
Salmonella

Arthropods

Ticks
Vectors of: Lyme borreliosis, Relapsing Fever, RMSF, other *Rickettsia*, *Babesia*, *Anaplasma*, *Ehrlichia*

Lice (pediculosis)
Vectors of: Epidemic typhus, Trench Fever

Mites (scabies)
Vectors of: Scrub typhus, Rickettsialpox

Mosquitoes
Vectors of: Malaria, Dengue, Chikungunya, West Nile, Yellow Fever

Fleas
Vectors of: Cat-scratch fever, Murine typhus, Bubonic plague, Tularemia

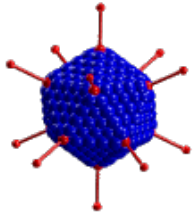
Helminths

Trematodes (Flukes)
Schistosoma (Schistosomiasis)
Clonorchis & Fasciola (Liver Flukes)
Paragonimus (Lung Fluke)

Cestodes (Tapeworms)
Taenia saginata (Beef Tapeworm)
Taenia solium (Pig Tapeworm)
Diphyllobothrium (Fish Tapeworm)
Echinococcus (Dog Tapeworm)

Nematodes (Roundworms)
Enterobius (Pinworm)
Trichuris (Whipworm)
Ascaris (Giant worm)
Ancylostoma & *Necator* (Hookworm)
Strongyloides (Strongy)
Toxocara (Dog Ascaris)
Trichinella (Trichinosis)
Onchocerca (River Blindness)
Loa Loa (Eye Worm)
Wuchereria & Brugia (Elephantiasis)

Viruses



RNA

Rhinovirus
Coxsackie
Enteroviruses
Poliovirus
Rotavirus
Norovirus
Hepatitis A
Hepatitis C
HIV
HTLV-1
Measles
Mumps
Rubella
Astrovirus

Influenza A, B
Parainfluenza
RSV
Human metapneumovirus
Coronavirus (MERS, SARS)
Ebola
Rabies

Vector borne

West Nile
Dengue
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Yellow Fever

DNA

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Herpes simplex
Varicella zoster
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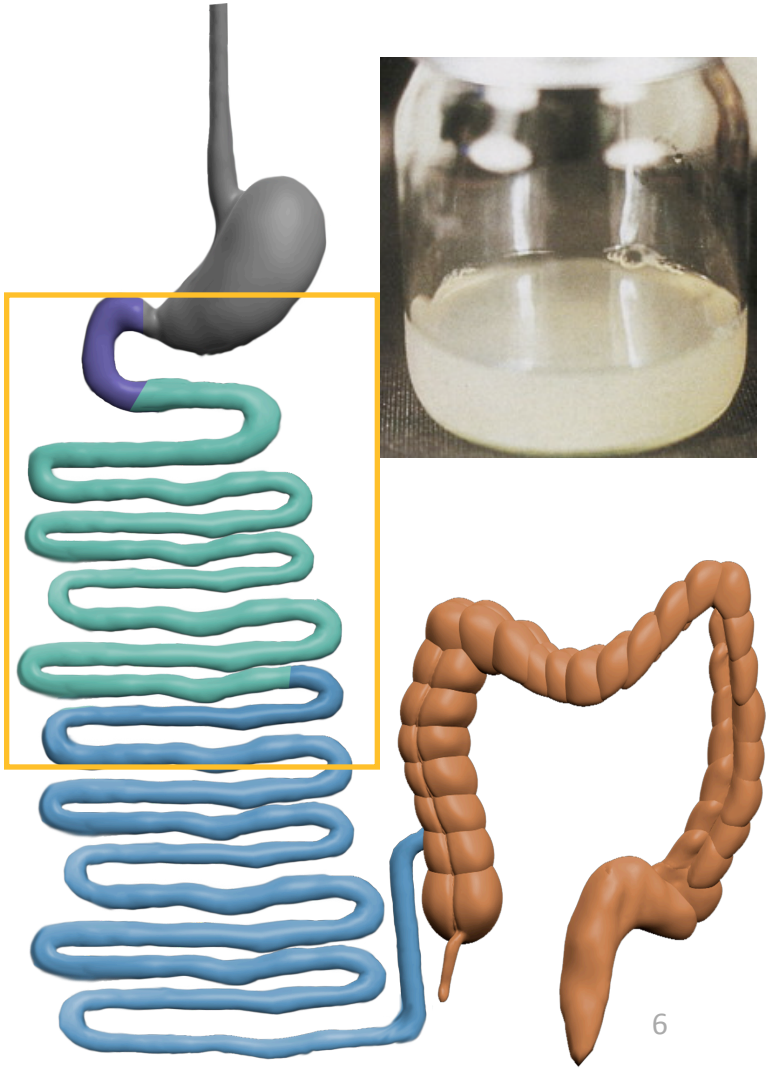
Smallpox
Molluscum contagiosum
Hepatitis B
Parvovirus
Human papillomavirus
BK polyomavirus

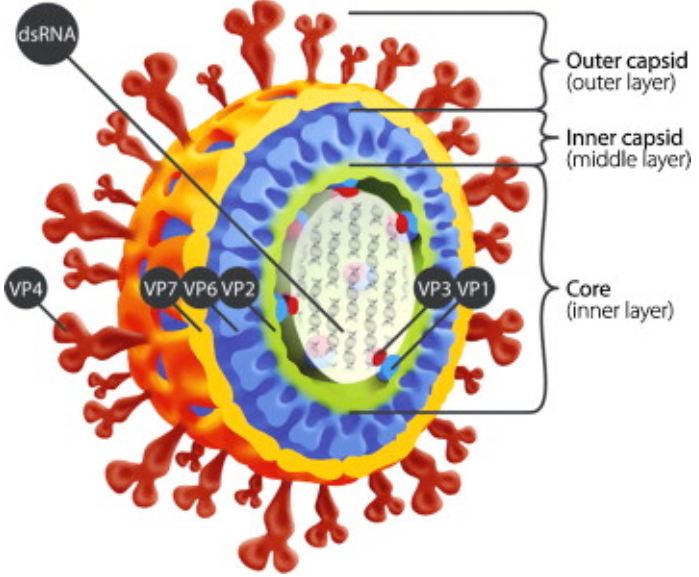
Watery Diarrhea

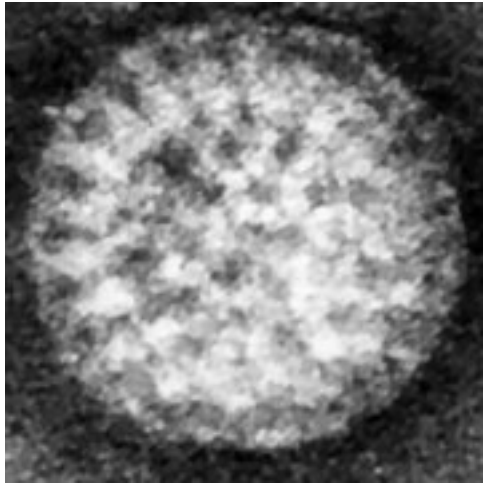
Clinical Features	**Large volume watery stools without inflammatory cells or blood. Can lead to dehydration. Possibly accompanied by nausea, vomiting, bloating, colicky**
Complications	Dehydration, electrolyte abnormalities, malnutrition
Management	Assess degree of dehydration, consider DDx, rehydrate, maintenance hydration
Anatomical Location	Proximal Small Intestine
Pathogenesis	Non-invasive, several are toxin mediated, secretory vs malabsorptive
Viruses	**Rotavirus, Norovirus, Adenovirus, Astrovirus (all non-enveloped capsids)**
Bacteria	*Vibrio cholerae*, Enterotoxigenic *E. coli* (ETEC), EPEC, EAEC
Protozoa	*Giardia*, *Cryptosporidium*



Rotavirus

- Most common cause of viral diarrhea worldwide.
- Infects most children by 2-5 years
  peaks 6 mo to 2 yrs
- Vomiting and fever commonly accompany diarrhea
- Peaks in Winter months
- Member of the *Reoviridae* family
- Rota- means “wheel” in latin- VP4 spikes in the three-layered capsid give its characteristic shape
- Double stranded RNA segmented genome
  - 11 segments-each codes for one protein





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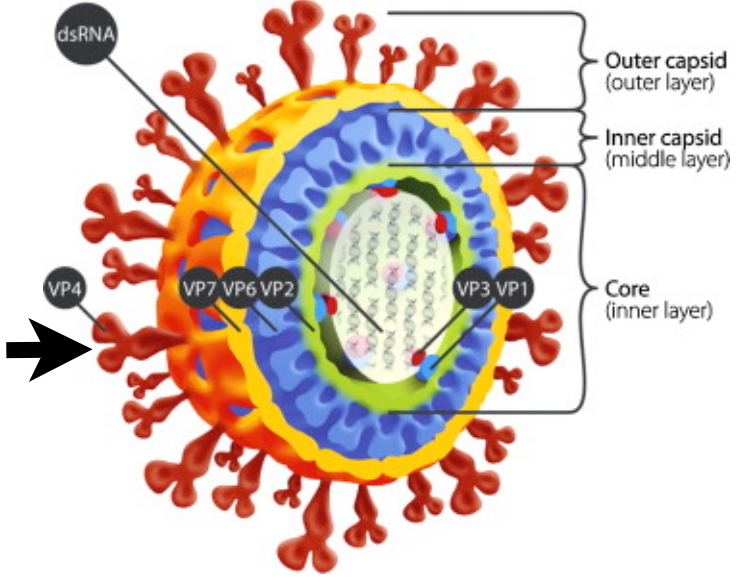

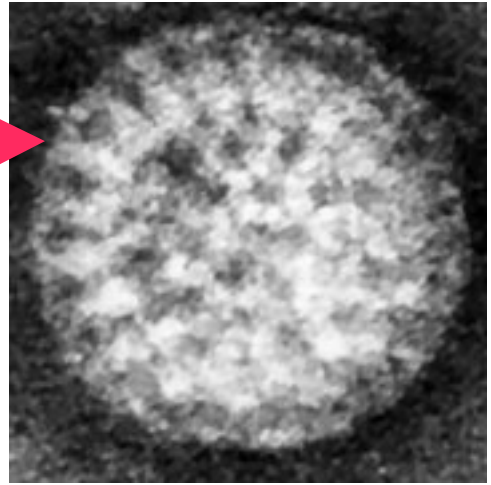

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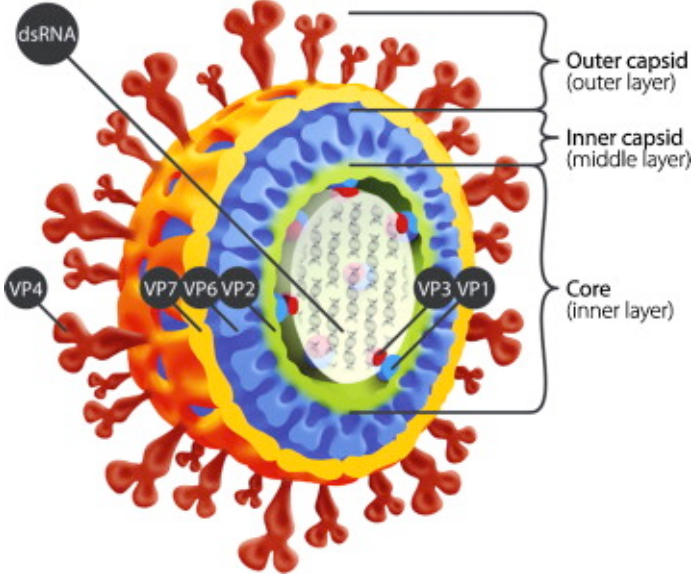

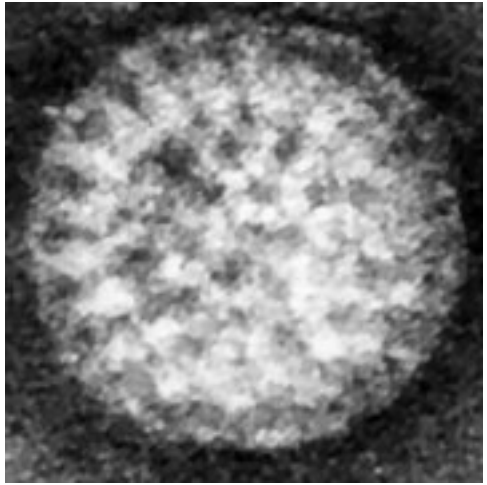

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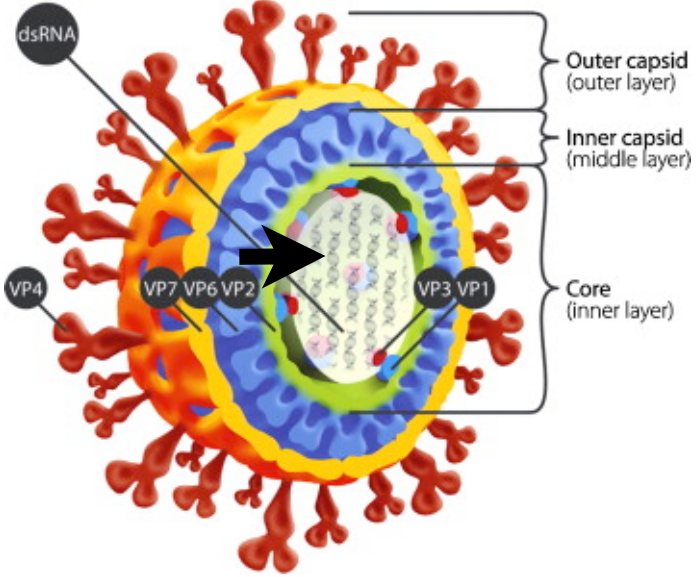

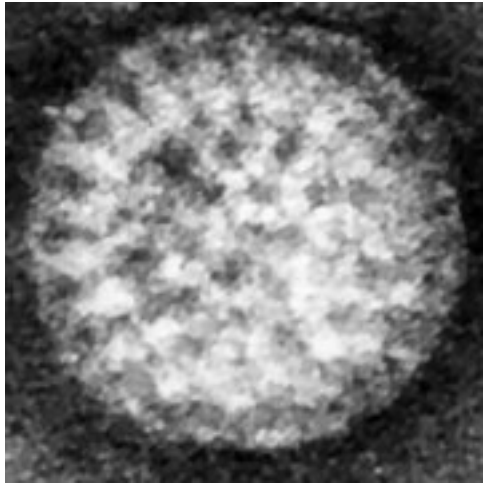

Rotavirus Entry into Host

- Fecal oral transmission
  - Contamination of hands, toys, water
  - Stable in environment
  - 10 trillion particles per ml in stool
  - Not destroyed by acid or digestive enzymes and resistant to bile salts in duodenum
    - Activated for attachment to epithelial cells trypsin cleavage of spike

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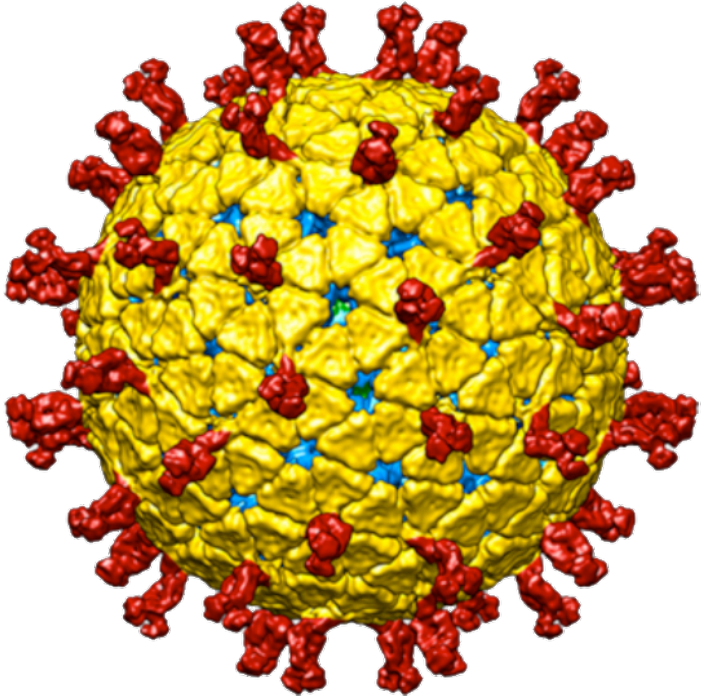
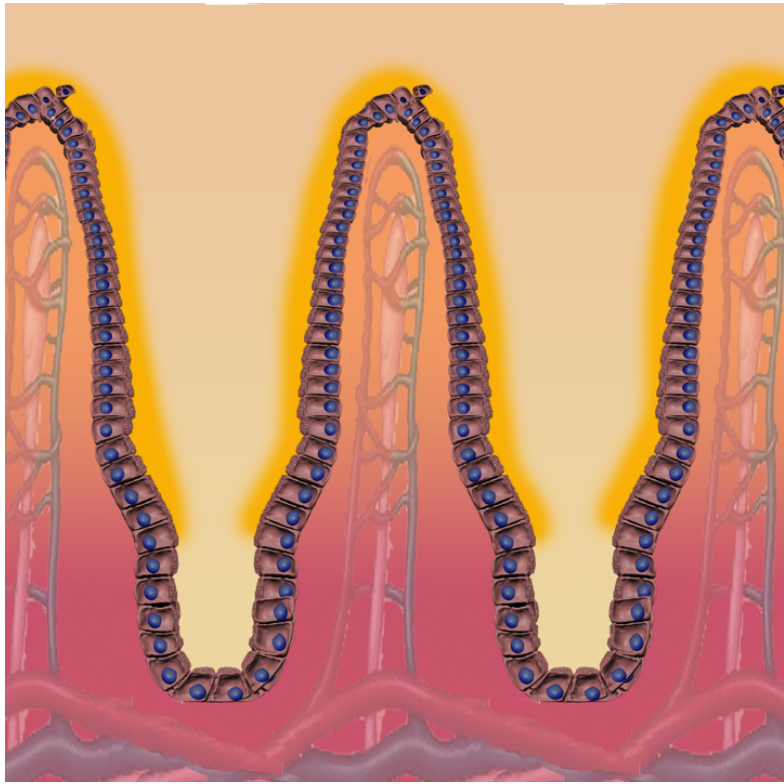
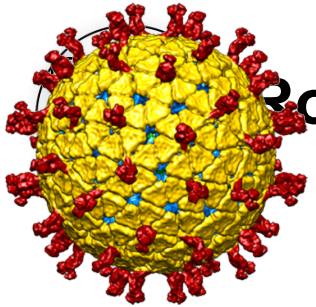


Rodriguez et al. 2014
PLoS Pathogens 10(5):e1004157

Rotavirus Colonization & Replication

- **Finds receptors at tips of intestinal villi**
  - Invades and replicates in mature enterocytes
  - Spreads systemically and causes fever
  - Infected cells are killed by lysis and by immune responses
  - villi become blunted





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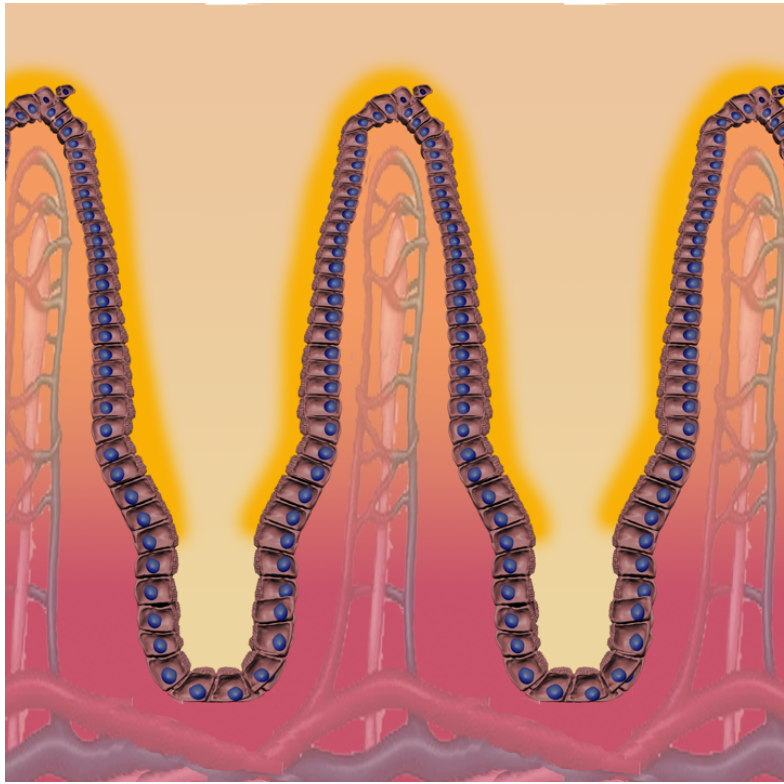

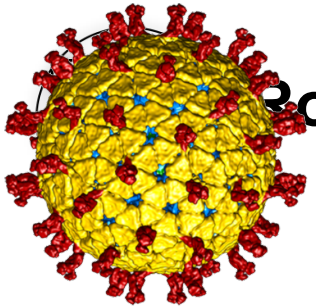

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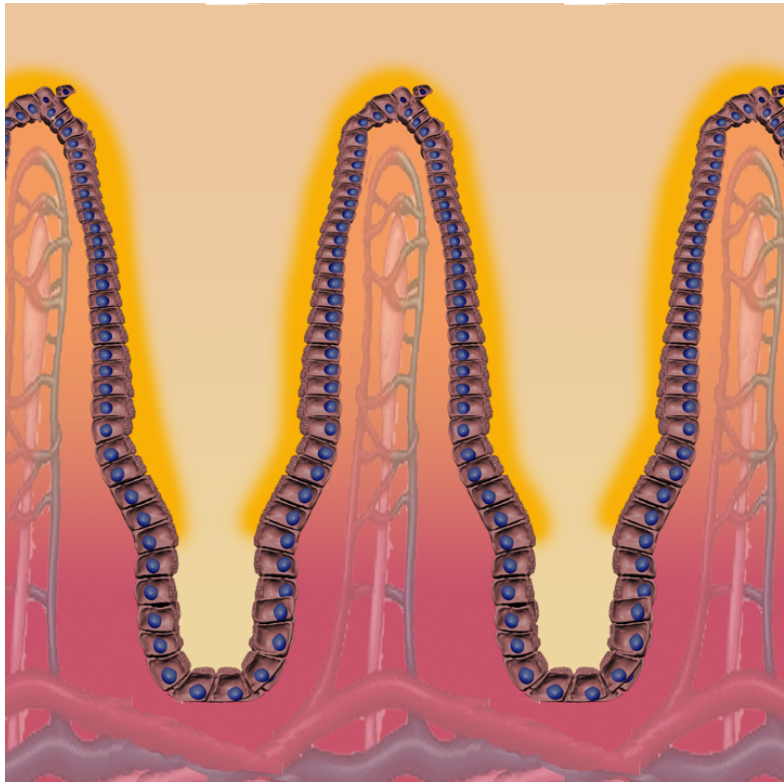

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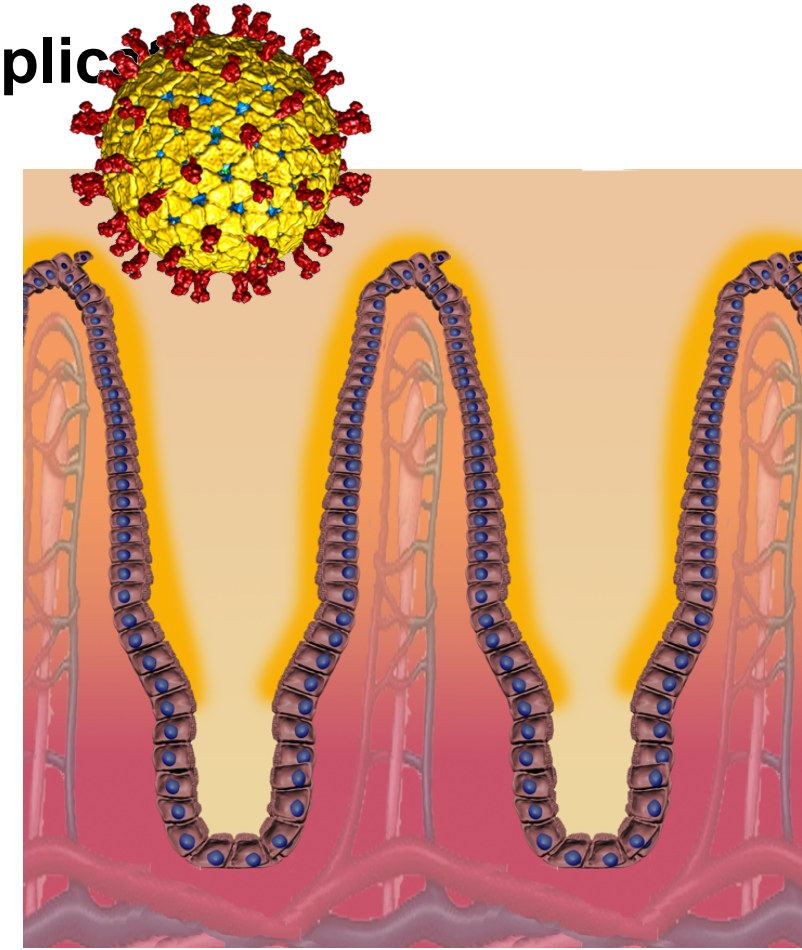

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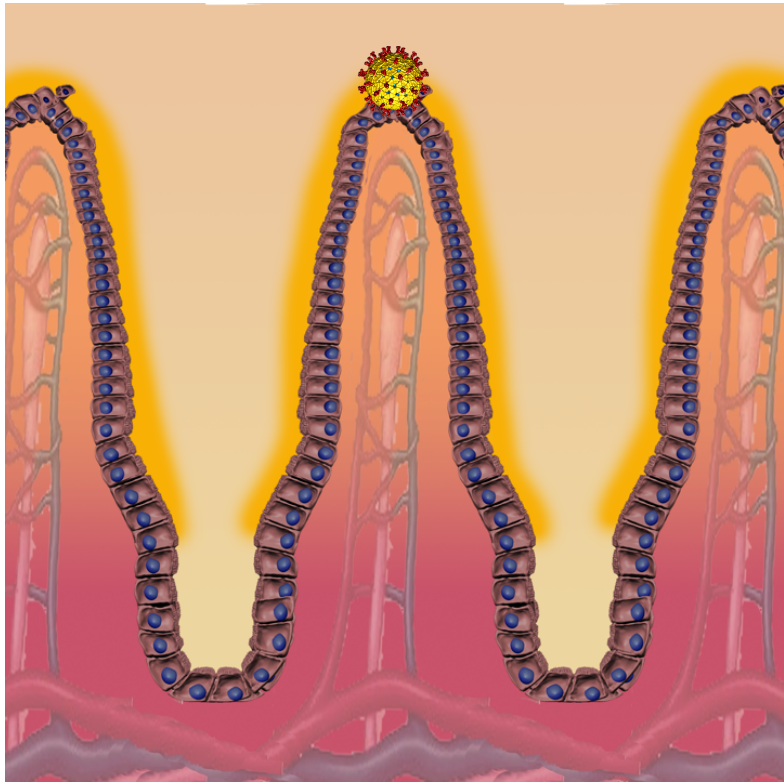

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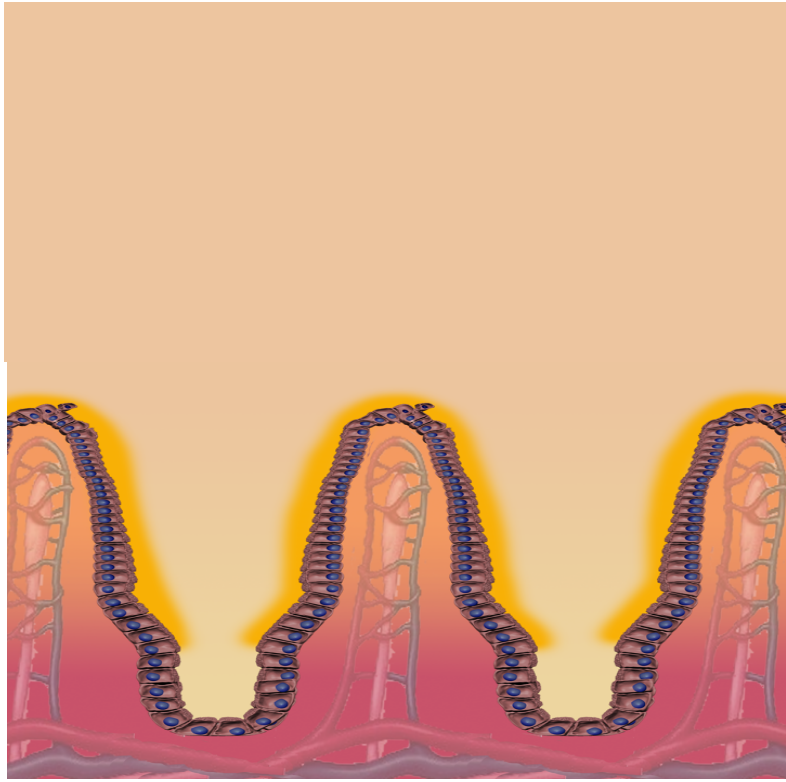
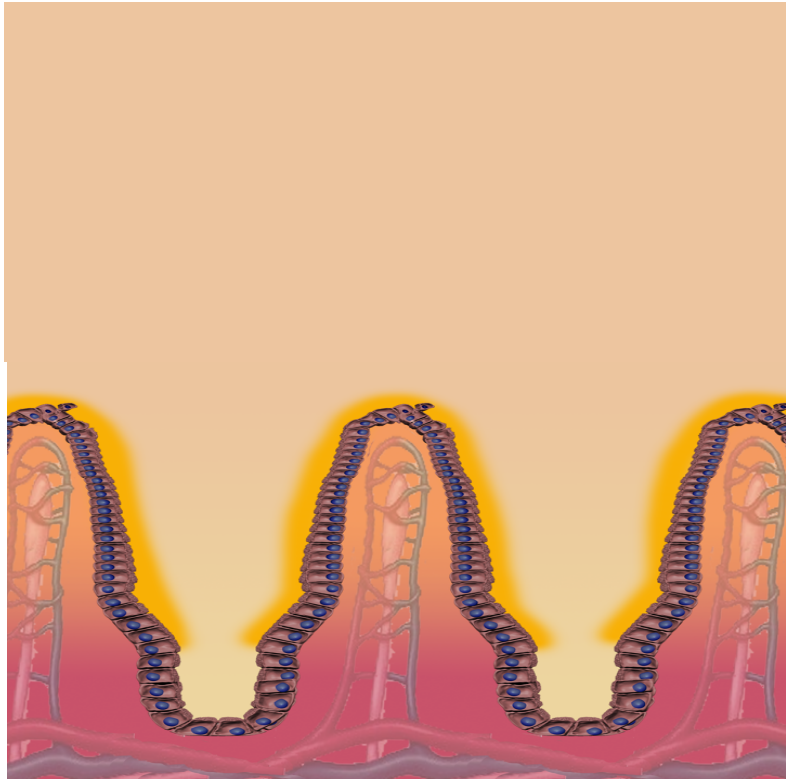


Rotavirus Colonization & Replication

Diarrhea is multifactorial

- Blunting of the villi
  - Less absorption of solutes
- Loss of brush border enzymes
  - osmotic diarrhea
- Non-structural protein 4 (NSP4) acts as an enterotoxin
  - loss of Cl- and leaky junctions
- Activation of the enteric nervous system
  - promotes fluid secretion



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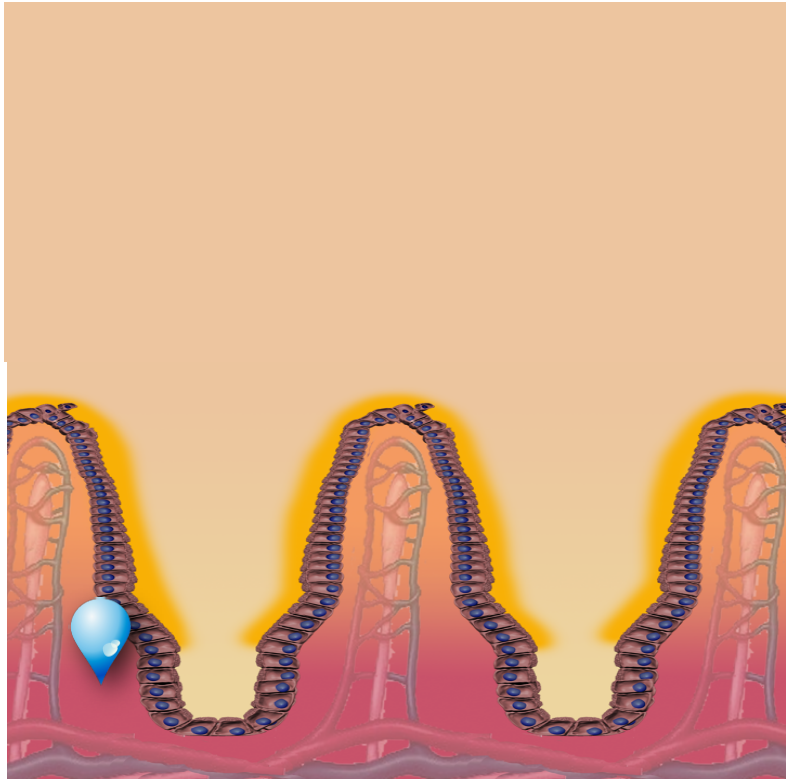

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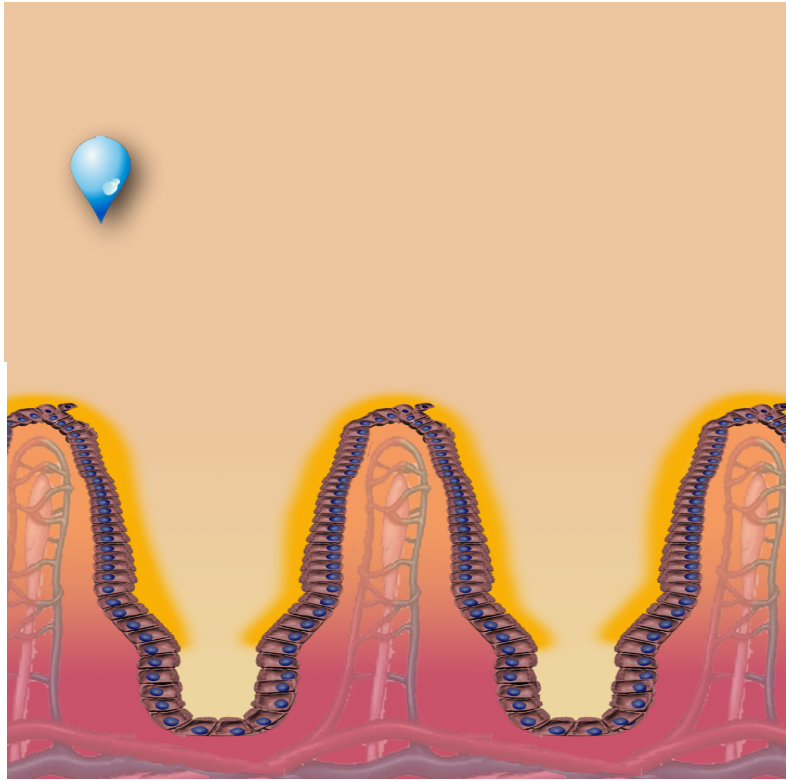

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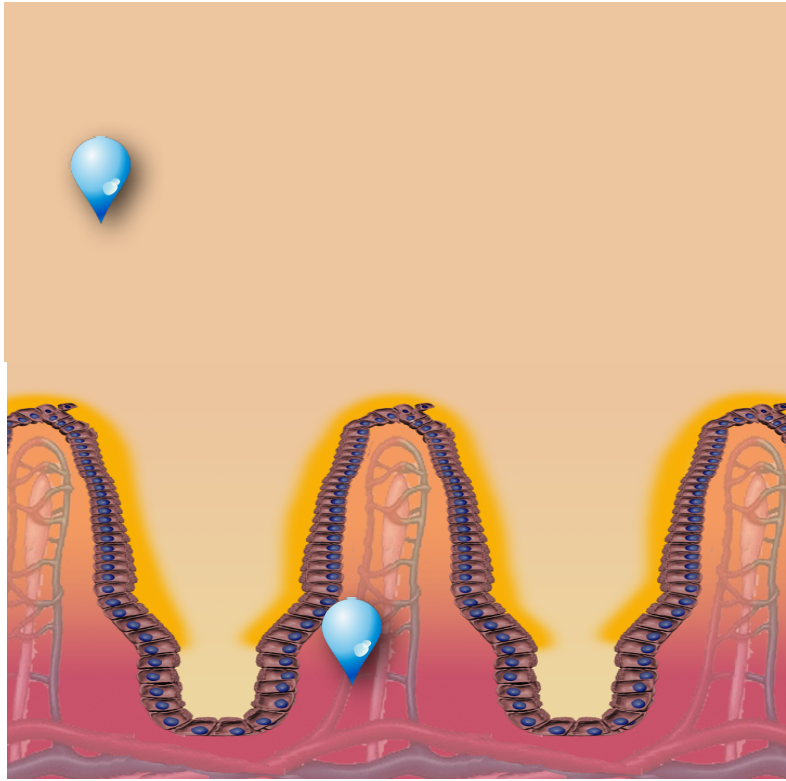

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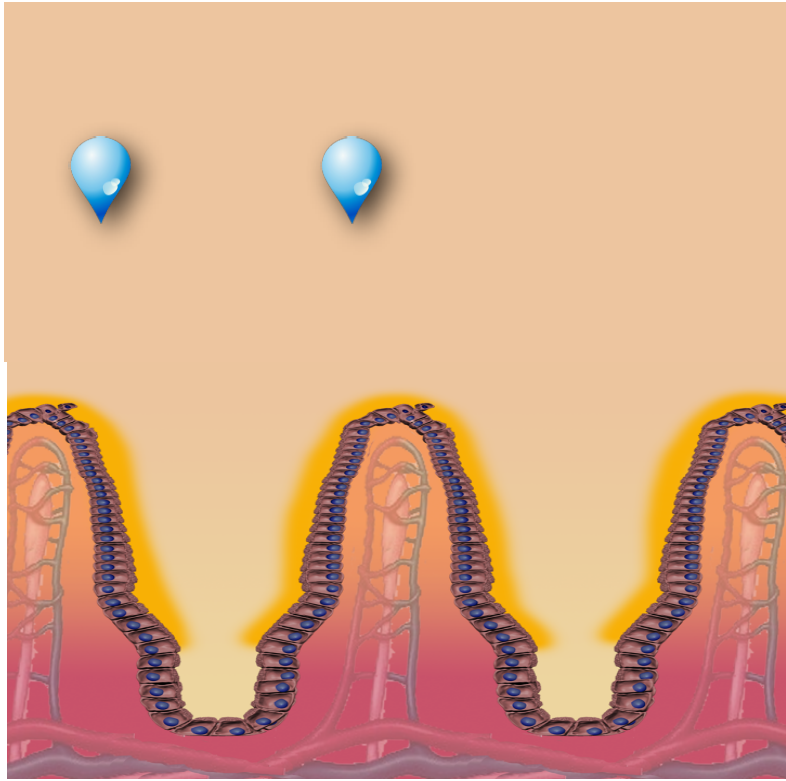

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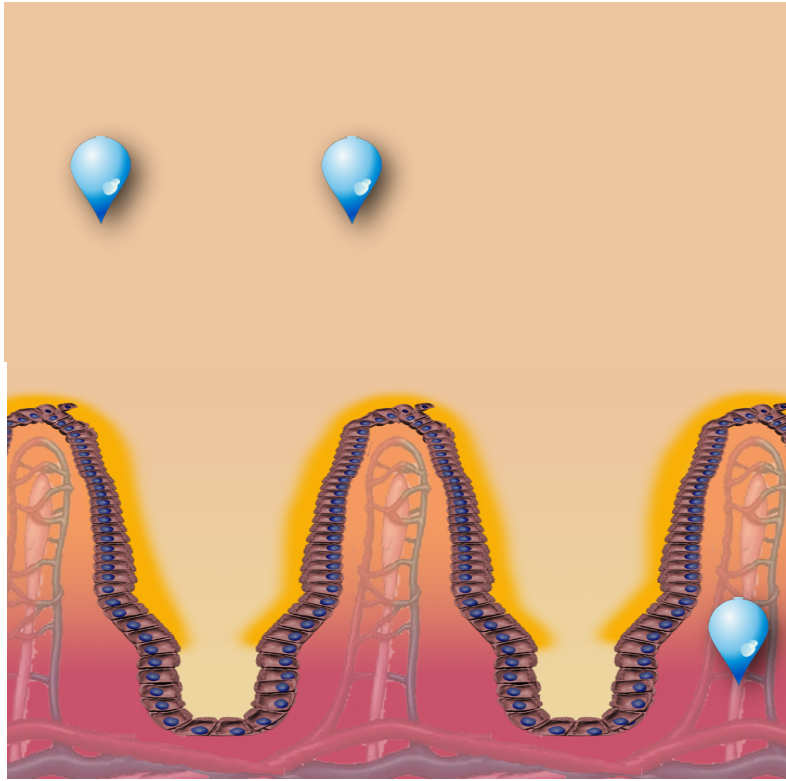

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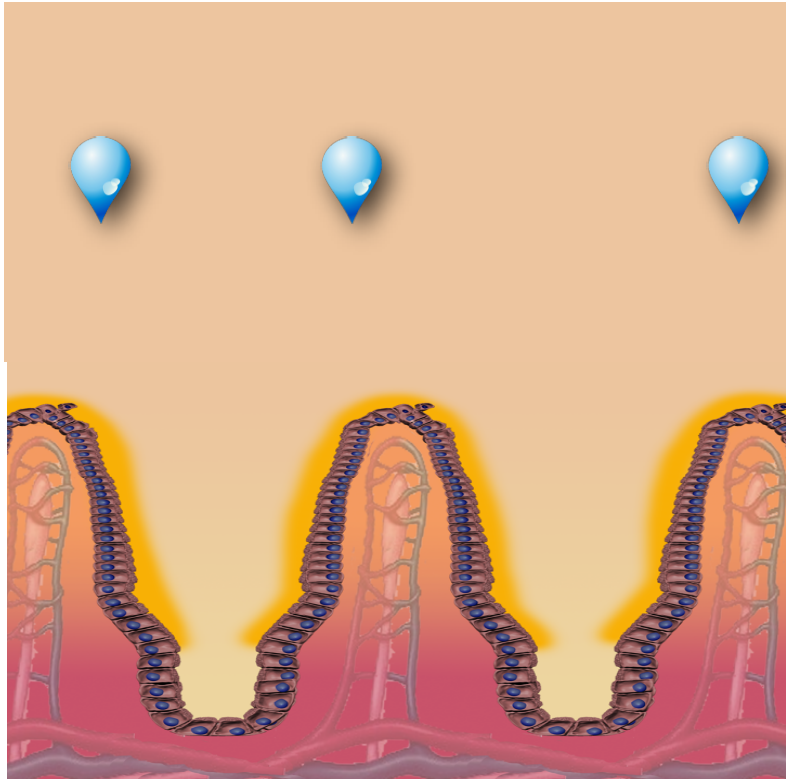
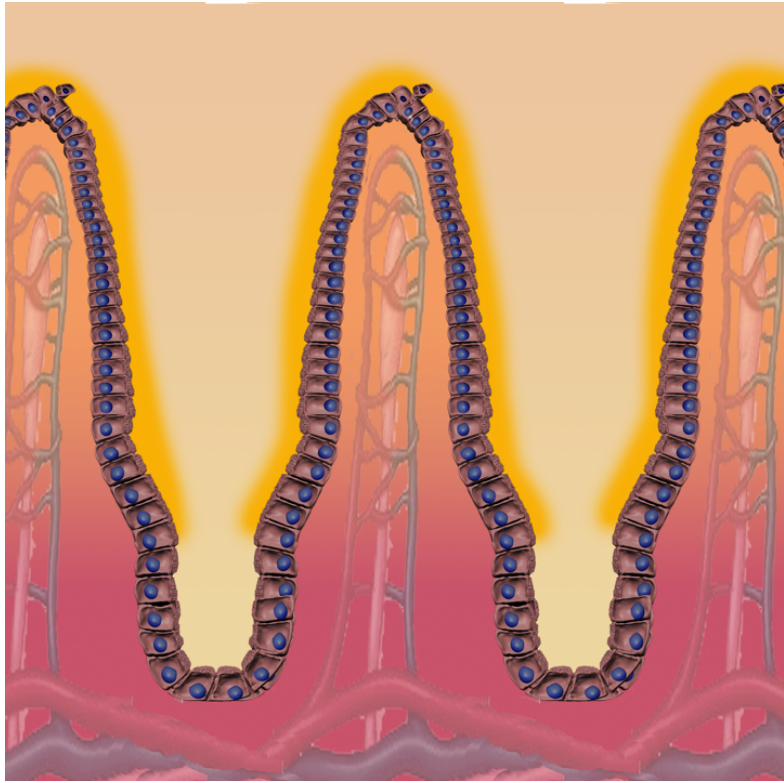


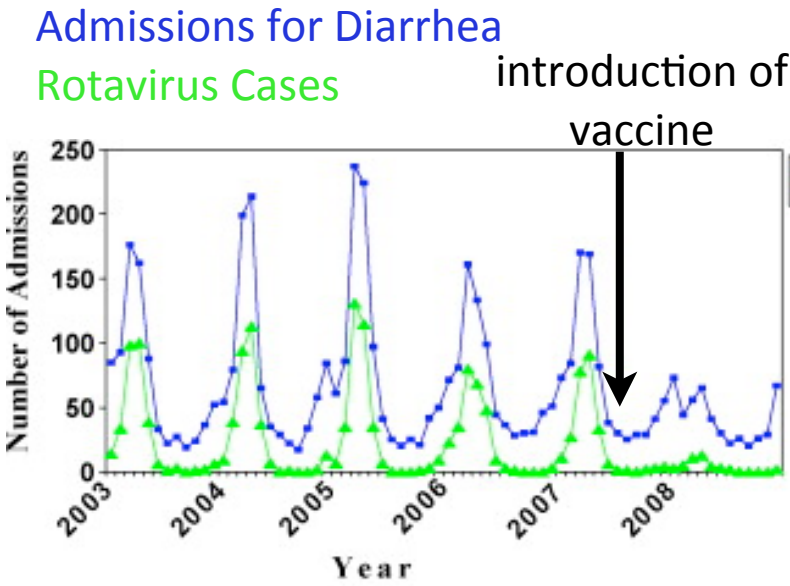
Rotavirus Colonization & Replication

- Mucosal infection is patchy
  - ORT is helpfjul
- In about one week viral replication stops
  - loss of susceptible cells
  - cell mediated immunity
  - interferon responses
  - antibodies?
- Cells repopulate the villi
- Infection in adults and re-infection in children is milder
  - IgA & immunological memory



Rotavirus prevention

- Two rotavirus vaccines are available and several in development
  - Human-bovine reassortant vaccine
  - Attenuated human rotavirus
- Rotavirus vaccination for all healthy children
  - Contraindicated in SCID
- A human-rhesus monkey reassortant vaccine discontinued
  - Increased risk of intussusception

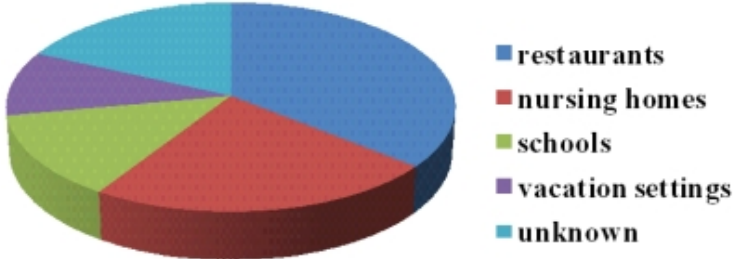


40% reduction in diarrhea and 85% reduction of rotavirus in 2008 vs 2003-2006

Norovirus

- Seasonal- “Winter vomiting disease”
- Significant nausea and vomiting followed by watery diarrhea.
  - Self-limited and quick resolution in 1-3 days.
  - more severe and prolonged in infants, elderly, and immunocompromised (weeks to months).
- Most common cause of outbreaks of viral gastroenteritis
  - i.e. cruise-ships, nursing homes, schools, military settings, restaurants & hospitals

Setting for Outbreak

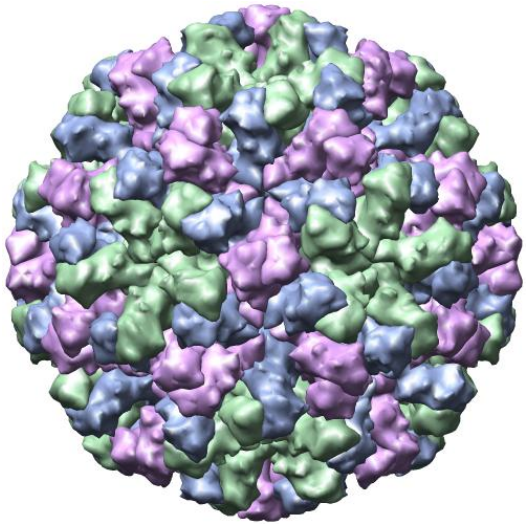


CDC data from 232 Norovirus outbreaks- 1997-2000

Norovirus

- Member of the *Caliciviridae* family
  - Strains named by location of outbreaks

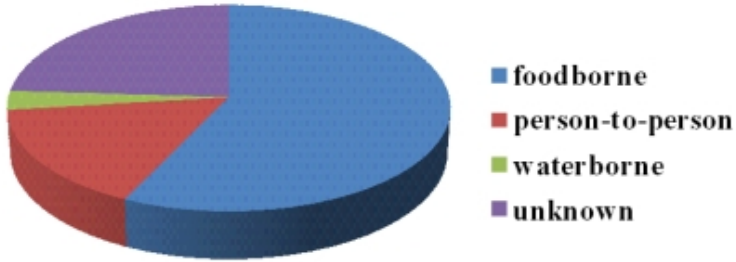
    Norwalk virus (Norwalk, OH), Dessert Shield, South Hampton, Snow Mountain.
- Non-enveloped icosahedral capsid- resistant to bile salts, detergents
- Positive strand RNA genome, non-segmented
- Does not grow in cell culture-
  - identification through PCR amplification or antigen detection immunoassays



Norovirus Entry

- Fecal oral or vomitus transmission
  - VERY infectious 5-10 particles can initiate an infection
  - Contaminated food and water
  - Person to person transmission is common in outbreaks
    - Fomites
    - Aerosolized vomit
  - Asymptomatic shedding occurs

Source of Norovirus



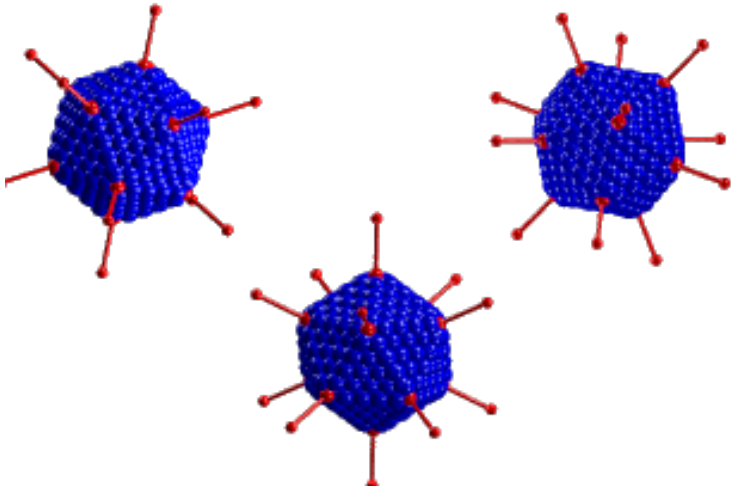
CDC data from 232 Norovirus outbreaks- 1997-2000

Norovirus Pathogenesis

- Pathogenesis is not well understood-
  - No animal models for human norovirus.
  - No cell culture system
- Preferred sites of replication not known
  - Enterocytes? but also dendritic cells, monocytes
- Volunteer studies show shortened microvilli, villus blunting, loss of enzymes and suggest transient malabsorption.
- Also marked decrease in gastric emptying may cause vomiting

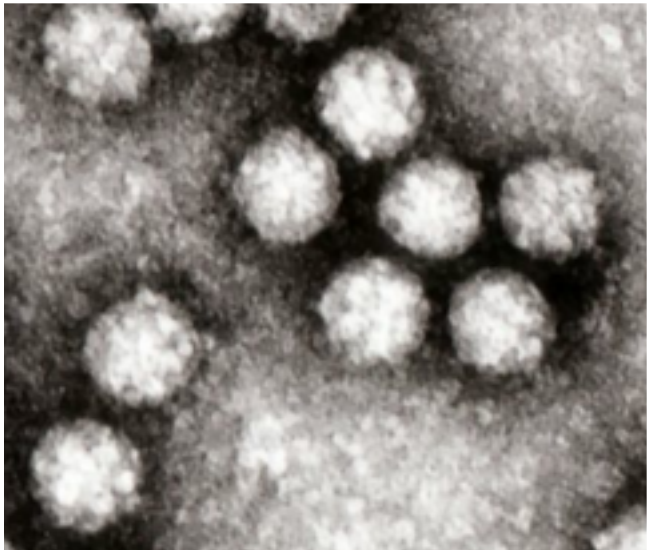
Enteric adenovirus 40, 41

- **Adenoviruses** are double-stranded DNA viruses that are not encapsulated
- 57 serotypes are known- two 40, and 41 cause mainly gastrointestinal symptoms: Febrile diarrhea
- Will not replicate in conventional viral cultures so diagnosis requires immunoassays for antigen detection or PCR
- No seasonality



Astroviruses

- Plus-strand single-stranded RNA- Non enveloped
- Some particles look like a “five-pointed star”
- It is the cause of acute gastroenteritis in many studies.



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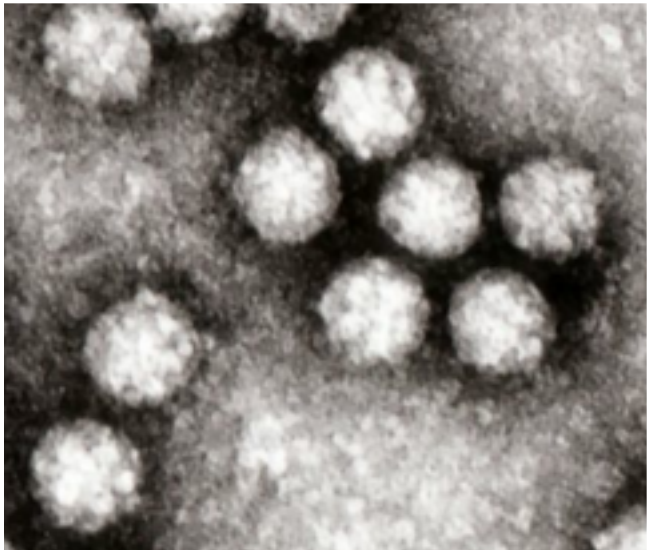

Credits: Watery Diarrhea- Viral

Slide 6: Rice Water Stools. From Figure 22.13 in: Gastrointestinal tract infections. Mims' Medical Microbiology. Goering, Richard V., BA MSc PhD. January 1, 2013. Pages 269-302. © 2013.
https://www.clinicalkey.com

Slide 7-8 Diagram of the rotavirus particle structure. From: Usonis, et al. 2012. *Vaccine*. Volume 30, Issue 31. Pages 4596-4605. The triple-layered particle consists of: the core (inner layer) with VP2 (green) as scaffolding protein, containing the viral genome of 11 segments of double-stranded RNA (shown schematically), VP1 (light blue), the RNA-dependent RNA polymerase (RdRp), and VP3 (red), the capping enzyme; the middle layer (inner capsid) made of VP6 (blue), determining the species [group]; and the outer layer (outer capsid), consisting of VP7 (a glycoprotein; orange) determining G types and VP4 (a protease-sensitive protein; deep red) determining P types.
https://www.clinicalkey.com

A rotavirus particle from a transmission electron micrograph made by Thomas Henry Flewett and left in the possession of Dr G.M. Beards.
http://commons.wikimedia.org/wiki/File:Flewett_Rotavirus.jpg

Slide 9: Structure of Rotavirus. From: Rodríguez et al. (2014) New Insights into Rotavirus Entry Machinery: Stabilization of Rotavirus Spike Conformation Is Independent of Trypsin Cleavage. PLoS Pathog 10(5): e1004157.
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004157

Slide 15: Monthly diarrhea and rotavirus-associated hospitalizations among children 1–23 months of age for 10 sentinel hospitals, New York, January 1, 2003 to December 31, 2008. In: Chang et al. 2010. *Vaccine*. Volume 28, Issue 3. Pages 754-758. Reduction in hospitalizations for diarrhea and rotavirus infections in New York state following introduction of rotavirus vaccine.
https://www.clinicalkey.com

Credits: Watery Diarrhea- Viral

Slide 16: Norovirus outbreak characteristics. The Centers for Disease Control collected data from 232 norovirus outbreaks between July 1997 and June 2000.
http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-factsheet.htm.

Slide 17 Norwalk virus. In October 1968, an outbreak of acute gastroenteritis among students and teachers in an elementary school in Norwalk, Ohio was investigated by the Centers for Disease Control and Prevention (5). During a two-day period, 50% of the students and teachers (116 of 232) developed a gastrointestinal illness with a secondary attack rate of 32% among contacts of primary cases. The illness was characterized by nausea and vomiting in more than 90% of cases and diarrhea in 38% of affected individuals, and the duration of illness was typically 12 to 24 h..
http://commons.wikimedia.org/wiki/File:Norwalk_Caspid.jpg

Slide 18: Figure 1: Norovirus outbreak characteristics. The Centers for Disease Control collected data from 232 norovirus outbreaks between July 1997 and June 2000.
http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-factsheet.htm

Slide 19: Symbol of gastroenteritis. Chicago Department of Public Health
Slide 20: Adenovirus structure.
http://commons.wikimedia.org/wiki/File:Adenovirus_structure.png

Slide 21: Transmission electron micrograph of Astrovirus particles.
http://commons.wikimedia.org/wiki/File:Astrovirus_4.jpg