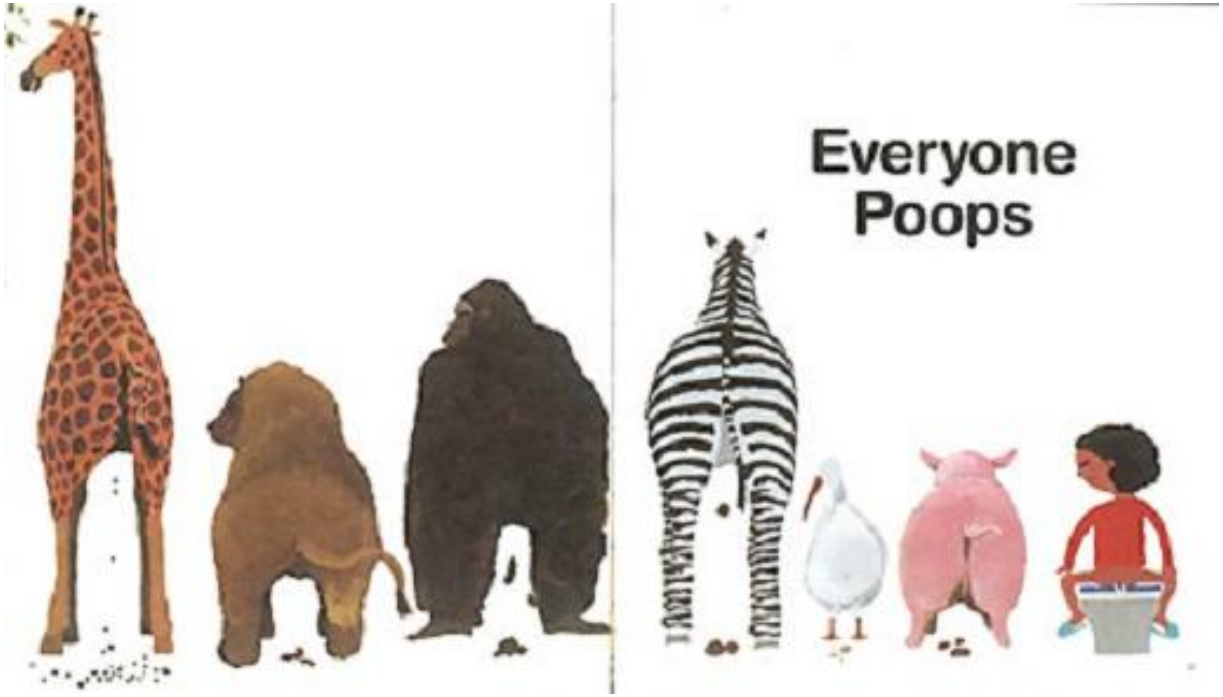
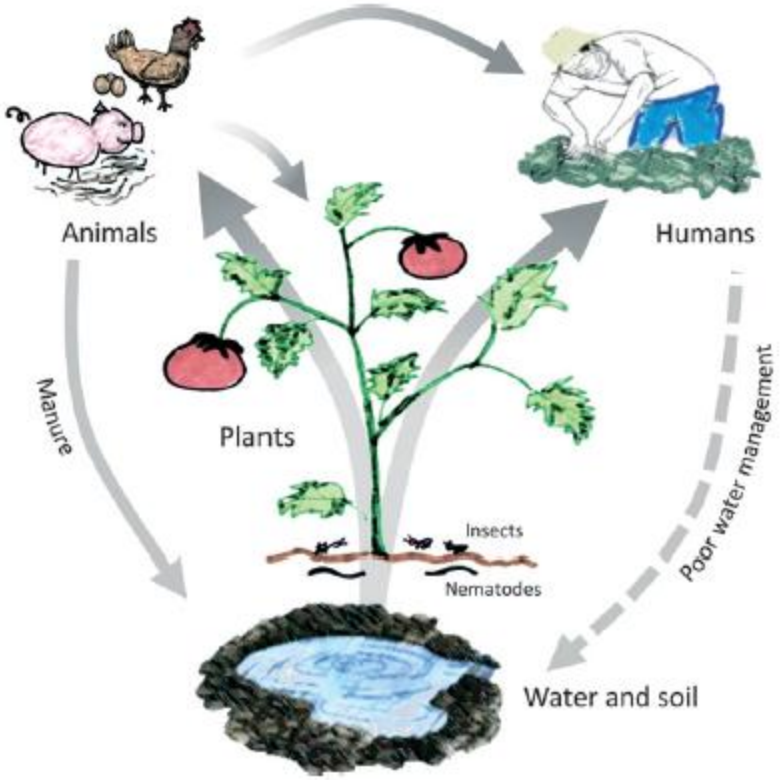
VIRAL DIARRHEAS

Irene Kourbeti
Consultant Internal Medicine/ Infectious Disease


Everyone
Poops



Besser *Food Microbiol* 2018; 71: 55-9

Outline

- Which are the viruses
- Epidemiology
- Treatment
- Vaccines
- Prevention
- Role of the infection in the immunocompromised

CMV colitis

TABLE 2. Diagnostics Available for CMV Testing and Relative Utility in IBD Clinical Practice

Test for CMV	Sample Required	Indicative of GI Infection	Sensitivity, %	Specificity, %	Applicability in Clinical Practice
Serology IgM, IgG	Blood	No	100	99	− (?)
Antigenemia assay	Blood	No	60–100	83–100	+
PCR on blood	Blood	No	65–100	40–92	++
PCR on tissue	Tissue	Yes	92–97	93–99	+++
PCR on stool	Stool	Yes	29–83	86–93	+
H&E	Tissue	Yes	10–87	92–100	+++
Immunohistochemistry	Tissue	Yes	78–93	92–100	+++

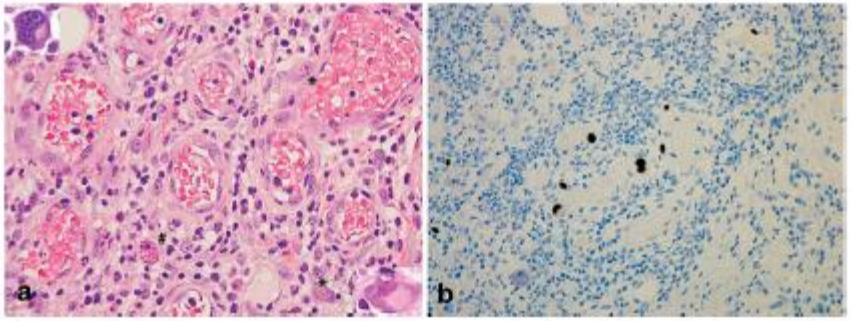
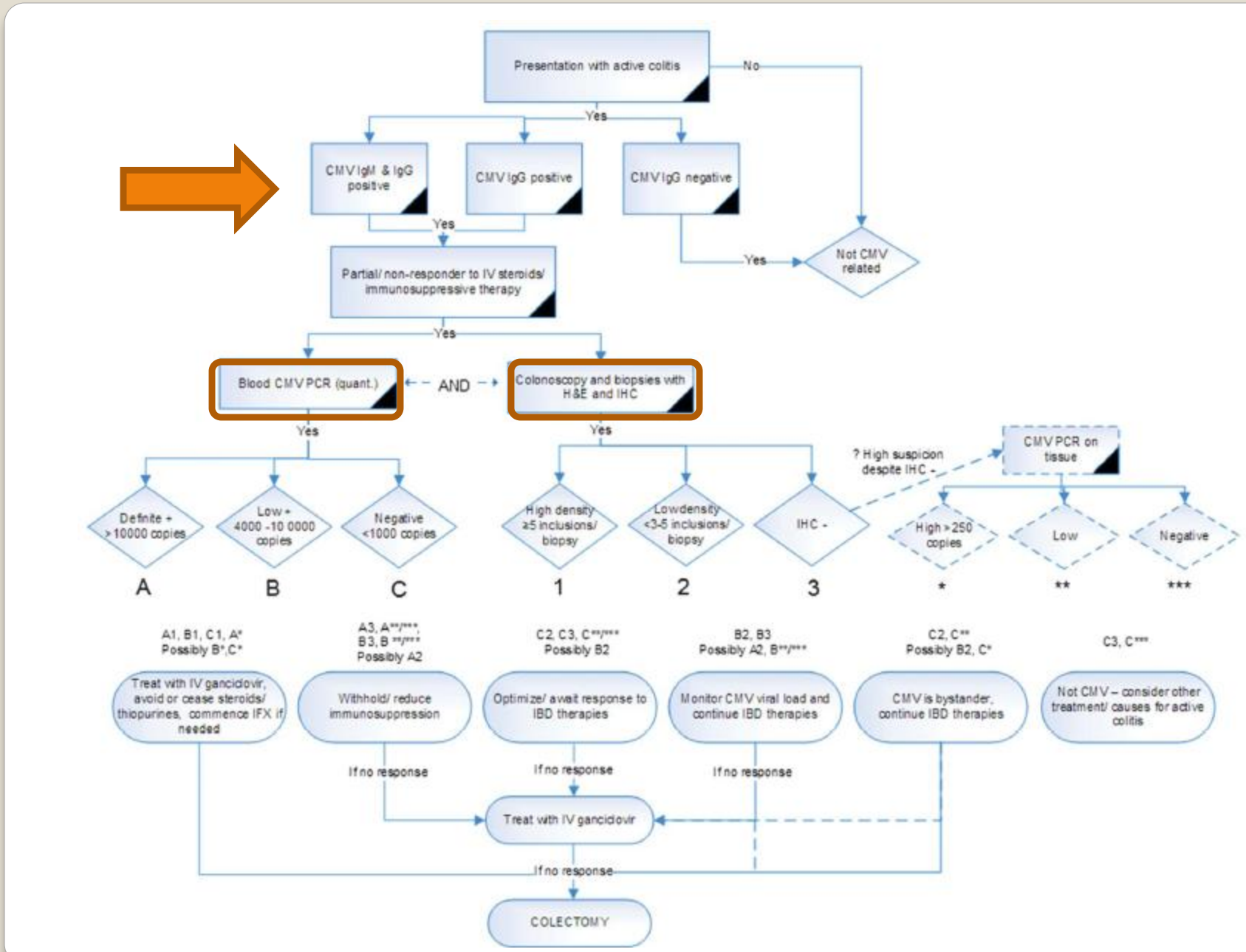


Fig. 1 **a** Hematoxylin eosin–stained slide at a high power showing cytomegalic cells containing basophilic intranuclear inclusion bodies (asterisk) and cells with a thickened nuclear membrane and smaller granular intracytoplasmic inclusions (number sign). **b** Immunohistochemical staining cytomegalovirus (CMV) at a high power highlighting CMV-infected endothelial cells. (From Baniak N. et al. Arch Pathol Lab Med [35]; used with permission)

Beswick Inflamm Bowel Dis 2016; 22: 2966-76

Feler Curr Infect Dis Rep 2019; 29: 5



Beswick Inflamm Bowel Dis 2016; 22: 2966-76

Enteric pathogens

Pathogen	Small bowel	Colon
Bacteria	*Salmonella**	*Campylobacter**
	Escherichia coli¶	*Shigella*
	Clostridium perfringens	*Clostridioides difficile*
	Staphylococcus aureus	*Yersinia*
	Aeromonas hydrophila	*Vibrio parahaemolyticus*
	Bacillus cereus	Enteroinvasive *E. coli*
	Vibrio cholerae	*Plesiomonas shigelloides*
		Klebsiella oxytoca (rare)
Virus	Rotavirus	Cytomegalovirus*
	Norovirus	Adenovirus
	Astrovirus	Herpes simplex virus
Protozoa	*Cryptosporidium**	*Entamoeba histolytica*
	*Microsporidium**	
	Cystoisospora	
	Cyclospora	
	Giardia lamblia	

* Can involve both the small and large bowel, but are most likely to occur as listed.
¶ EPEC, EAggEC, EHEC, ETEC may all contribute; routine laboratories and cultures will not differentiate these from E. coli which are normal flora.

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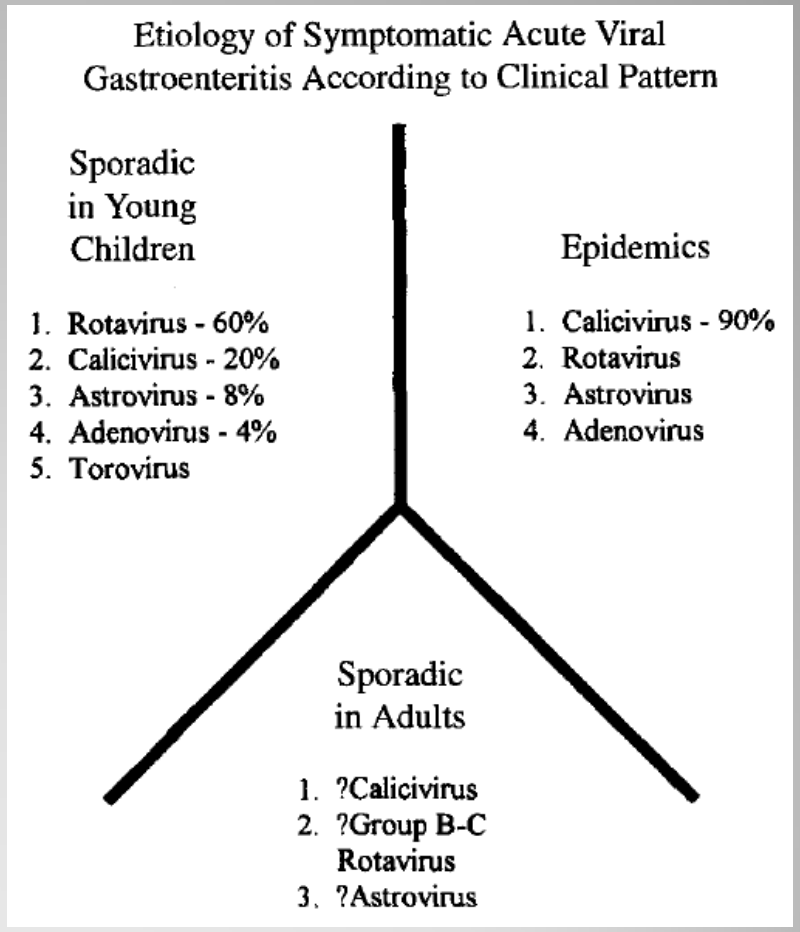


Goodgame Gastroenterol Clin N Am 2001; 30: 779

Table 1. General characteristics of the main viral agents responsible for gastroenteritis worldwide

Family	Genus	Biological characteristics
Caliciviridae	Norovirus (genogroups I–VI)	Small, round, non-enveloped, positive-sense, ss-RNA, 27–35 nm diameter; 7,400–7,700 nt
	Sapovirus (genogroups I–V; genogroups GVI to GXIV were recently proposed) [106]	ss-RNA, 41–46 nm diameter; 7.1–7.7 kilobases
Adenoviridae	Mastadenovirus Subgenera (A–G); at least 52 serotypes; 53 genotypes	Non-enveloped, linear ds-DNA; 70–100 nm in diameter; 26–45 kilobases
Astroviridae	Astrovirus (8 serotypes: HAstV1–HAstV8)	Non-enveloped, ss-RNA, 28–30 nm in diameter; 6.1–7.3 kilobases
Reoviridae	Rotavirus (groups A–G)	Non-enveloped, dsRNA, 71 nm in diameter; approximately 18.5 kilobases

Sidoti J Infect Dev Ctries 2015; 9: 551-61

Table 1. Overview of the pathogenesis studies performed for new viruses identified in the gastrointestinal tract ^.

Viral Family	Virus Species	Antibody Response Observed?	Associated with Diarrhea in Case-Control Studies?
Picornaviridae	Aichi virus	Yes [29]	No [30,53] *
Coronaviridae	Torovirus	Yes [34]	Yes [35] **
Astroviridae	MLB astrovirus	Yes [54]	Yes [55]/No [56,57]
Astroviridae	VA/HMO astrovirus	Yes [58]/No [58] ***	No [55]
Picornaviridae	Saffold virus	Yes [59]	No [53,60,61]
Picornaviridae	Cosavirus	-	No [32,45,62,63]
Picornaviridae	Klassevirus/salivirus	Yes [64]	Yes [48,53]/No [65]
Polyomaviridae	MW polyomavirus	Yes [66]	No [67]
Polyomaviridae	MX polyomavirus	-	No [68]
Polyomaviridae	STL polyomavirus	Yes [69]	No [70,71] *
Parvoviridae	Bufavirus	-	No [72,73] *

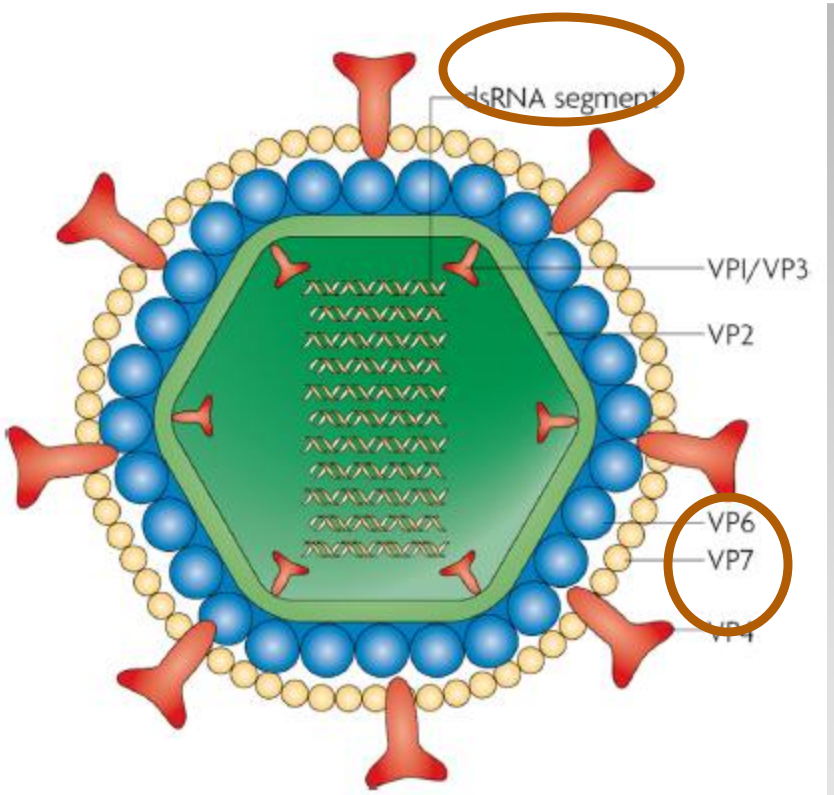
Viruses causing gastroenteritis: The Known, The New and Those Beyond

Oude Munnink Viruses 2016; 8:42

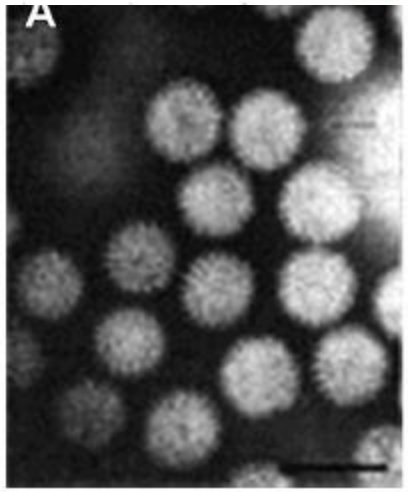
- Calicivirus
- Humans and animals
- All ages
- Outbreaks and sporadic cases
- Semiclosed settings
- Foodborne transmission occurs
- Indistinguishable clinical symptoms
- RT-PCR, EIA
- Lack of culture system

Human sapoviruses

Oka Clin Microbiol Rev 2015; 28: 32-53

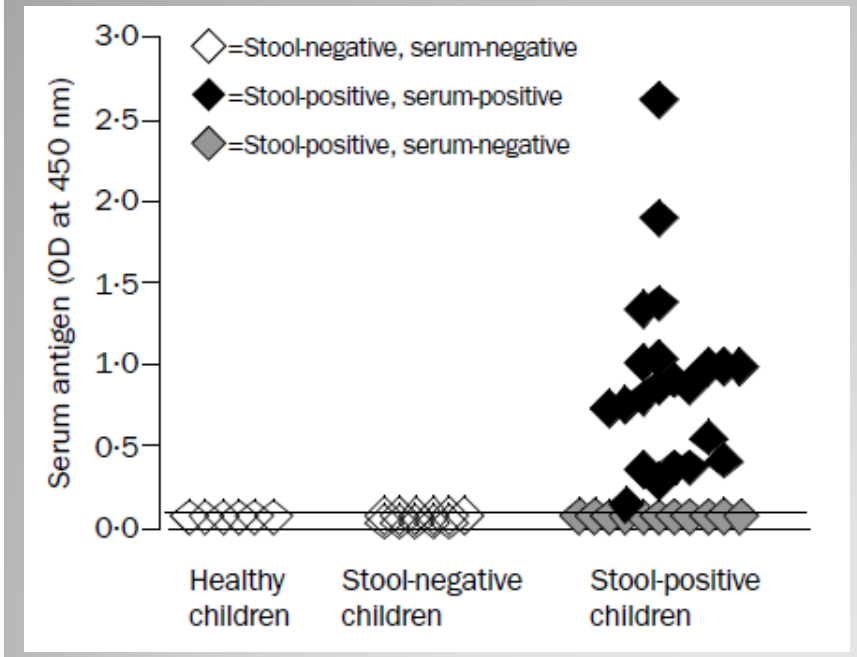


- Reoviridae
- Humans susceptible to spp **A**,B,C and H
- Host specific barriers are permeable to some extent
- Underappreciated role in adults



Rotavirus

Banyai Lancet 2018; 392: 175-86
Esona Clin Lab Med 2015; 35: 363-91
Farkas Expert Rev Anti Infect Ther 2015; 13: 1337-50



- Rotavirus antigen and RNA are present in serum
- RV escapes the GI tract resulting in antigenemia and possible viremia
- Animal data suggest that RV antigen detected in serum is infectious
- Widely distributed virus

Rotavirus: To the Gut and Beyond

Blutt Lancet 2003; 362: 1445-9
Blutt Curr Opin Gastroenterol 2007; 23: 39-43

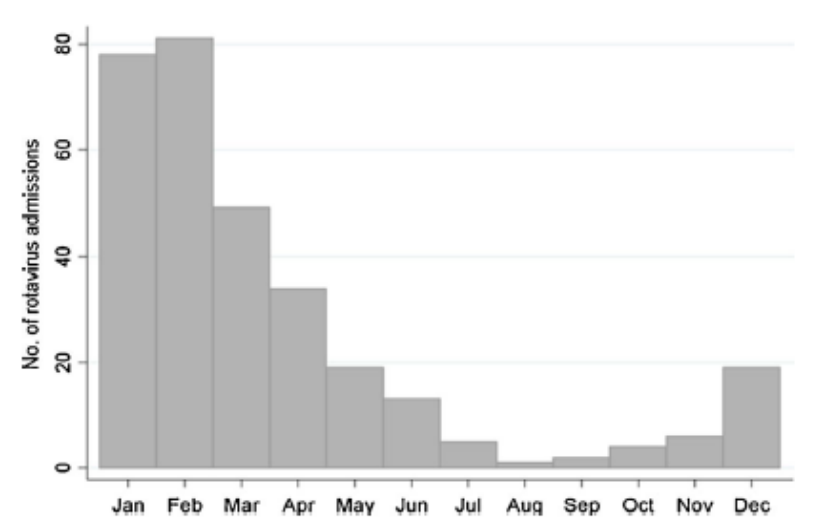


Fig. 1 Monthly distribution of rotavirus gastroenteritis admissions

- Hospitalizations- strong association:
1. Solar radiation
2. Mean temperature
3. Solar radiation
4. Atmospheric pressure
5. Wind speed
- This model predicted >80%

Meteorological factors and RV hospitalizations

Hervas Eur J Clin Microbiol Infect Dis 2014; 33: 1547-53

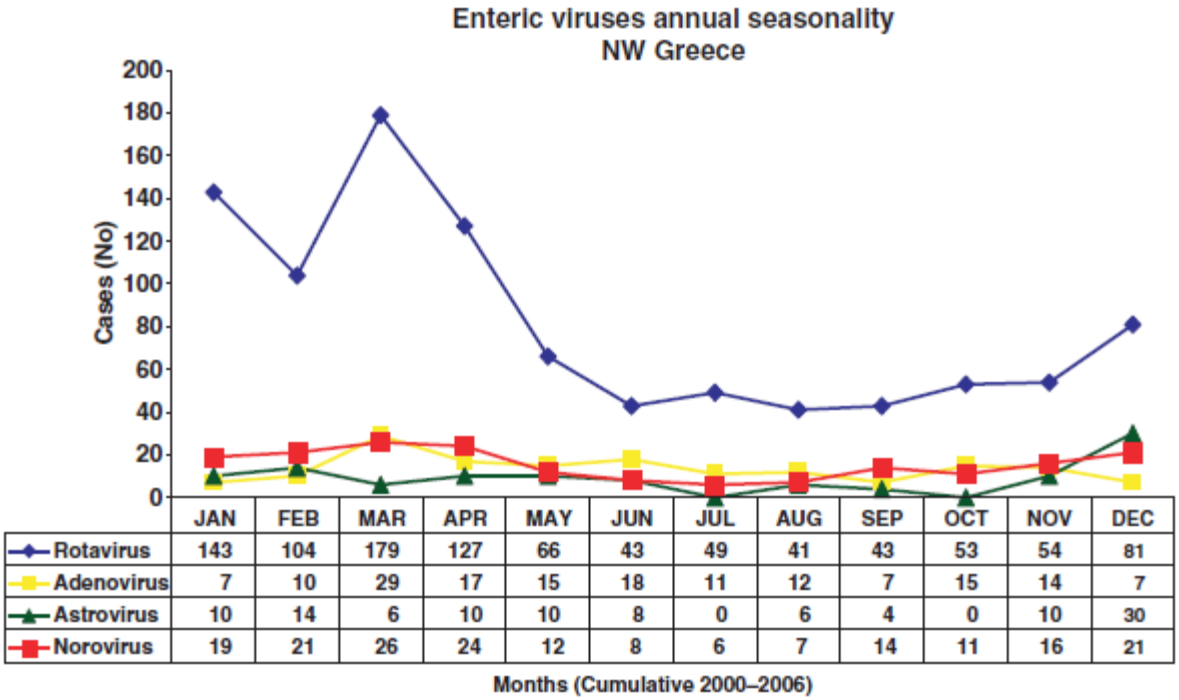


TABLE 1. Viral enteropathogens detected by enzyme immunoassay

Pathogen	Mono-infection Cases (% of total)	Co-infection	
		Viral–viral co-infections	Viral–bacterial co-infections
Rotavirus	941 (20.4)	32 viral–viral (adenovirus, 10; astrovirus, 20; adeno-astrovirus, 2)	10 viral–bacterial (*Salmonella* spp., 3; *Yersinia enterocolitica*, 2;; *Campylobacter jejuni*, 5)
Adenoviruses	142 (3.1)	16 viral–viral (rotavirus, 10; astrovirus, 4; rota-astrovirus, 2)	4 viral–bacterial (all *Salmonella* spp.)
Astroviruses	70 (1.5)	26 viral–viral (rotavirus, 20; adenovirus, 4; rota-adenovirus, 2)	12 viral–bacterial (all *Salmonella* spp.)
Noroviruses	185 (4)	None	None

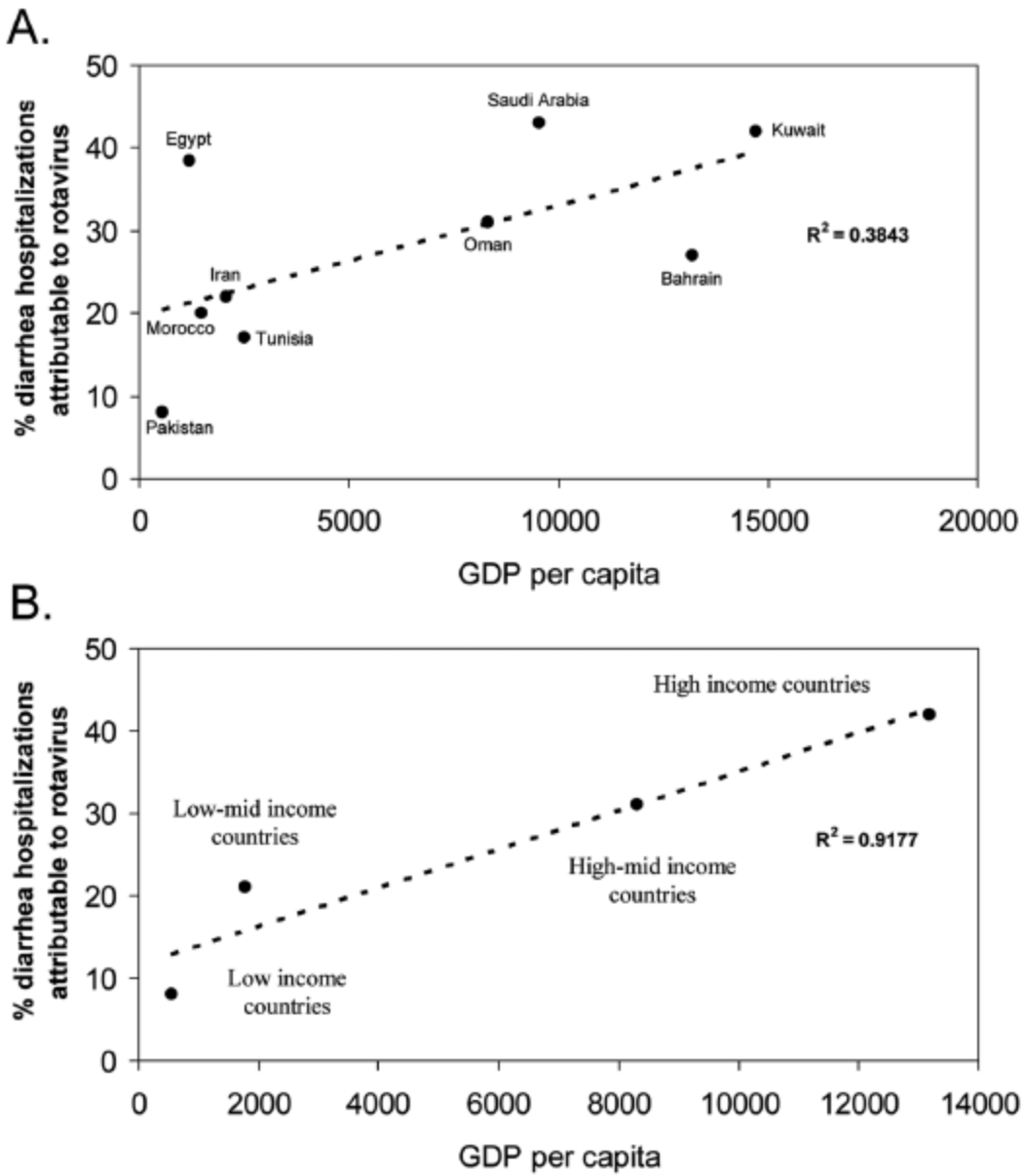
Levidiotou Clin Microbiol Infect 2009; 15: 596-8

Mammas Minerva Pediatr 2012; 64: 333-9

- Elderly are considered at high risk- lack of studies
- G2 seems to be the predominant genotype
- Winter and fall
- Studies from Morocco and Israel reported significant decline in hospitalizations caused by RV associated GI infection among children <5 years
- Otherwise - significant burden in the area

Rotavirus in the Middle East and North Africa

Zaraket Vaccine 2017; 35: 6047-58



Malek J Infect Dis 2010; 202; S12-S22

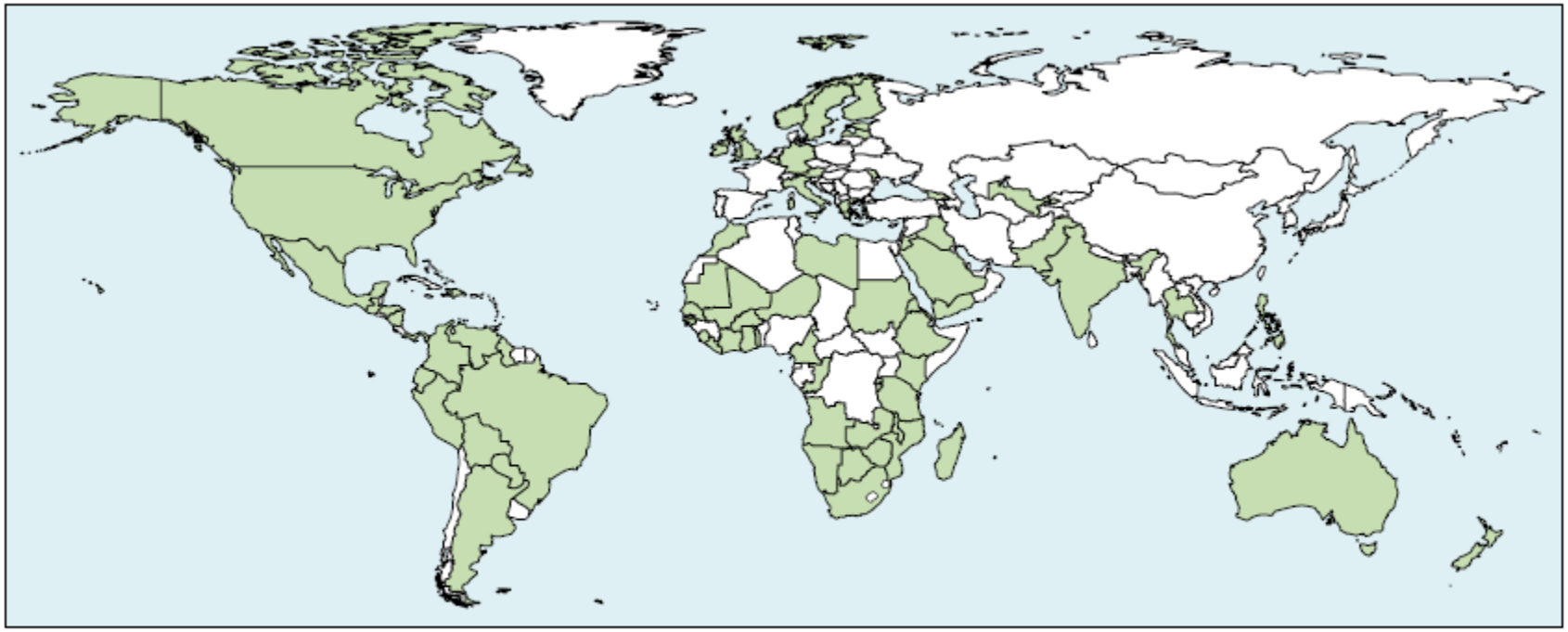
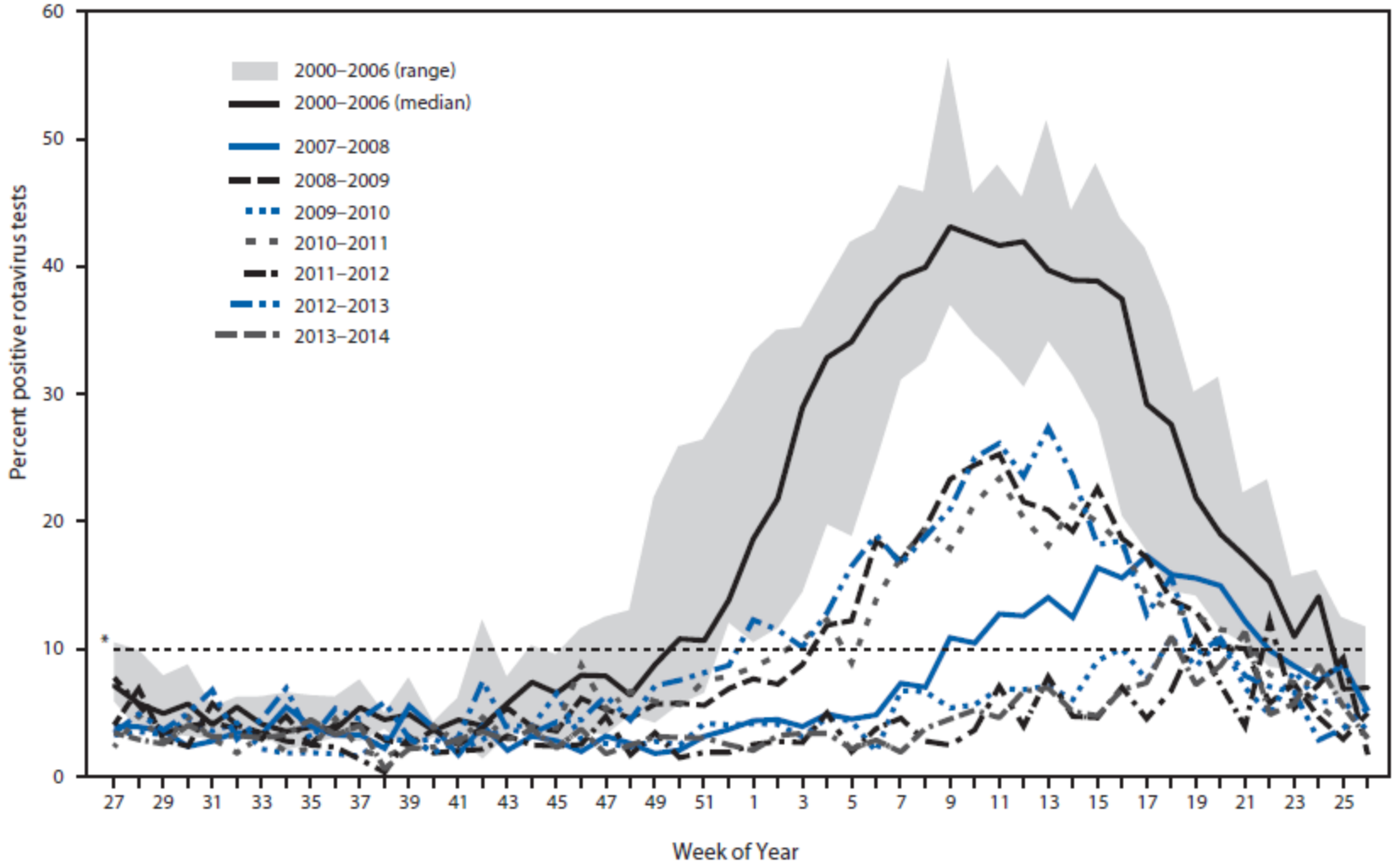


Figure 2: **Current rotavirus vaccine introduction map**
As of April, 2018, 95 countries have introduced rotavirus vaccines; this includes 88 national introductions, three ongoing phased introductions (Pakistan, India, and Philippines), and four pilot or sub-national introductions (Canada, Italy, Sweden, and Thailand). Data are from the ROTA council.[109]

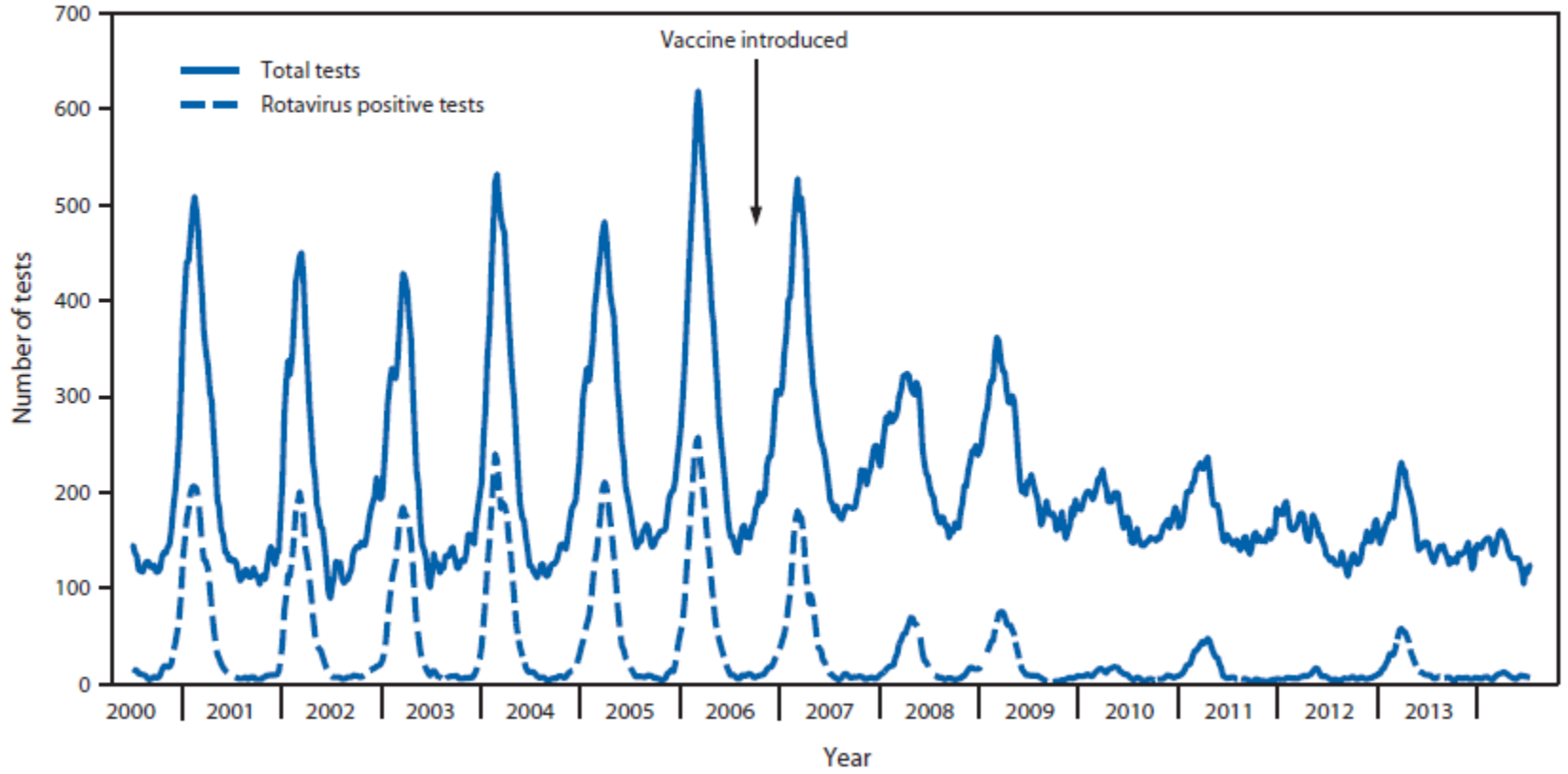
Banyai Lancet 2018; 392: 175-86
Isanaka N Engl J Med 2017; 376: 1121-30

FIGURE 1. Rotavirus season duration and peak activity by reporting years (prevaccine 2000–2006 and postvaccine 2007–2011), NREVSS data — United States, 2000–2014



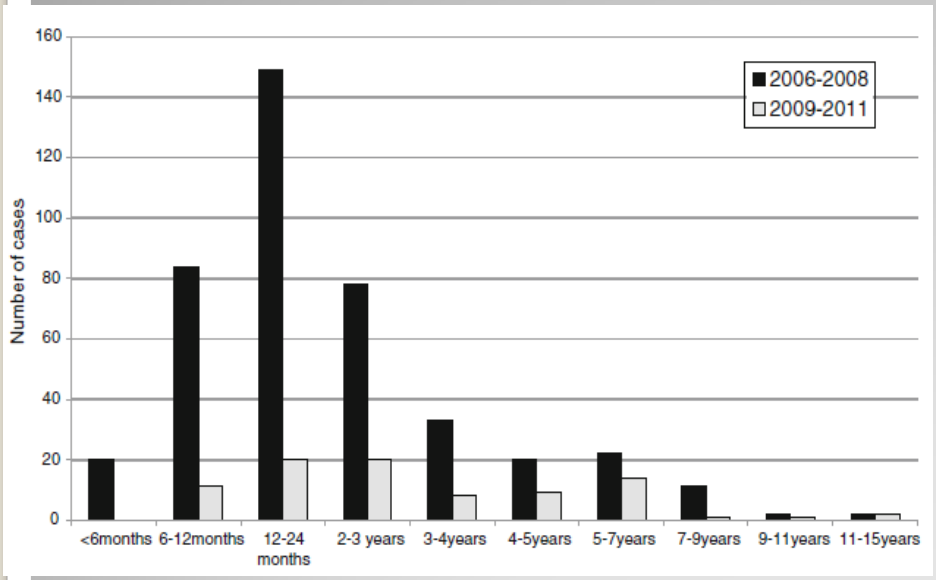
Aliabadi MMWR 2015; 64: 337-42

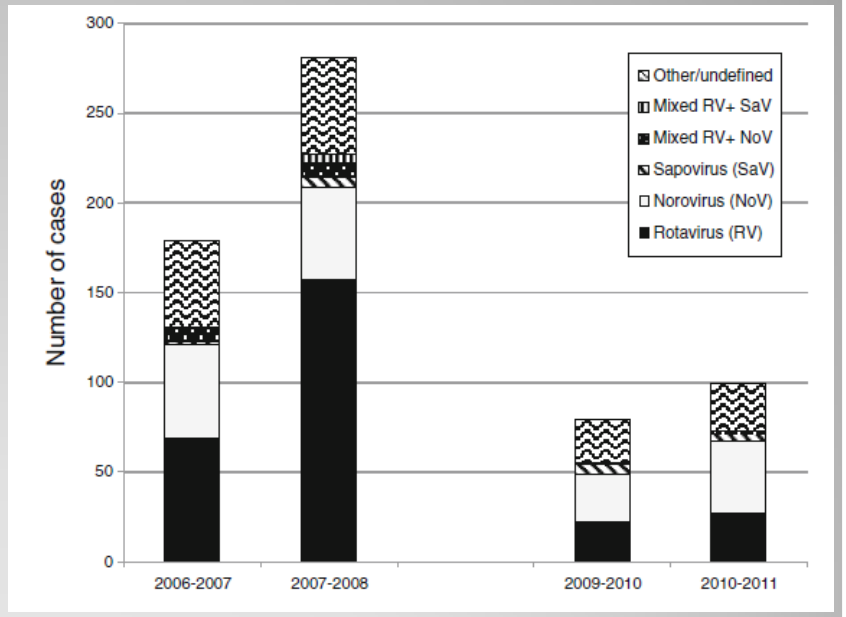
FIGURE 2. Total and positive rotavirus tests, NREVSS data — United States, 2000–2014



Aliabadi MMWR 2015; 64: 337-42

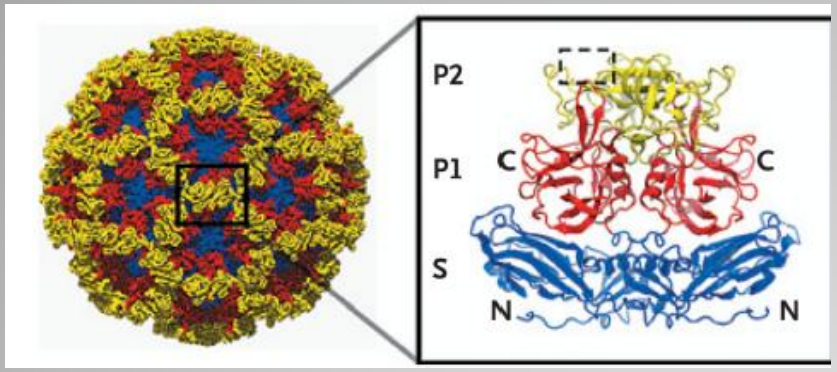
Doro Infection Genetics and Evolution 2014



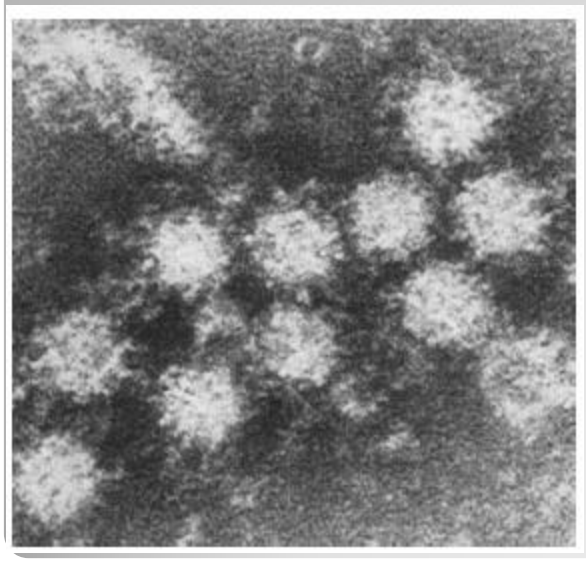


Reduction in RV but not NoV hospitalizations

Hemming Eur J Pediatr 2013; 172: 739-46



- Caliciviridae
- Nine GI, 22 GII, one GIV
- Recombinant genomes may have increased fitness and transmissibility
- Zoonotic transmission has not shown to occur



Norovirus

Banyai Lancet 2018; 392: 175-86

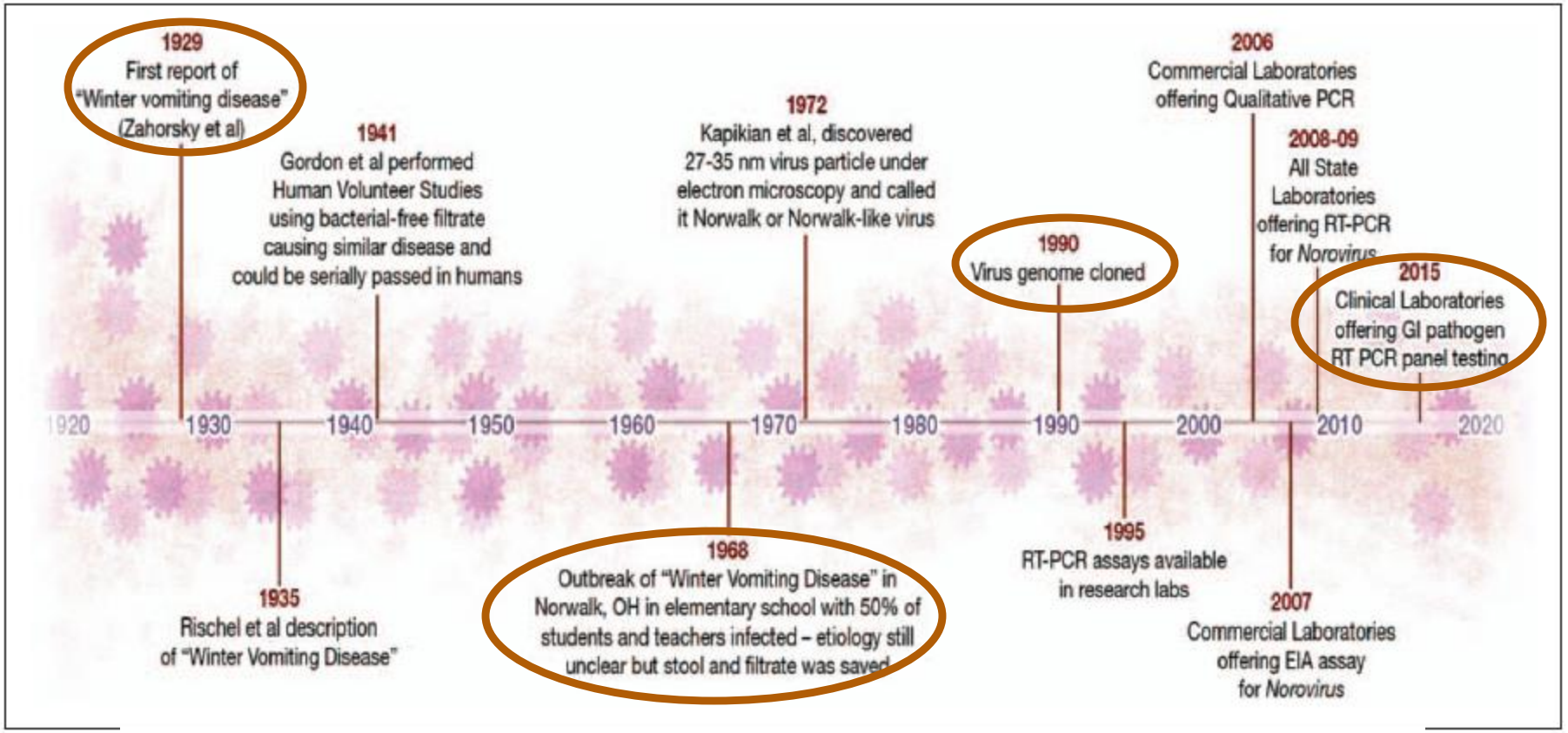


FIGURE 1.

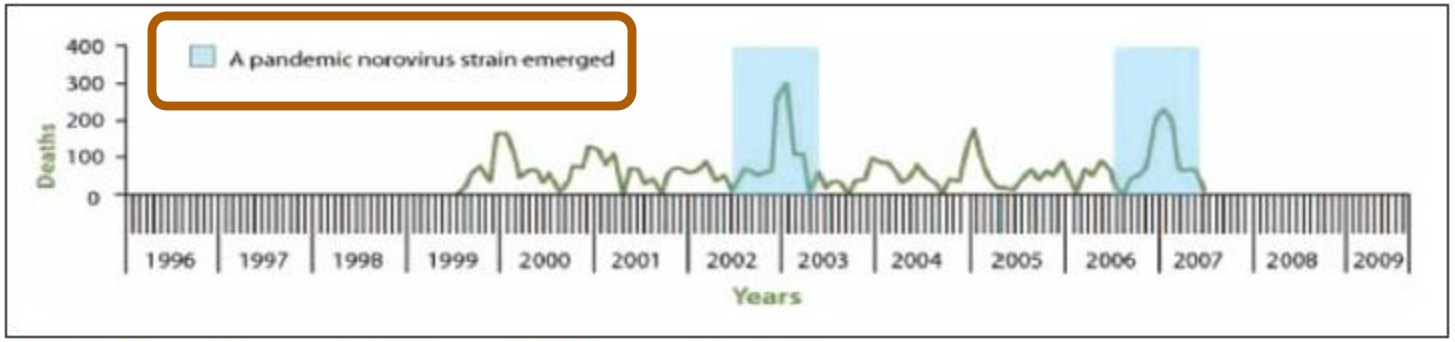
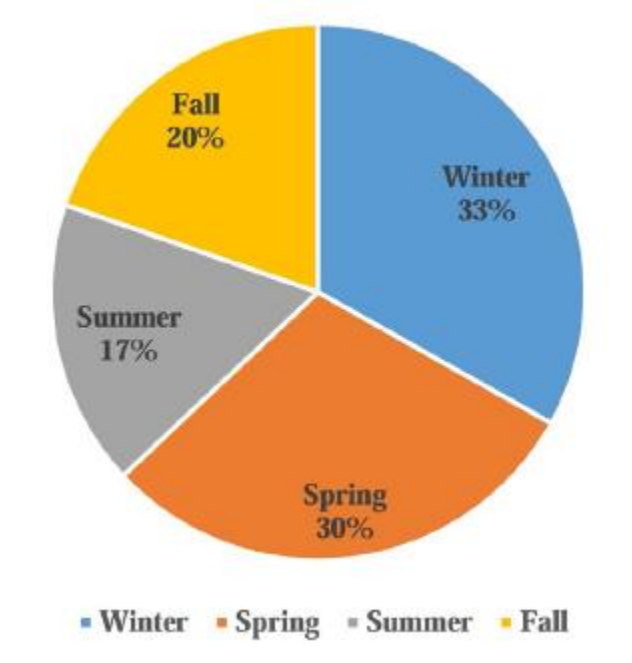


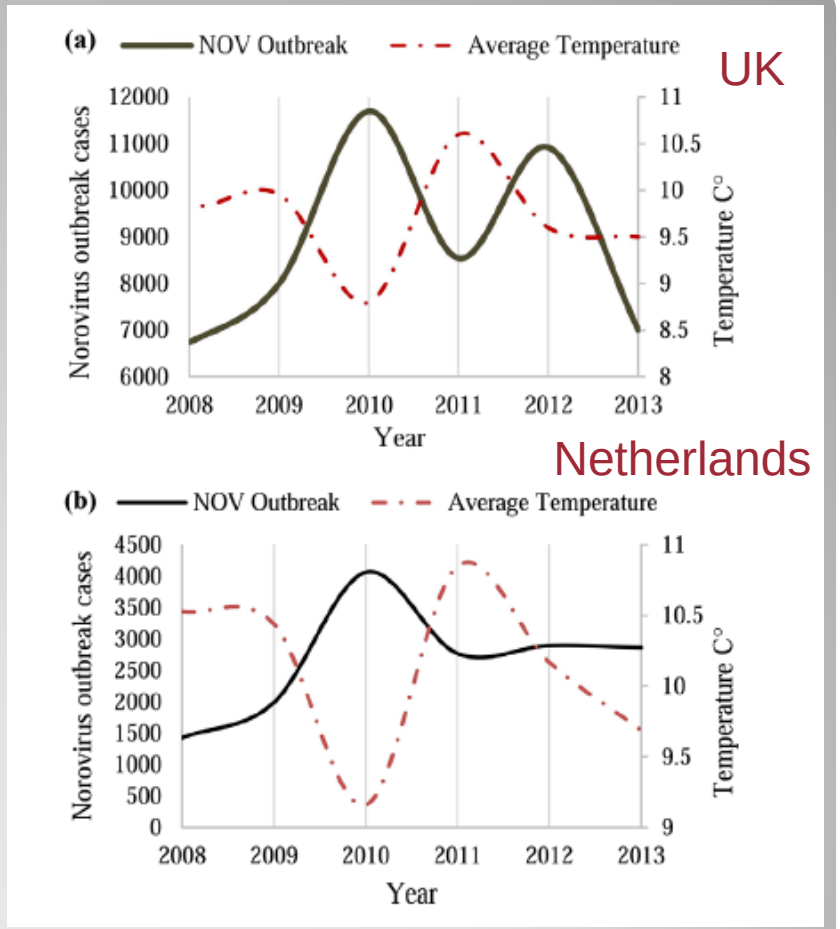
FIGURE 2. Norovirus associated deaths in US: 1996–2008 (from [9]).

Hartono Curr Opin Allergy Clin Immunol 2016; 16: 557-64

Karst J Virol 89: 5756-9



Foodborne NoV outbreaks, USA

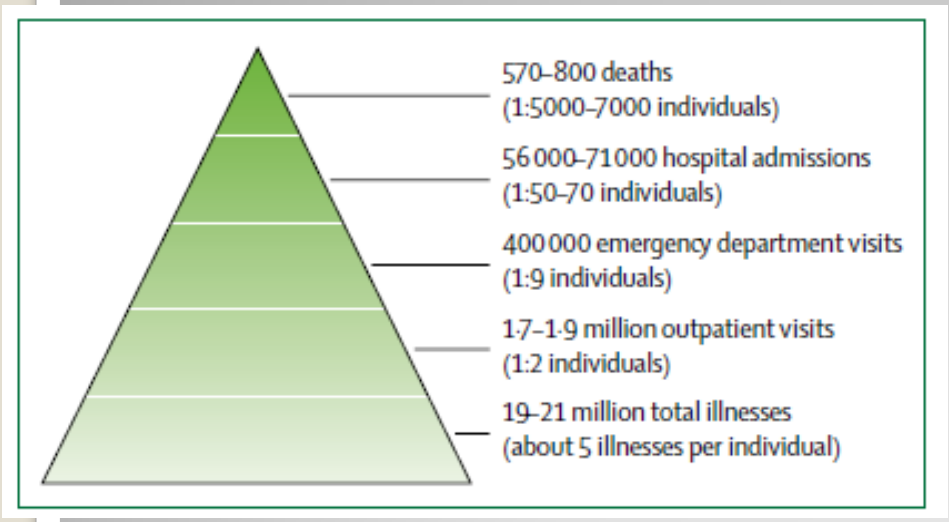


Environmental indicators for norovirus outbreaks

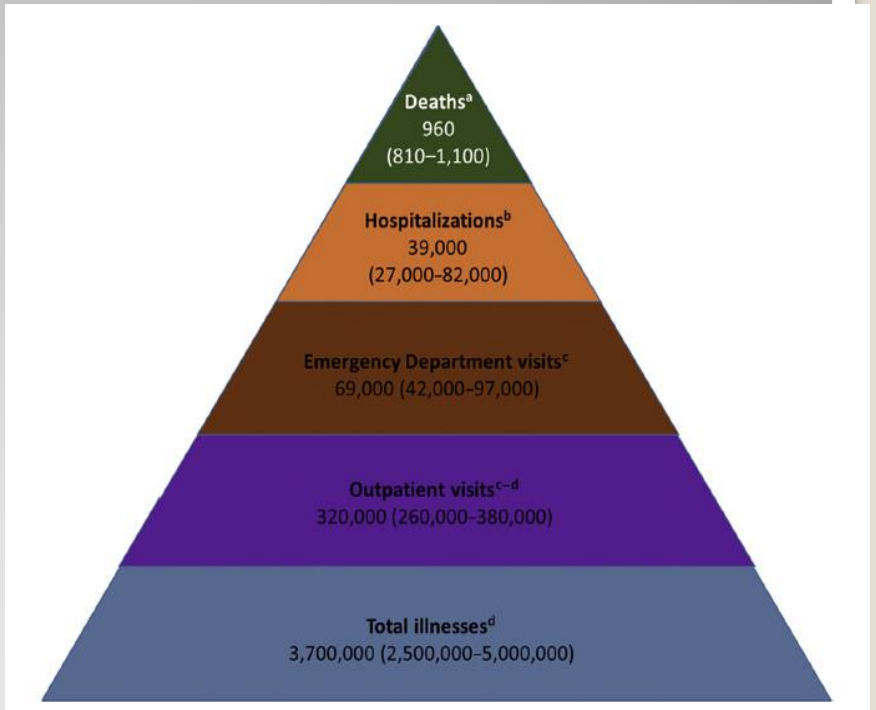
Shamkhali Chenar Int J Environ Health Res 2017; 27: 40-51

Ballard Curr Opin Infect Dis 2015; 28: 408-16

Norovirus burden



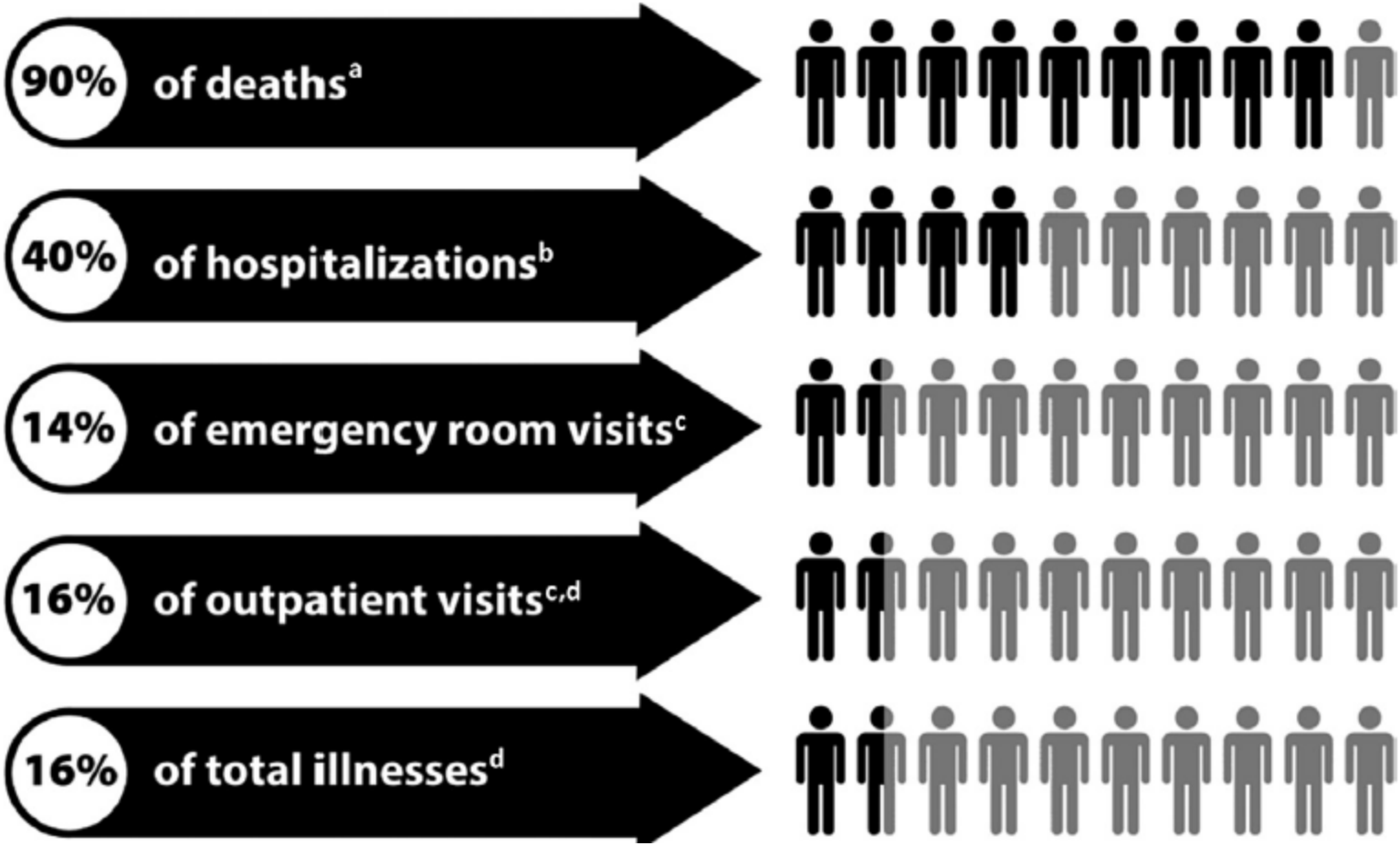
Adults >65 years



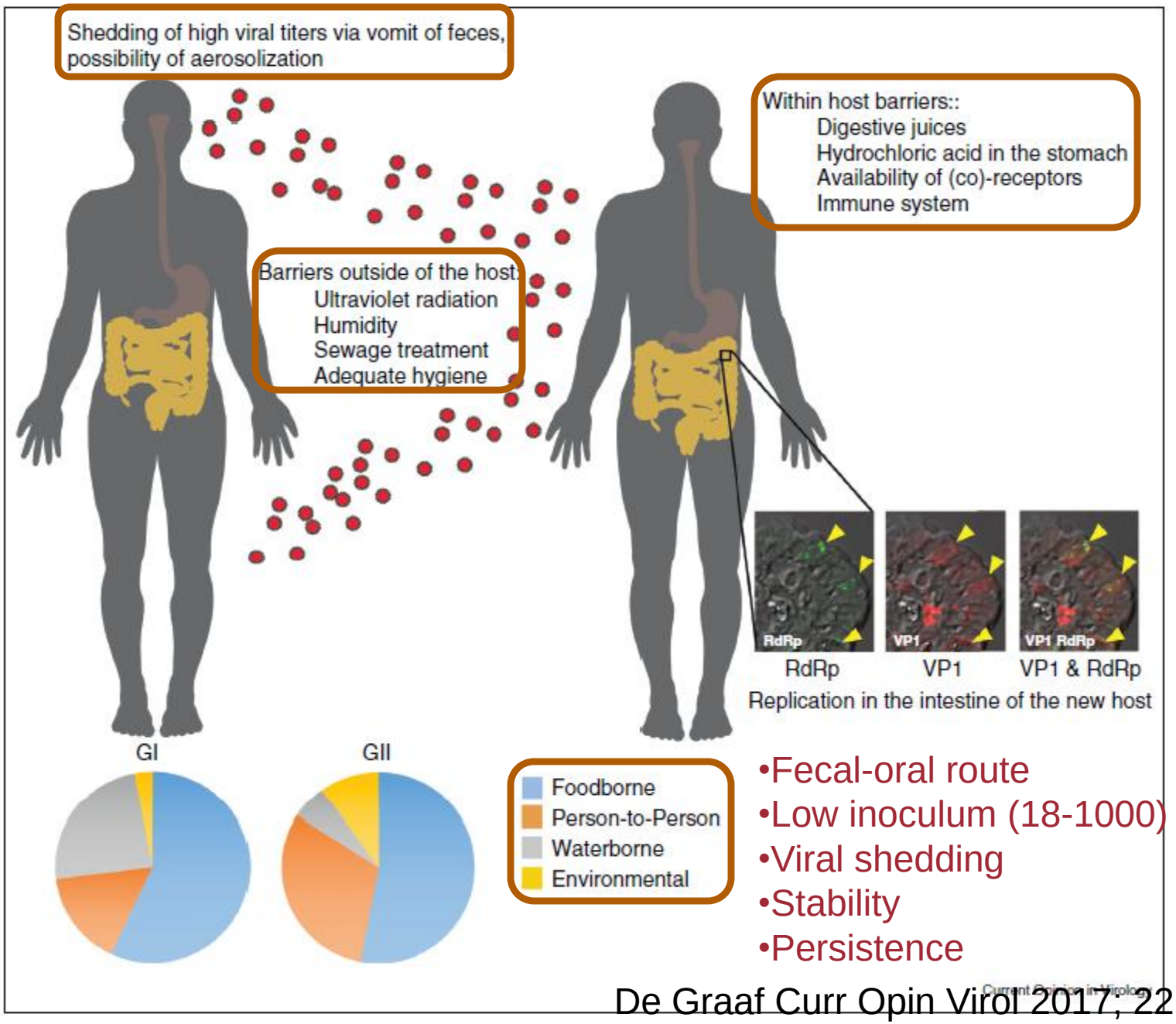
Norovirus is 2nd only to Cdiff as a cause of death in adults >65 years old

Cardemil Infect Dis Clin N Am 2017; 839-70
Banyai Lancet 2018; 392: 175-86
Hall Clin Infect Dis 2012; 55: 216-23
Fisher Curr Opin Infect Dis 2017; 30

Proportions of annual norovirus burden in US in adults>65 years



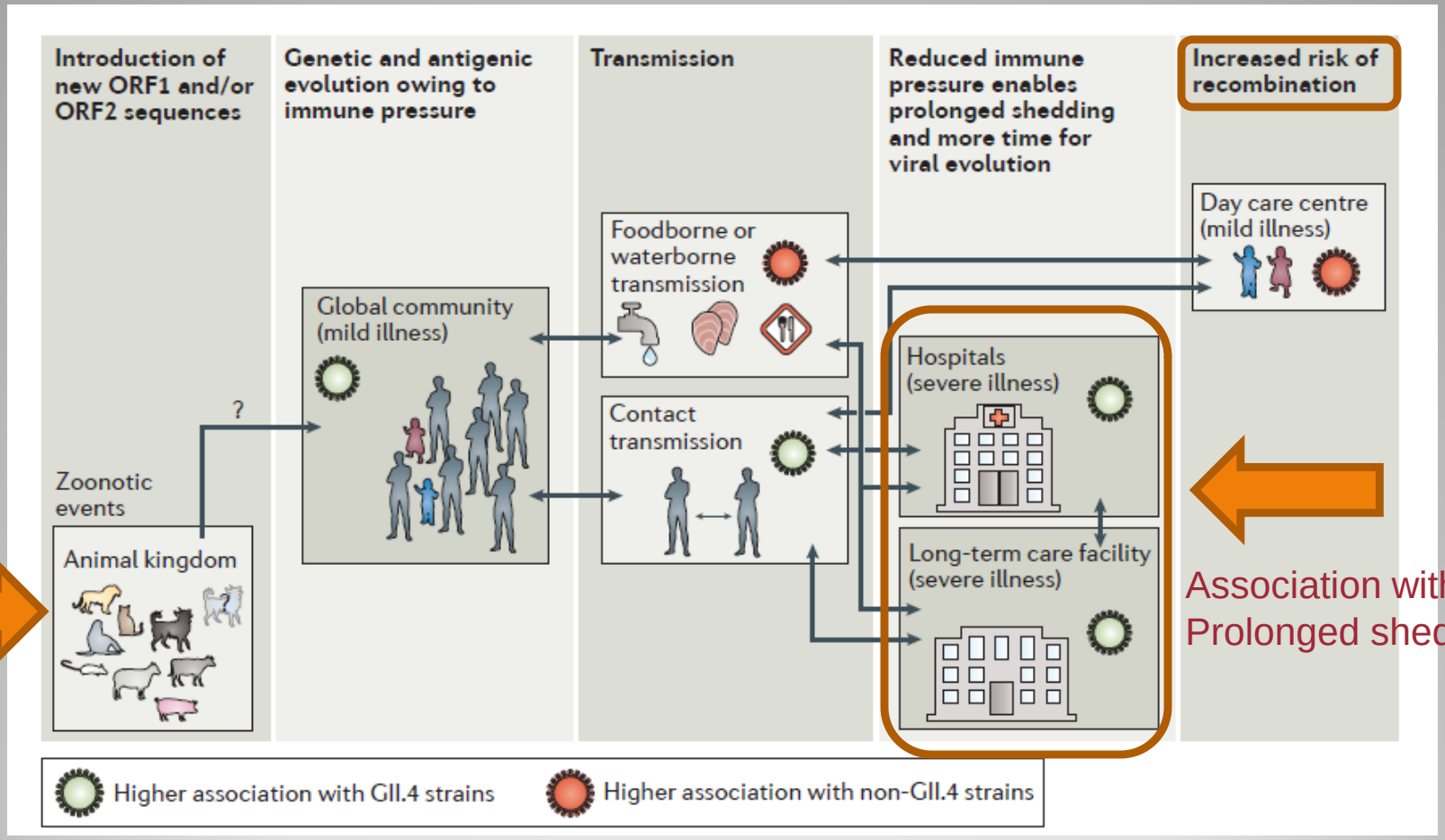
Cardemil Infect Dis Clin N Am 2017; 839-70



- Fecal-oral route
- Low inoculum (18-1000)
- Viral shedding
- Stability
- Persistence

De Graaf Curr Opin Virol 2017; 22: 64-70

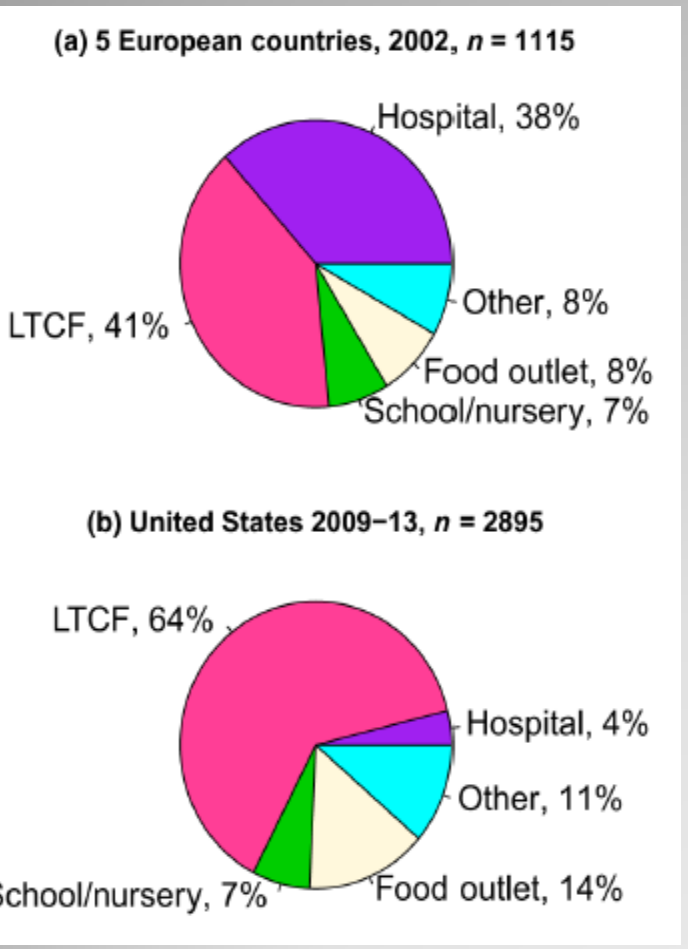
Hall J Infect Dis 2012; 205: 1622- 24

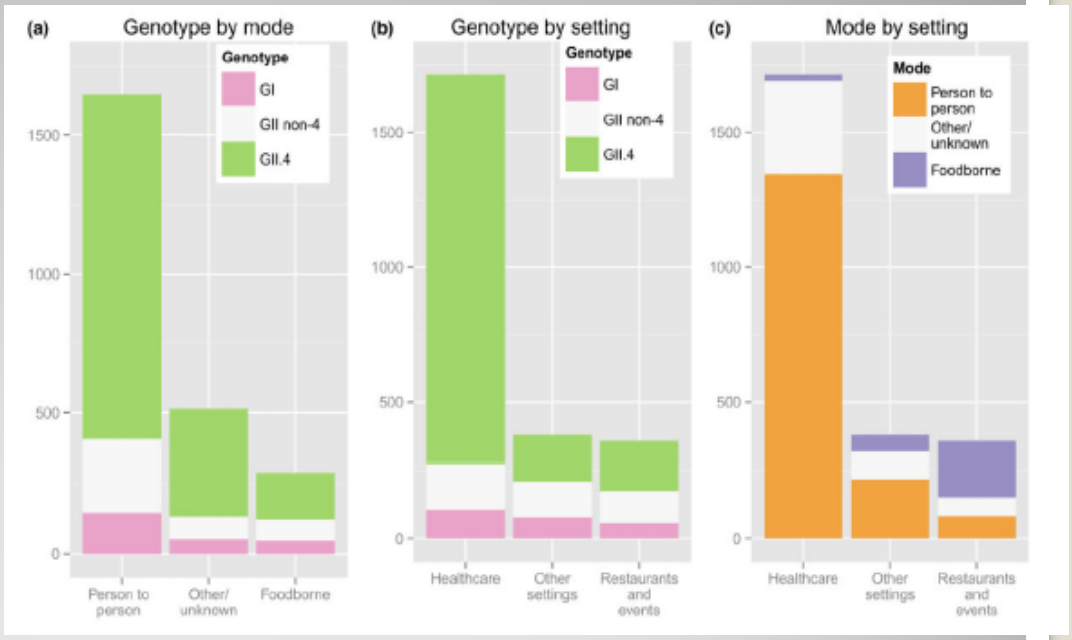


Association with GII.4
Prolonged shedding

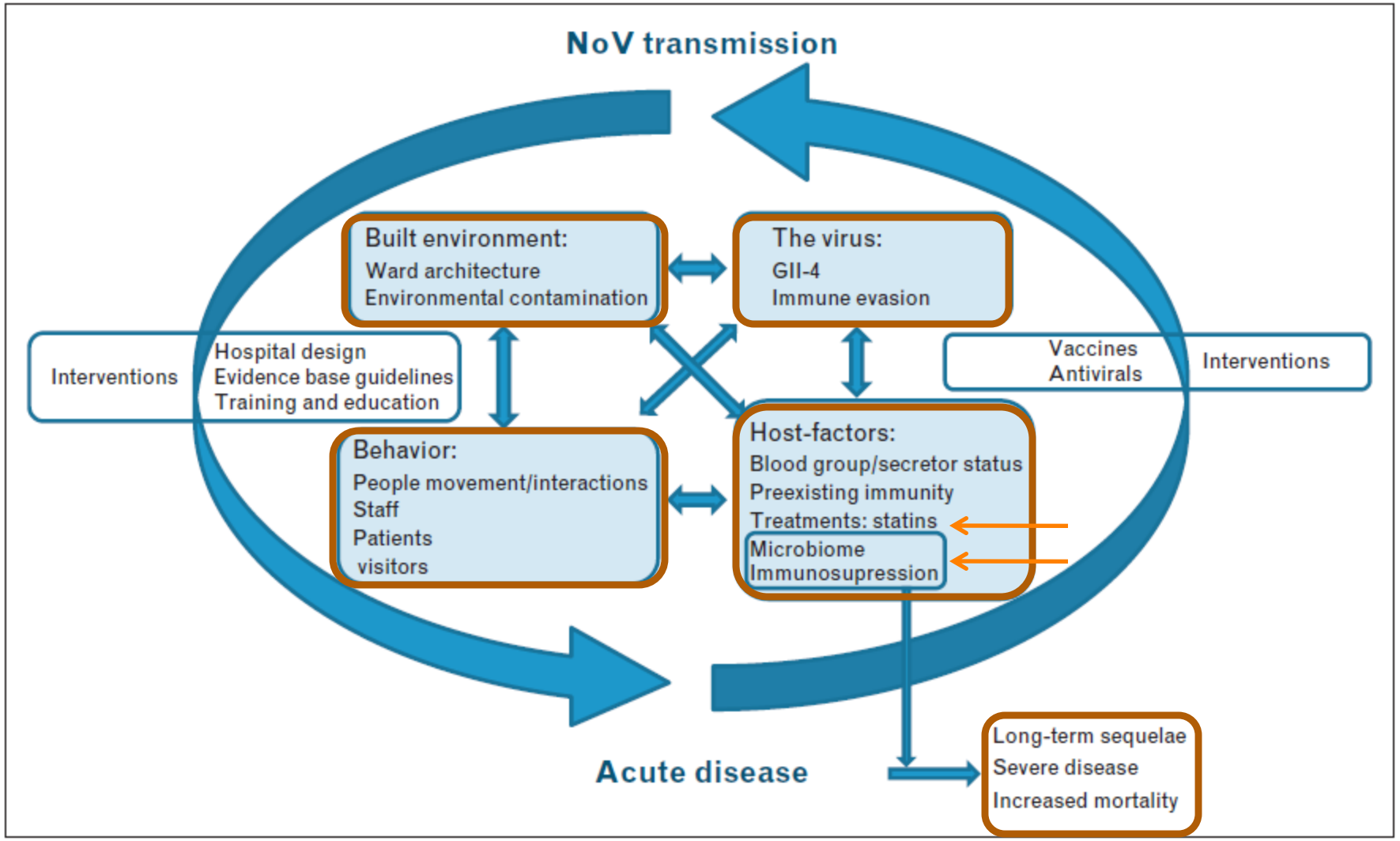
Norovirus epidemiology in the community

De Graaf M Nat Rev Microbiol 2016; 14: 421-33

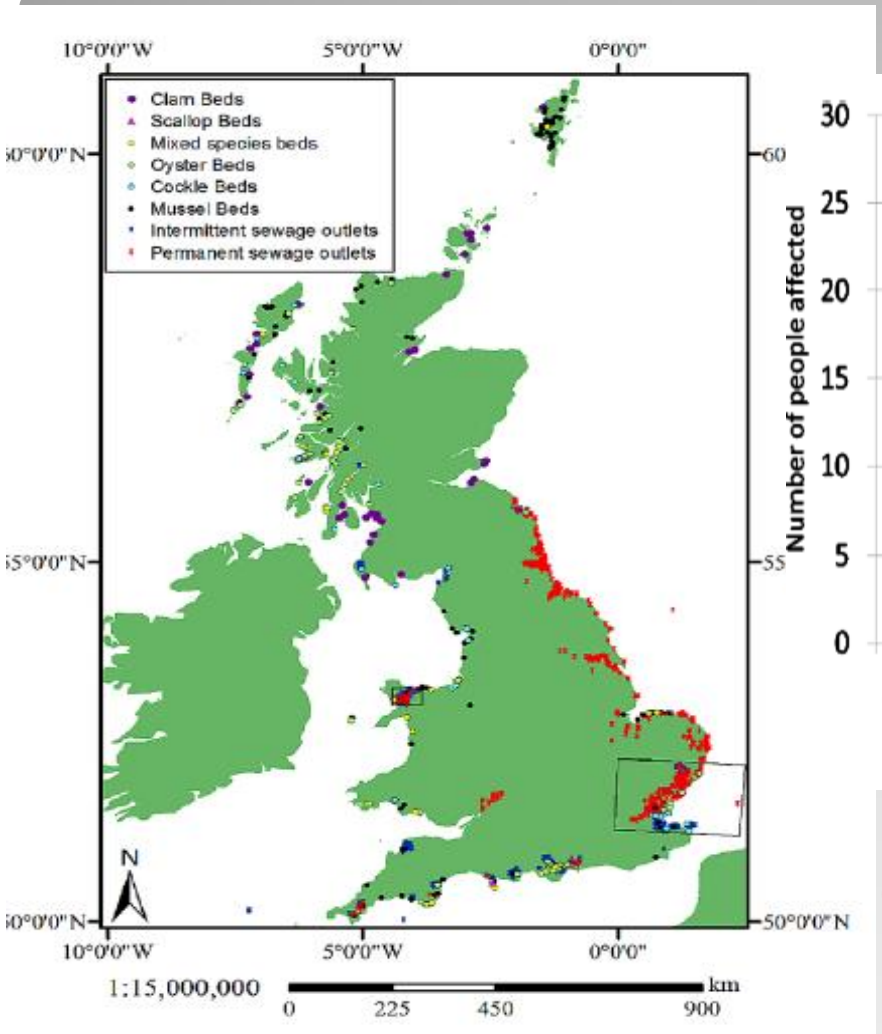


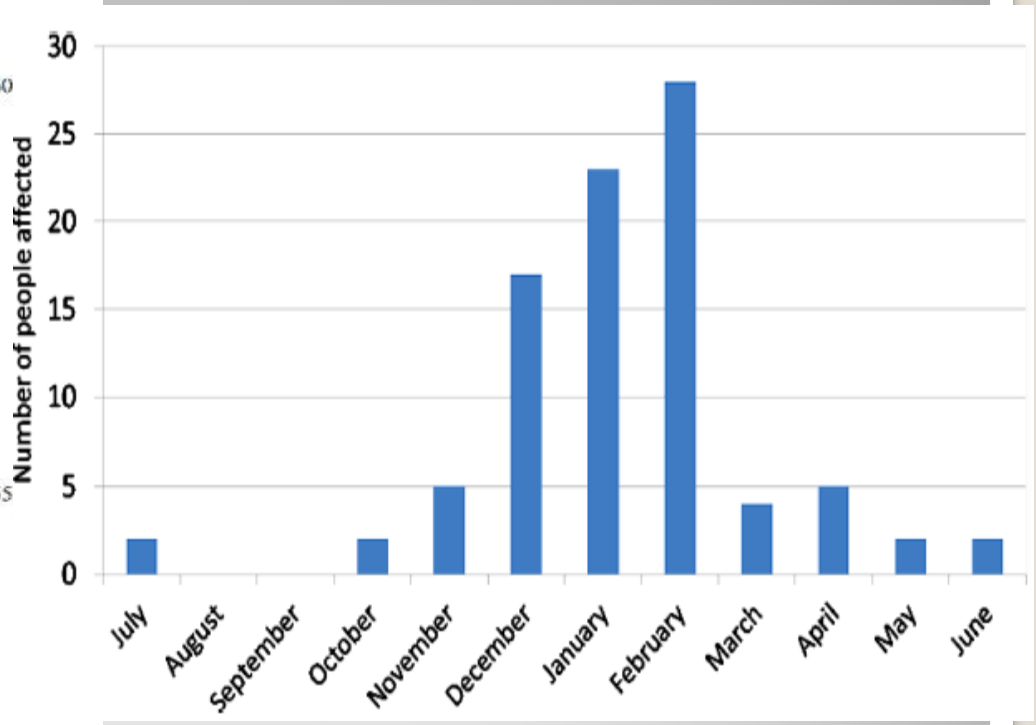


Barclay Clin Microbiol Infect 2014; 20: 731-40



Iturriza-Gomara Curr Opin Infect Dis 2014; 27: 437-43

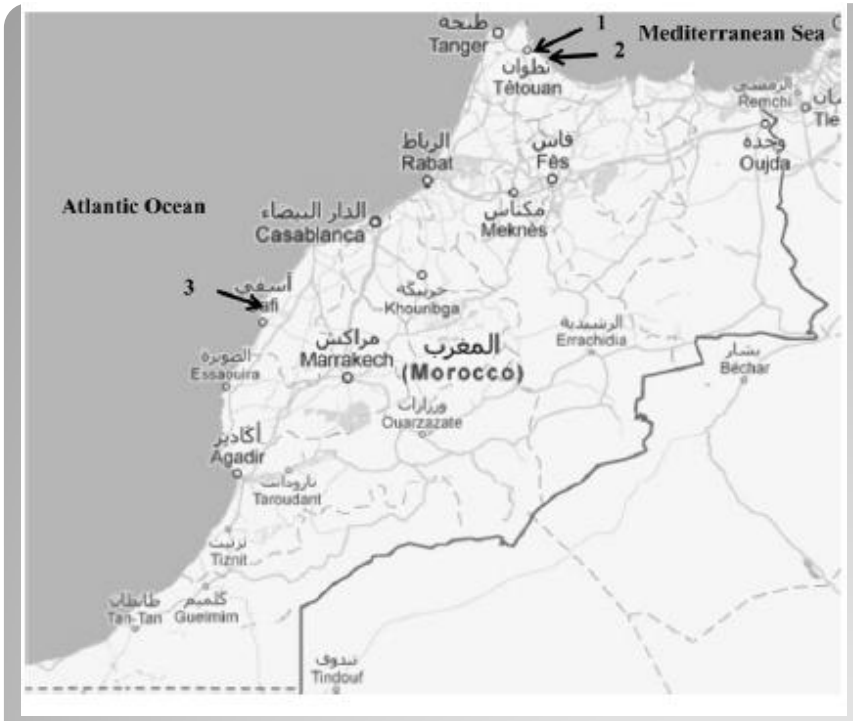




Oyster consumption and NoV infections

Norovirus contamination in shellfish and the environment

Hassard Food Environ Virol 2017; 9: 123-41

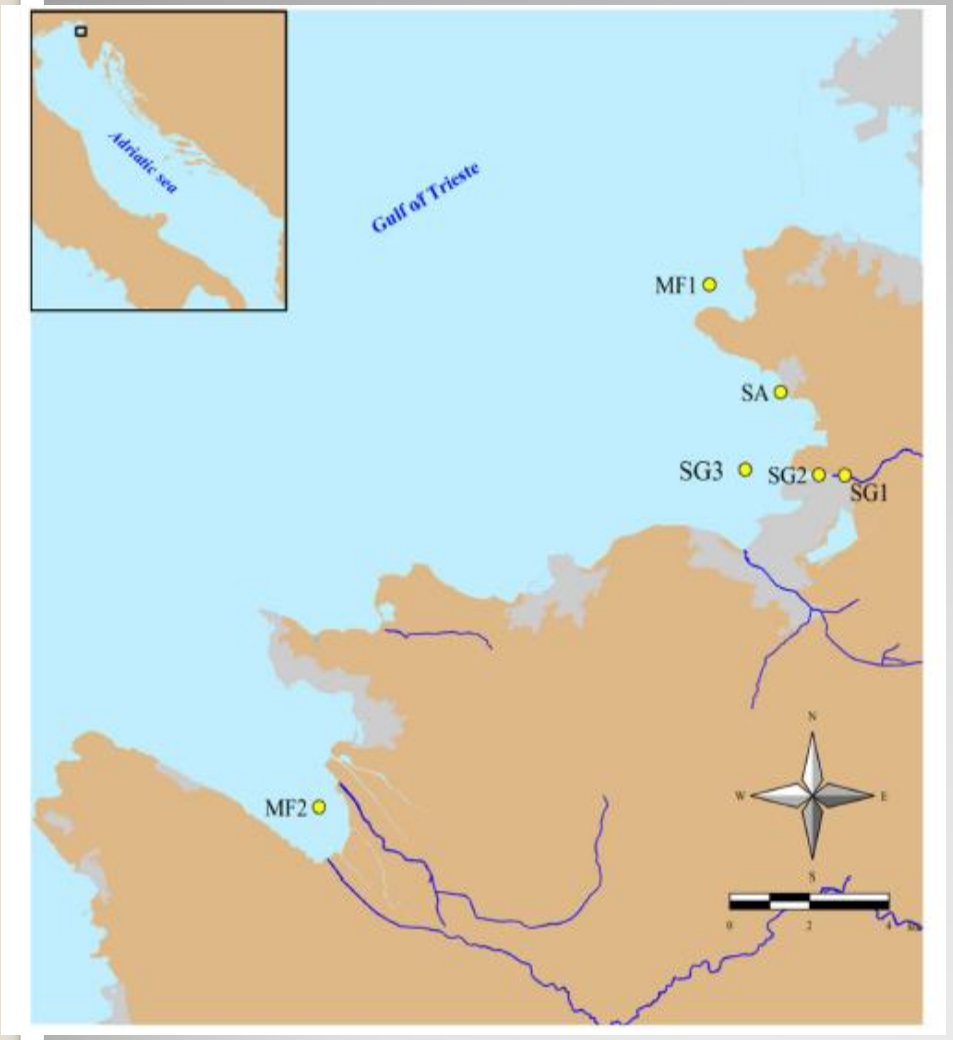


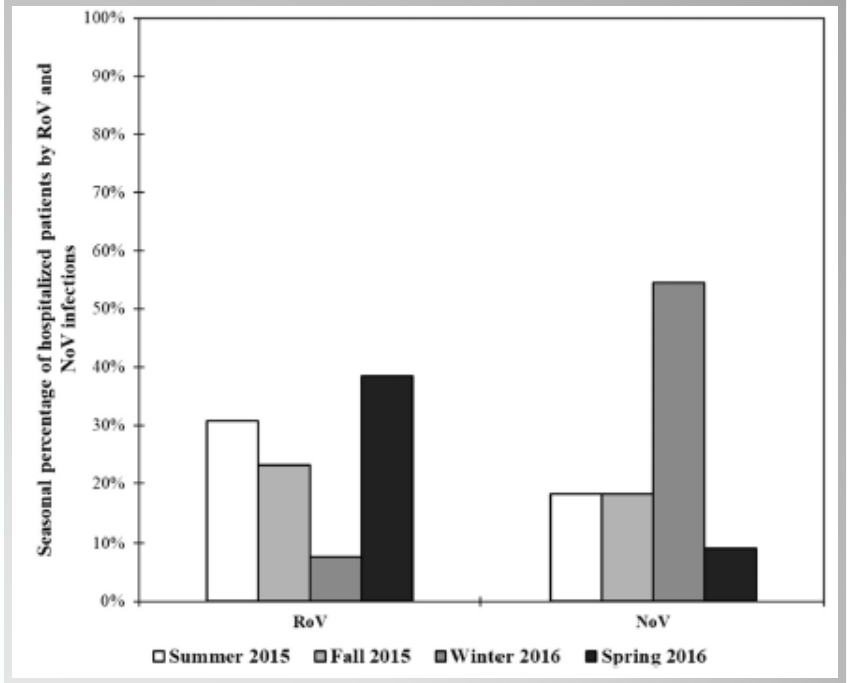
- AdV in 20% of mussels samples in Casablanca
- Tunisia: NoV in in 35% of mussels
- Italy- clams (mussels of concern)
- Galicia- all clams
- Tunisia: clams

•NoV detected in 30% of samples (Clams>oysters)
•SaV detected in 13% (oysters and clams)

Norovirus and other enteric viruses in shellfish

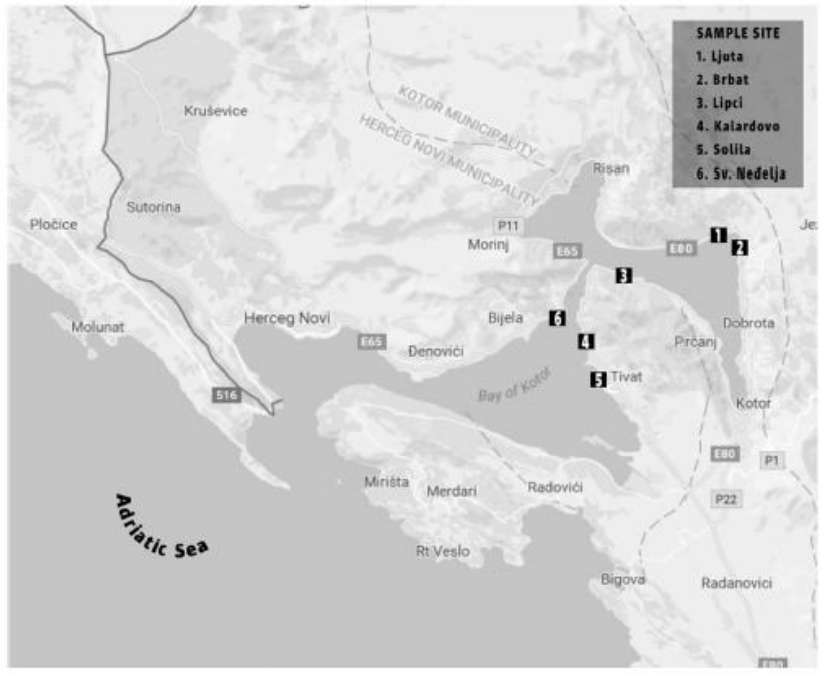
Benabbes Food Environ Virol 2013; 5: 35-40
Fusco Food Environ Virol 2017; 9: 187-94
Pavoni Foodborne Pathog Dis 2013; 10: 533-9





Contamination in Slovenia

Gonsalves Marine Pollution Bulletin 2018; 128: 307-17



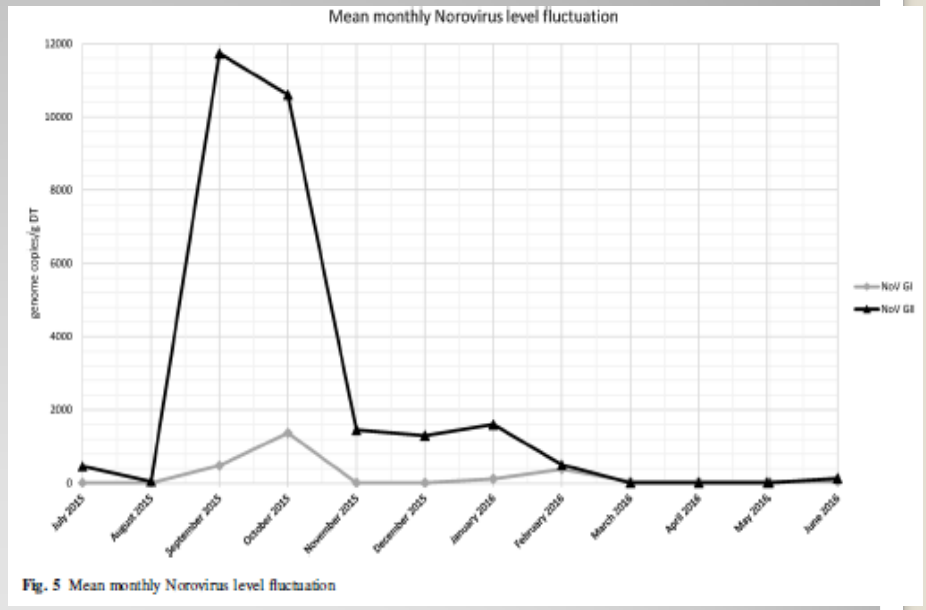
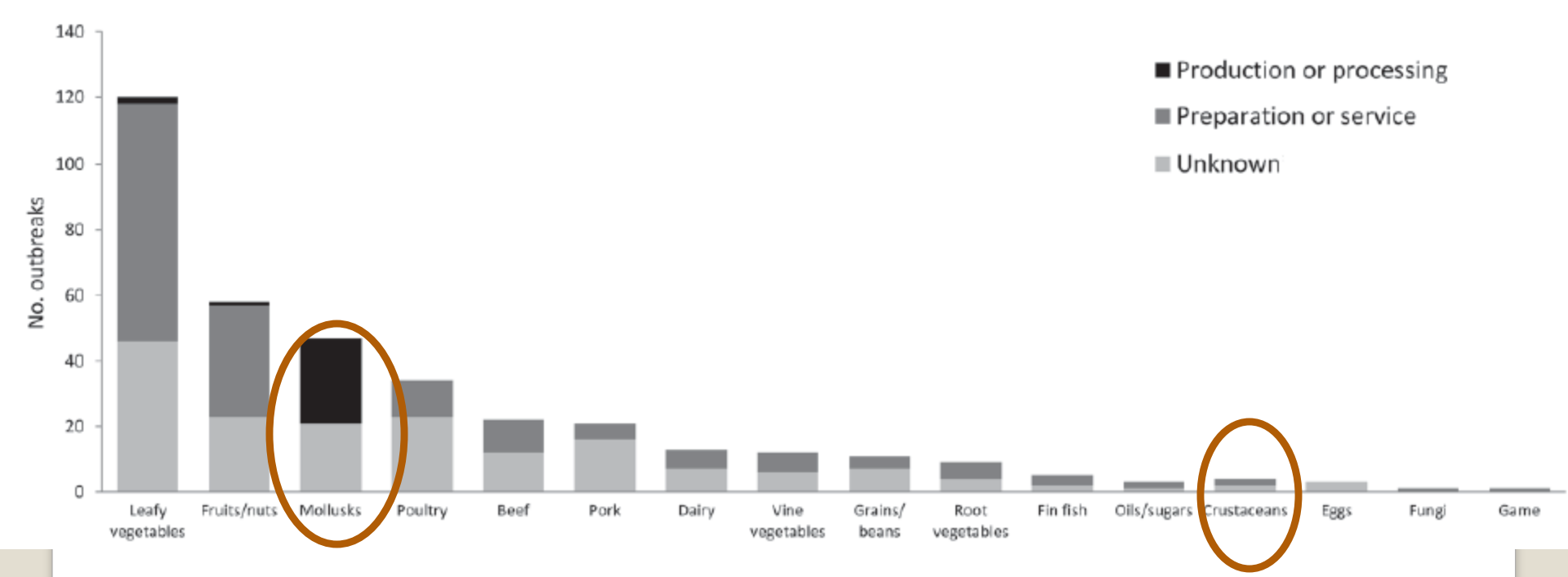


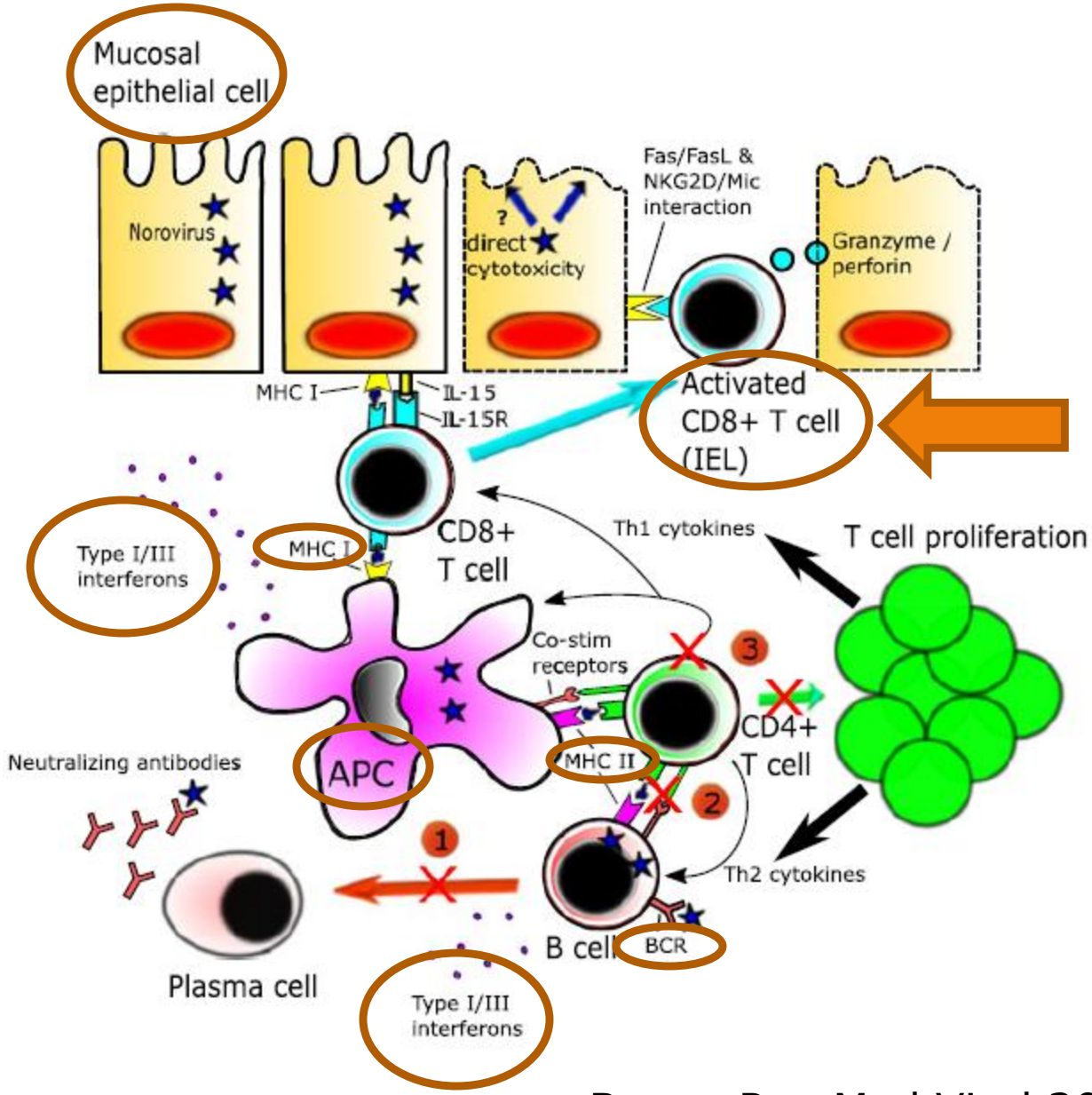
Fig. 5 Mean monthly Norovirus level fluctuation

Contamination in Montenegro

Ilic Food Environ Virol 2017;



Hall Emerg infect Dis 18: 1566-73



Brown Rev Med Virol 2017; e1926
Roth Curr opin Virol 2016; 16: 24-30

Clinical presentation

- Asymptomatic infection to severe dehydrating diarrhea
- Carriage up to 50%
- Incubation 24-72h
- Non-bloody diarrhea and vomiting
- Nausea, abdominal cramps, fever
- Headache, myalgia, malaise
- Self-limited recovery within 2-5 days
- Different story in immunocompromised

Table 1
Laboratory methods for detection of norovirus

Method	Characteristics	Availability	Use in Clinical Setting?	Use in Outbreak Setting?
Conventional RT-PCR, real-time RT-PCR	• Gold standard test • High sensitivity • Frequently detects specimen in asymptomatic and healthy patients	Public health and reference laboratories	Not widely[a]	Yes
Multiple enteric pathogen tests (xTAG GPP, FilmArray gastrointestinal panel, and Verigen Enteric Pathogens Test)	• Detects multiple viral, bacterial, and parasitic pathogens simultaneously • High sensitivity • Expensive	Public health and clinical laboratories	Yes	Yes
Enzyme immunoassay, immunochromatographic	• Low sensitivity, high specificity	Public health and clinical laboratories	Not recommended for individual patients	Yes, for rapid screening of multiple samples
Electron microscopy	• Detect multiple viral pathogens • Low sensitivity • Expensive	Reference laboratories	No	No

Calicivirus (norovirus, sapovirus)[k]; enteric adenovirus; enterovirus/parechovirus[k]; rotavirus	NAAT	Stool
Rotavirus, enteric adenovirus	EIA	Stool
Enteric adenovirus[l]; enterovirus/parechovirus	Viral culture	Stool

Cardemil Infect Dis Clin N Am 2017; 839-70
Shane Clin Infect Dis 2017; 65: e45-80
Buss J Clin Microbiol 2015; 53: 915-25

Table 1 Current FDA approved molecular testing platforms for the diagnosis of norovirus

Test/manufacturer	Testing platform	FDA approval	Turnaround time (TAT)	Sensitivity (%)	Specificity (%)
xTAG Gastrointestinal Pathogen Panel (GPP) Luminex Molecular Diagnostics, Inc. [32]	RT-PCR multi-pathogen panel (11 analyte targets including Norovirus I and II)	2013	<6 h	100 (71.8–100)[a]	90.8 (86.2–94)[a]
Xpert Norovirus Cepheid [33]	RT-PCR for Norovirus I and II	2014	1 h	98.5 (91.7–100)[b]	98.8 (97.8–99.4)[b]
Bio Fire Film Array Gastrointestinal Panel bioMérieux [32]	RT-PCR multi-pathogen panel (22 analyte targets including Norovirus I and II)	2014	1 h	91.7 (62.5–100)[a]	99.5 (97.2–100)[a]
Verigene Enteric Test Nanosphere, Inc. [34]	PCR with gold nanoparticle hybridization (9 analyte targets including Norovirus)	2014	2 h	100 (73–100)[c]	100 (99–100)[c]

Angarone Curr Infect Dis Rep 2016; 18: 17


STOP!
STOP
Is your visit necessary?


STOP!
NOROVIRUS
which causes gastro-enteritis
is circulating in the community


STOP THE SPREAD OF NOROVIRUS
Norovirus (commonly known as the Winter Vomiting Bug) is a highly contagious infection that causes sickness and diarrhoea.
RECOGNISE IT
Norovirus will cause a sudden onset of diarrhoea and/or vomiting which can last between 24 and 72 hours. Some people may have a raised temperature, headaches and aching limbs.
AVOID IT
Wash your hands regularly with soap and water, especially after using the toilet and before preparing and eating foods. Dry your hands thoroughly each time.
CONTAIN IT
DO NOT visit hospitals or your GP if you develop symptoms of Norovirus. Call NHS Non-emergency number 111 or call your GP for advice. Drink plenty of fluids to avoid dehydration.
STOP IT
Stay at home for at least 48 hours after the last episode of vomiting or diarrhoea to reduce the risk of passing the virus to others.
DON'T GIVE NOROVIRUS A CHANCE!
PRESTON'S COLLEGE


Around half of those exposed to norovirus will also become sick.
That's a 50% attack rate.
Don't spread it. If you get ill, stay at home.
#NoToNorovirus www.nhsinform.scot/norovirus
healthier scotland


Diarrhoea and sickness
Norovirus
stop the spread
• Stop the spread - wash your hands
• Keep it to yourself - stay at home until you are symptom-free for at least 48 hours
• Get advice - visit www.choosewellcumbria.co.uk
NHS
Cumbria
Clinical Commissioning Group

- Patient cohorting and isolation precautions
- Healthcare personnel who have recovered from recent suspected norovirus infection may be the best suited to care for the patients
- Hand hygiene
- PPE (gown, gloves, face masks)
- Environmental cleaning

Key infection control recommendations for the control of norovirus

Kambhampati J Hosp Infect 2015; 89: 296-301

- Patient transfer and ward closure
- Personnel leave
- Visitors
- Necessary stool diagnostic studies

Key infection control recommendations for the control of norovirus

Kambhampati J Hosp Infect 2015; 89: 296-301

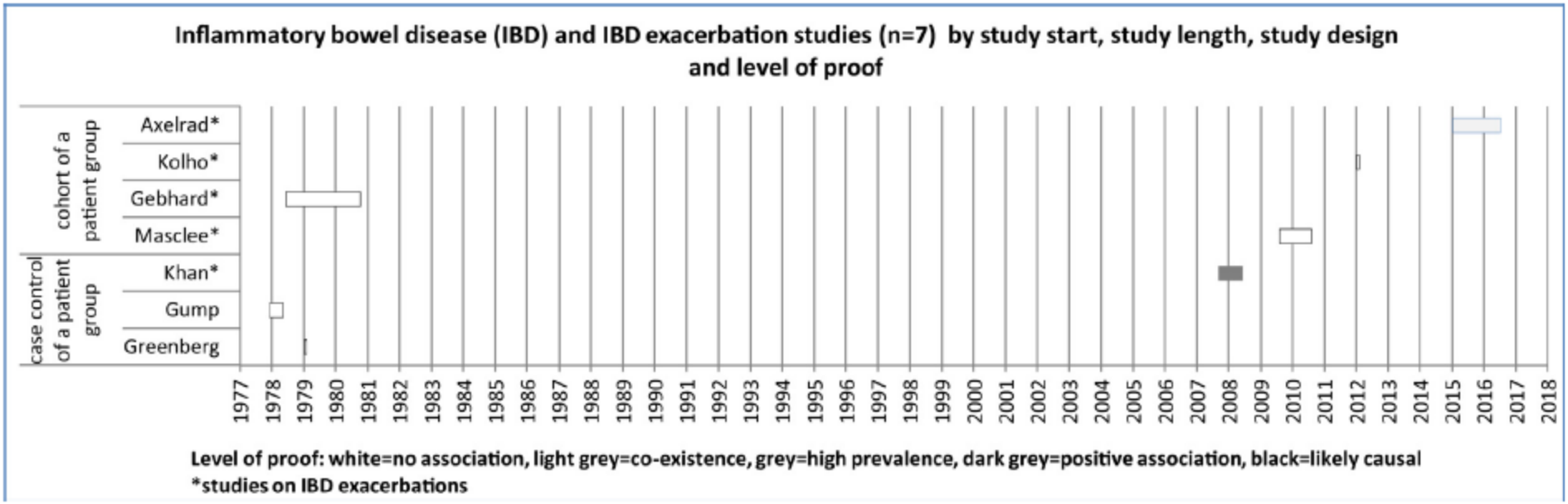
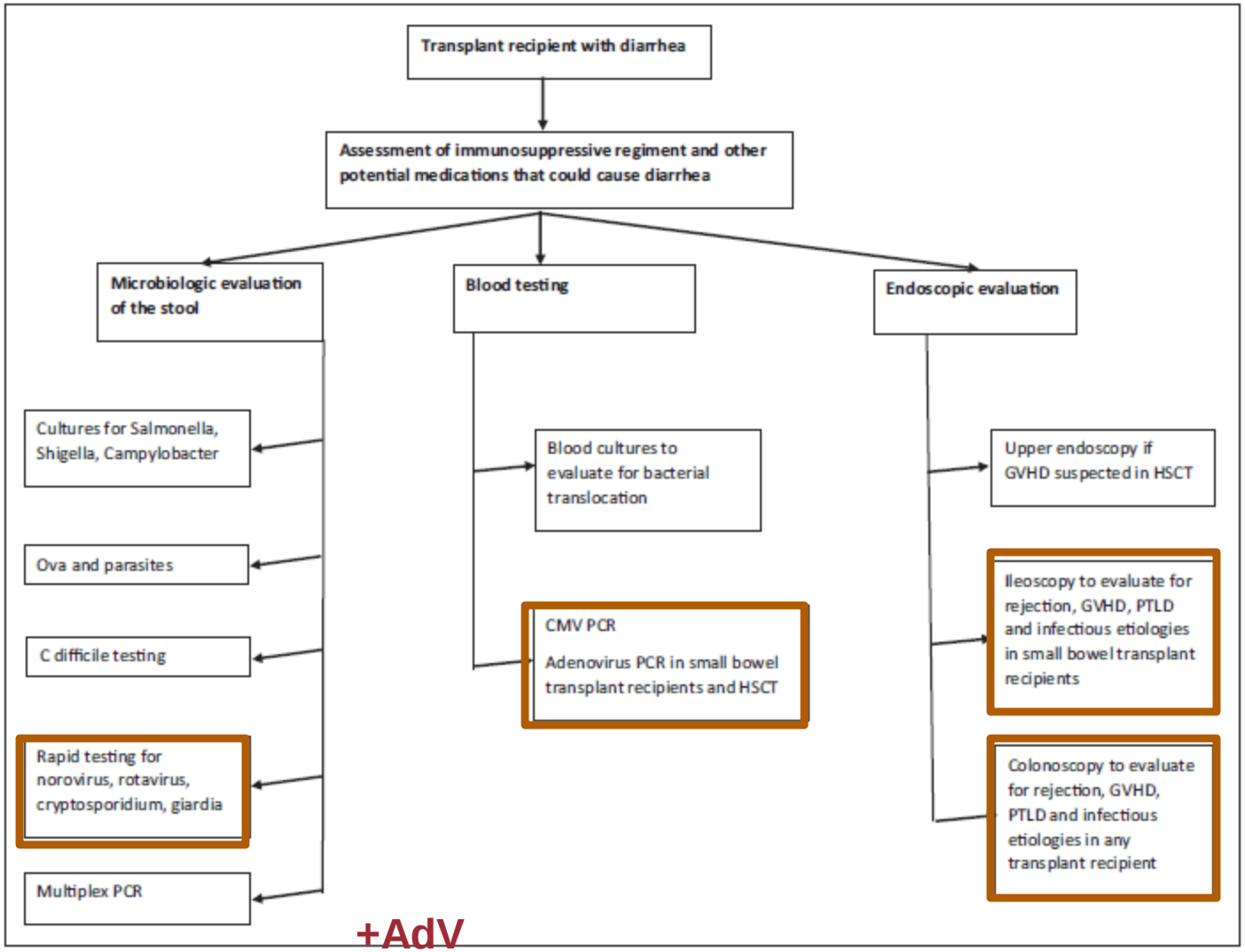


Fig. 6. IBD or IBD exacerbation studies (n = 7) by study start, study length, study design and level of proof for norovirus as a causal agent.

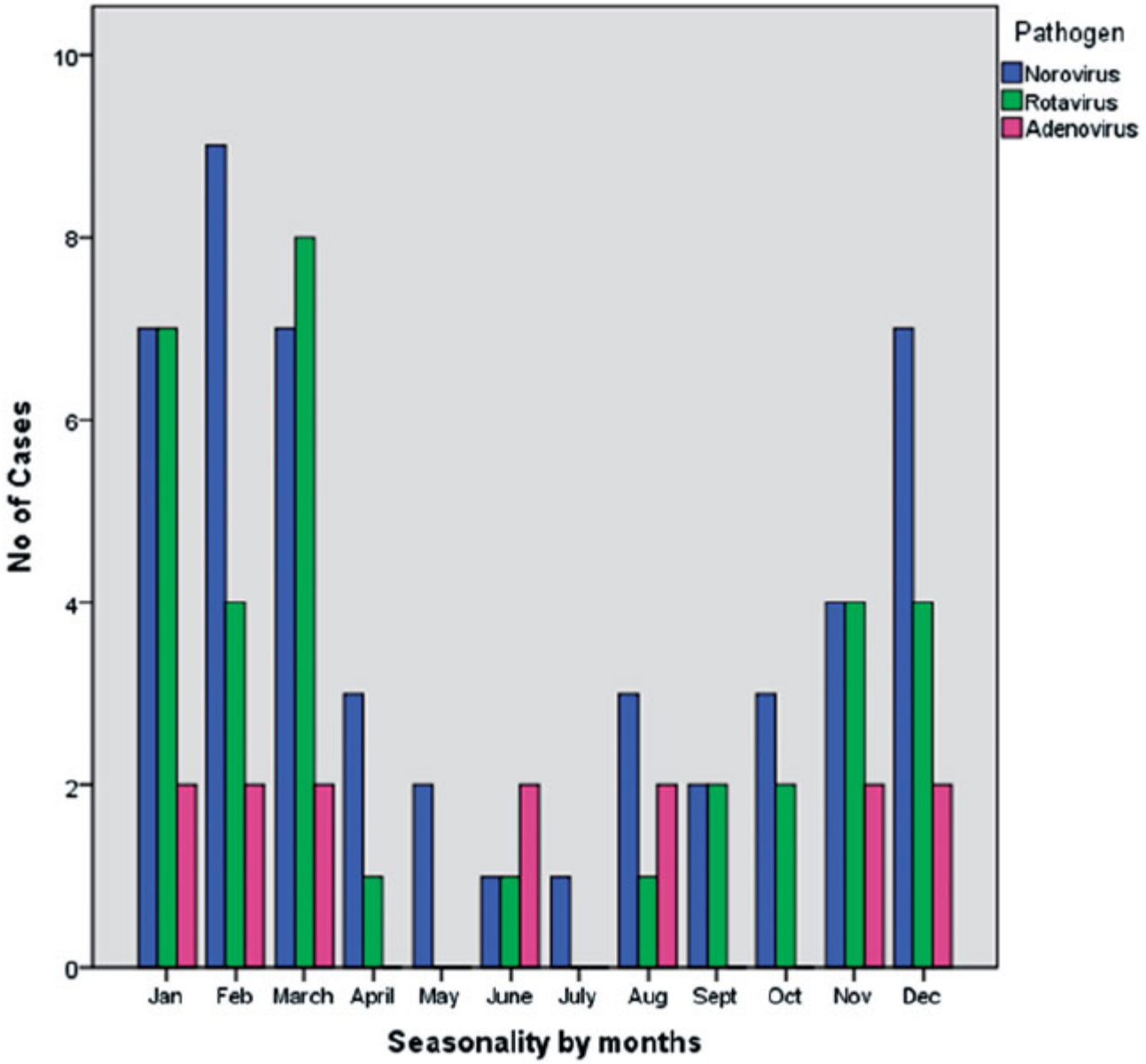
A causal relationship between IBD and NoV was not established

Petrignani J Clin Virol 2018; 105: 1-10

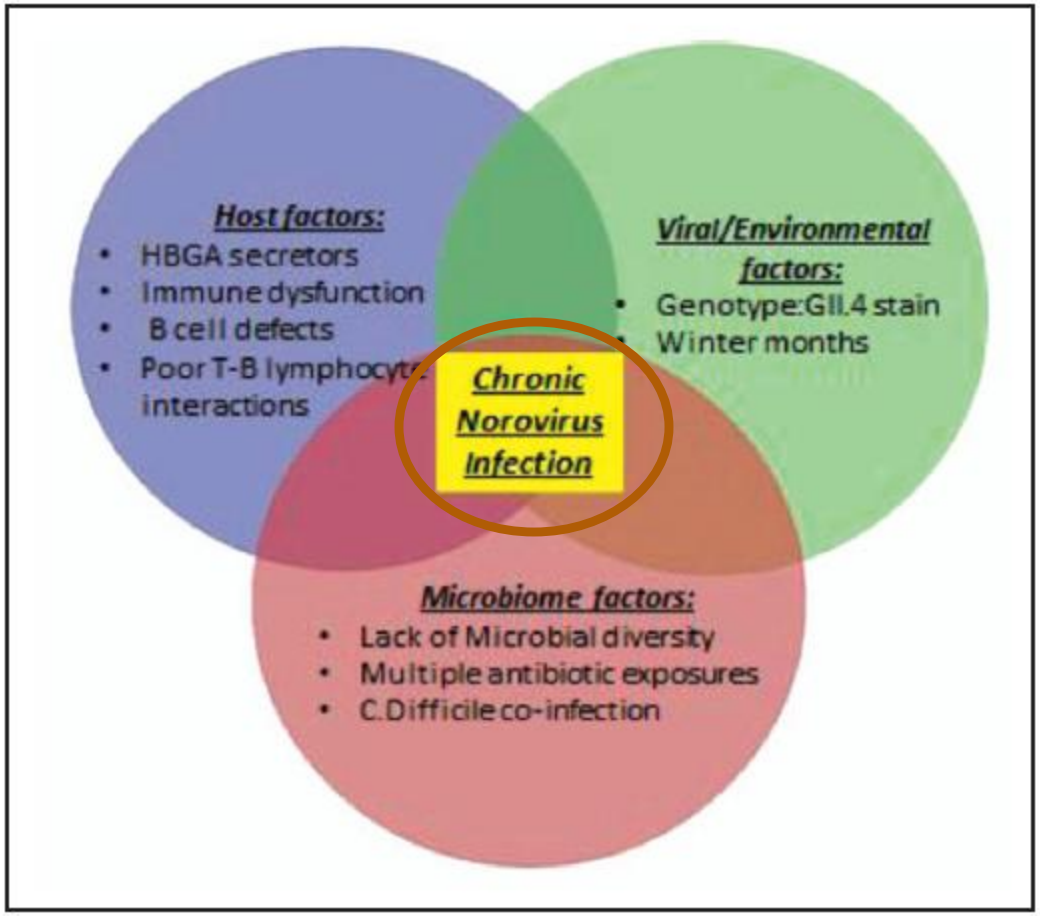


Florescu Curr Opin Crit Care 2017; 23: 364-71

Lee Transpl Infect Dis 2014; 16: 347-58

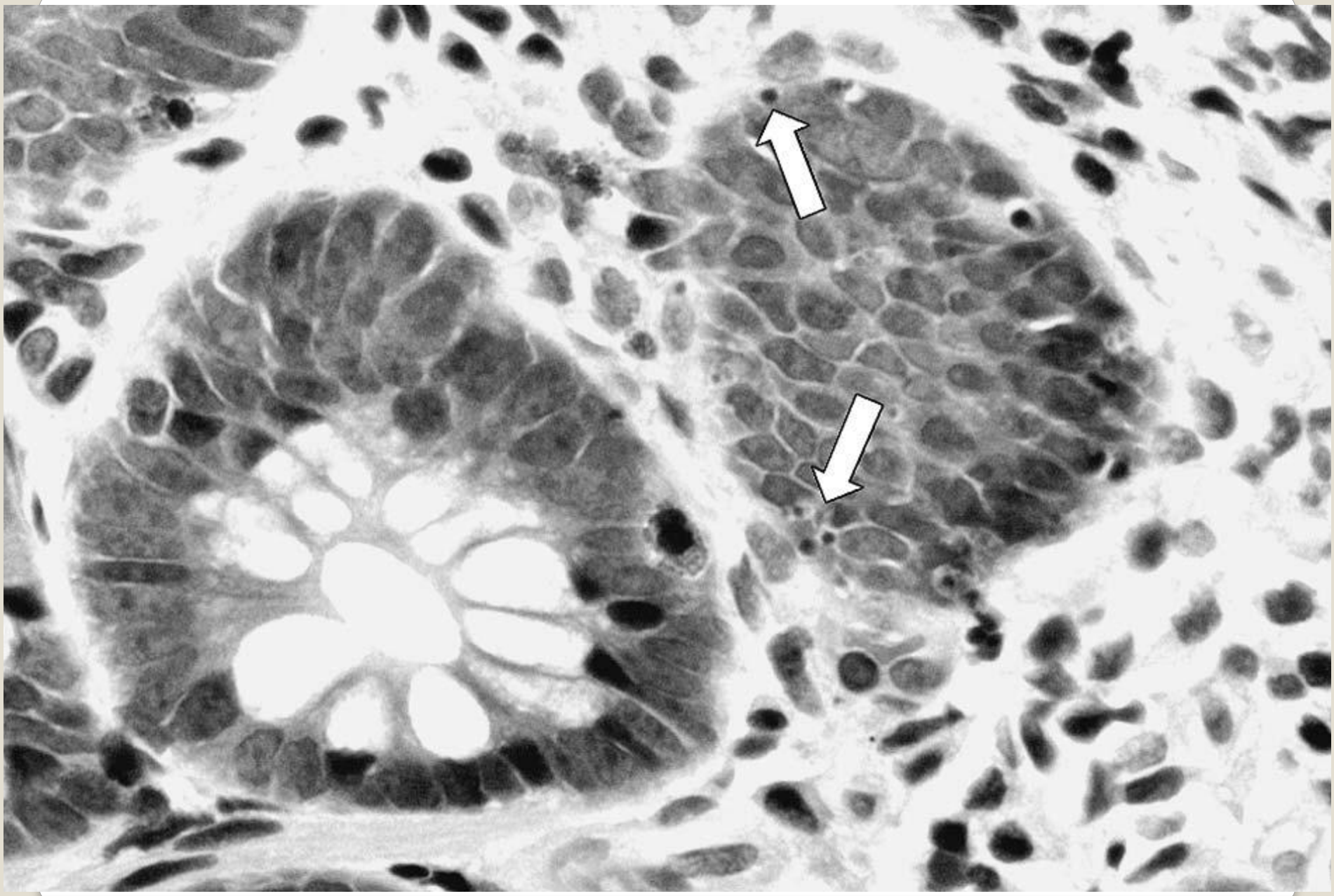


Ghosh Infect Dis (Lond) 2017; 49: 113-9

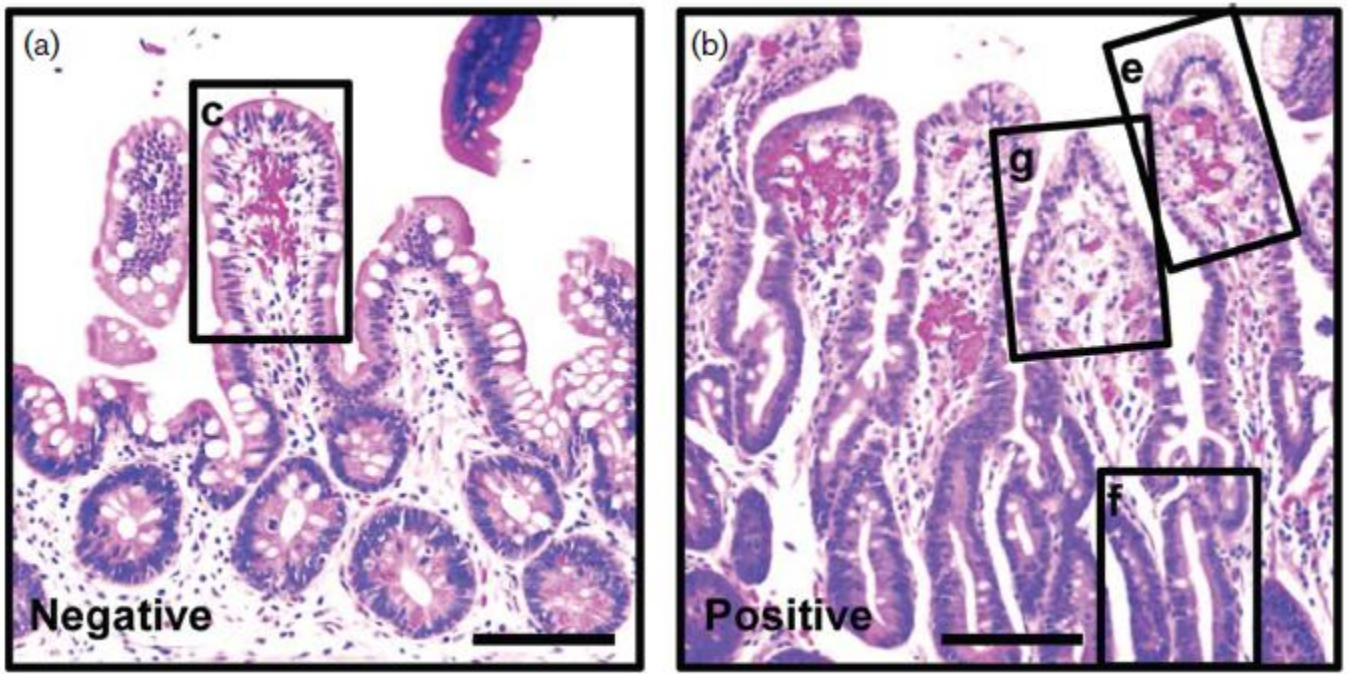


Can it be an innocent bystander?

Hartono Curr Opin Allergy Clin Immunol 2016; 16: 557-64
Angarone Curr Infect Dis Rep 2016; 18: 17
Newman Clin Exp Immunol 2016; 184: 347-57

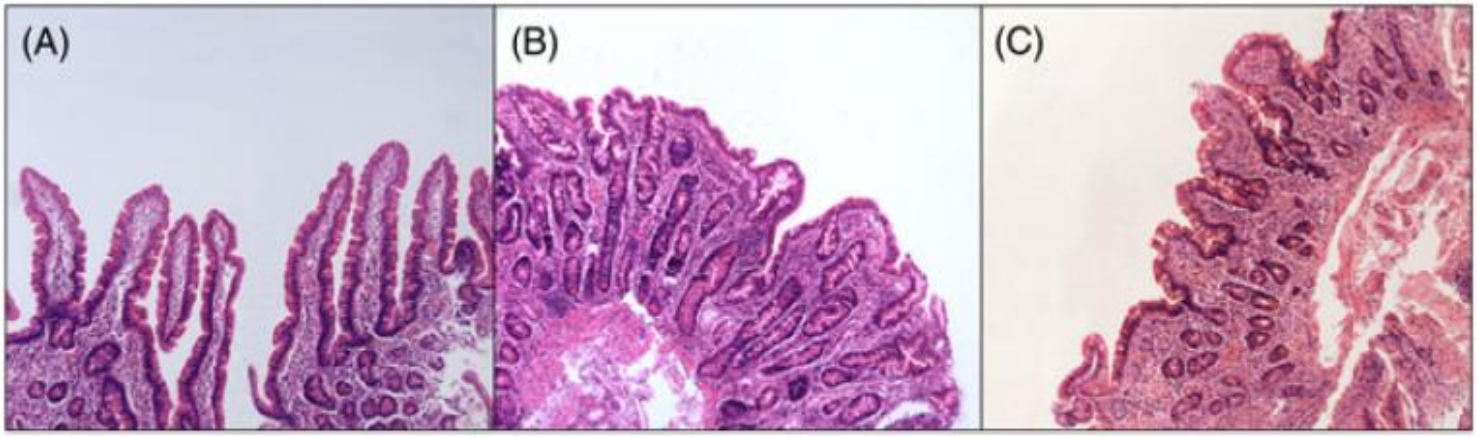


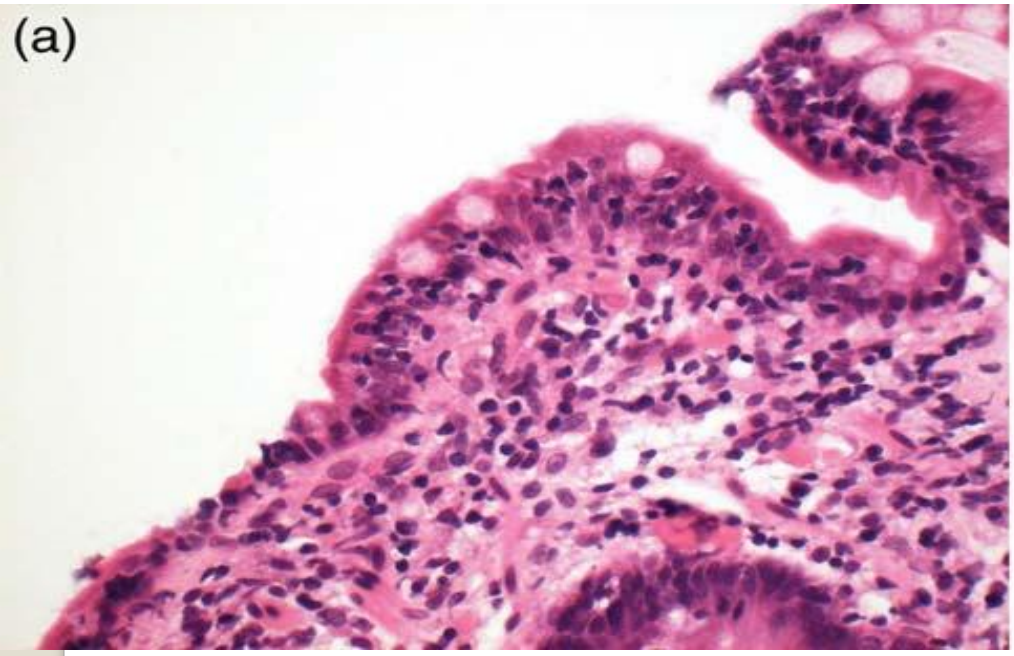
Kaufman JPGN 2005; 40: 328-33

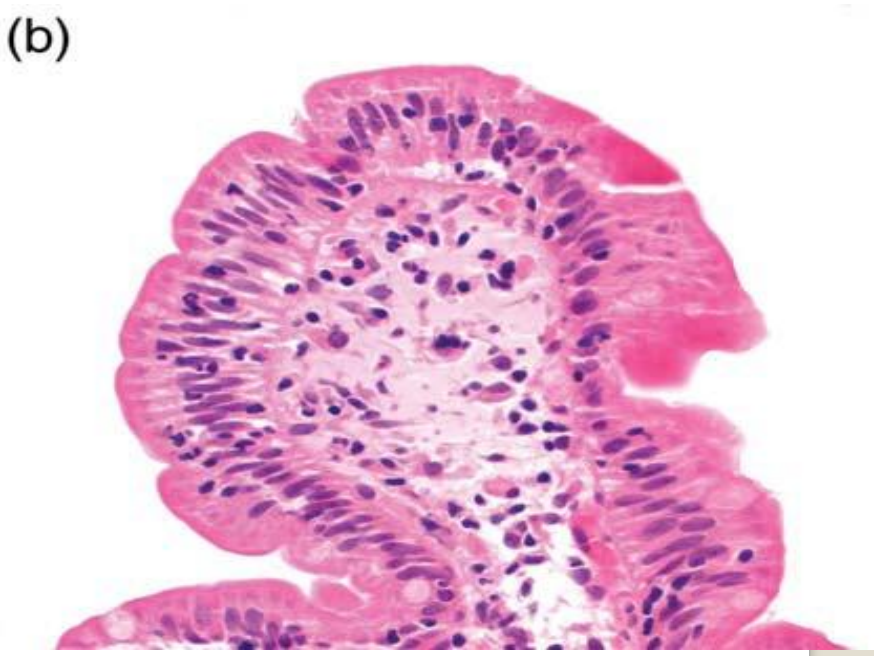


Karandikar J Gen Virol 2016; 97: 2291-300

Persistence of norovirus in common variable immunodeficiency







Brown Rev Med Virol 2017; e1926

Woodward Clin Experim Immunol 2017; 188: 353-62

Attributes of an ideal norovirus drug

Specific treatment and/or prevention of norovirus infection

Rapid onset of action

Effective when administered within 12–24 h of onset of symptoms

Oral, topical, or parenteral route of administration

One week or less duration of treatment

Virus-specific target-based mechanism of action

Nontoxic

Therapeutic safety window >10-fold

Stability at room temperature for 3 years of more

High barrier to emergence of resistance

Low cost

- Attachment, receptor binding, entry and uncoating blockers
- Protease inhibitors
- Polymerase inhibitors
- Unknown targets
- HSIG in immunosuppressed
- Norovirus vaccines

Anti-Norovirus therapeutics

Galasiti Expert Opin Ther Pat 2016; 26: 297-308
Florescu Pediatr Transplantation 2008; 12: 372-5
Ghosh Current Drug Metabolism 2018; 19: 170-91

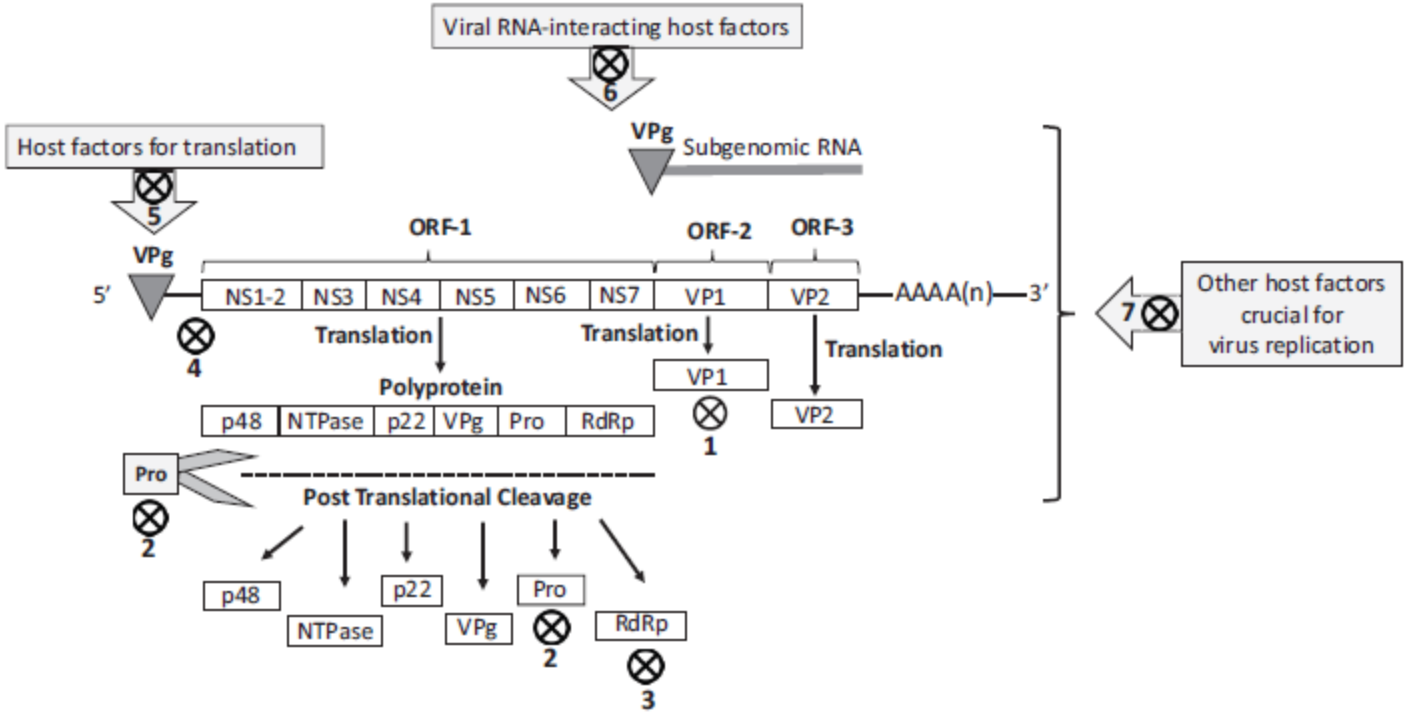
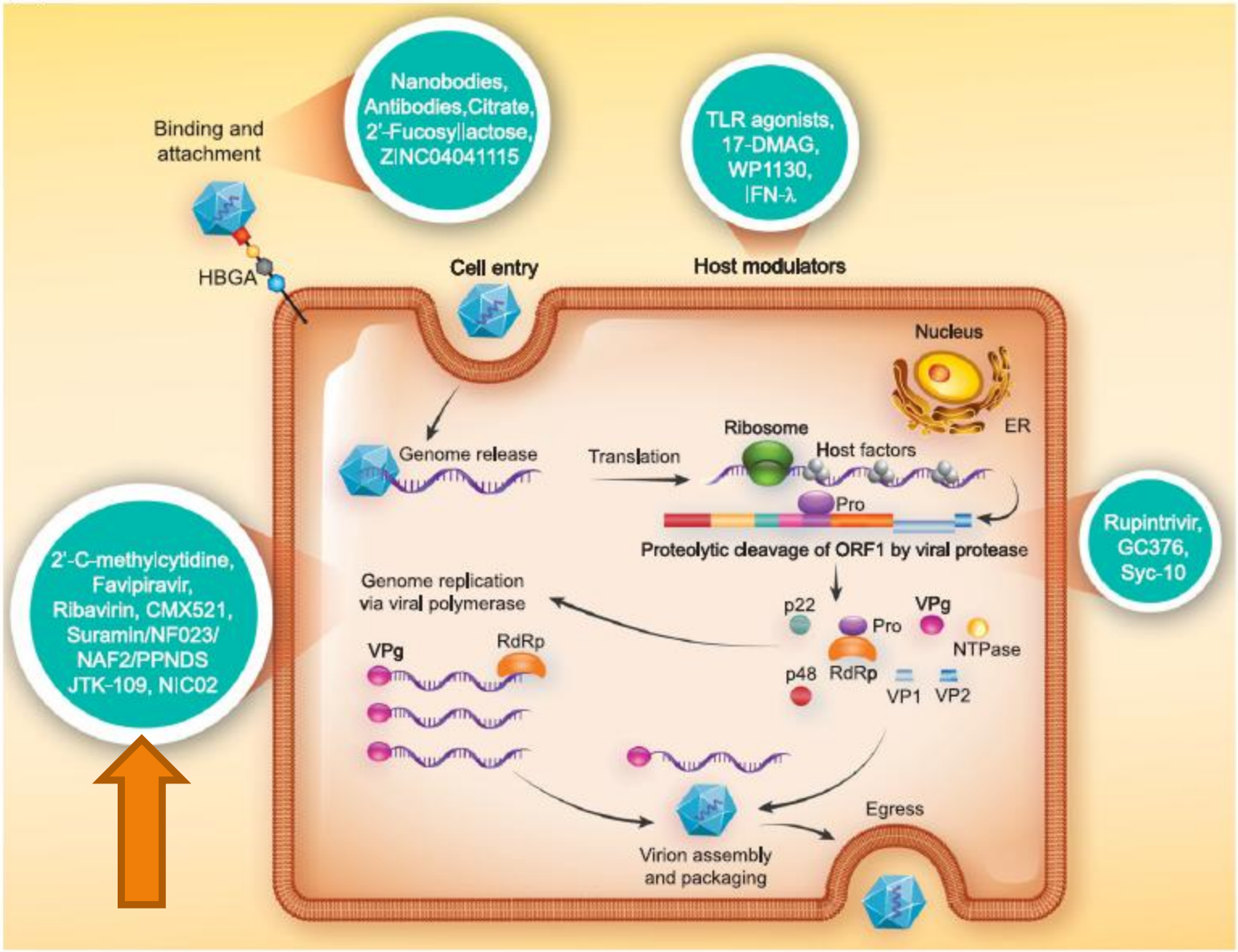


Fig. (1). The norovirus genomic RNA, subgenomic RNA, and structural (VP1 and VP2) and nonstructural (p48, NTPase, p22, VPg, 3CLpro and RdRp] viral proteins. The VPg protein covalently binds to the 5'- end of the viral genomic and subgenomic RNA, whilst the 3'- end of the viral RNA is polyadenylated. Anti-noroviral targets, including potential targets, have been shown with symbol ⊗. ⊗ **1.** Virus capsid (VP1)-host cell receptor binding blockers: carbohydrate analogs of fucose (citrates, glucomimetics), heparan sulfate analogs (Suramin), soluble histones, tannic acid, and HBGA-blocking monoclonal antibodies. ⊗ **2.** 3C-like cysteine protease (3CLpro) inhibitors: peptidyl transition state (TS) inhibitors, latent peptidyl TS inhibitors, peptidyl TS mimics, Macrocyclic peptide inhibitors, and Rupintrivir. ⊗ **3.** RNA-dependent RNA-polymerase inhibitors: nucleoside (Ribavirin, Favipiravir and 2'-C-methyl-cytidine) and non-nucleoside (Suramin and NF023) analogs. ⊗ **4.** Targeting viral RNA: Peptide-conjugated phosphorodiamidate morpholine oligomers (PMO), and siRNA. ⊗ **5.** Targeting VPg-host factors interactions: Hippuristanol. ⊗ **6.** Targeting viral RNA-interacting host factors: potential inhibitors of factors, such as La, PTB, DDX3, PCPB2, and hnRNPs. ⊗ **7.** Targeting other host factors/pathways crucial to virus replication, such as inhibitors of cellular deubiquitinases (WP1130 and 2-Cyano-3-Acrylamide Compound-6), molecular chaperone hsp90, and cholesterol pathways.

Ghosh Current Drug Metabolism 2018; 19: 170-91



Netzler Med Res Rev 2018; 1-27

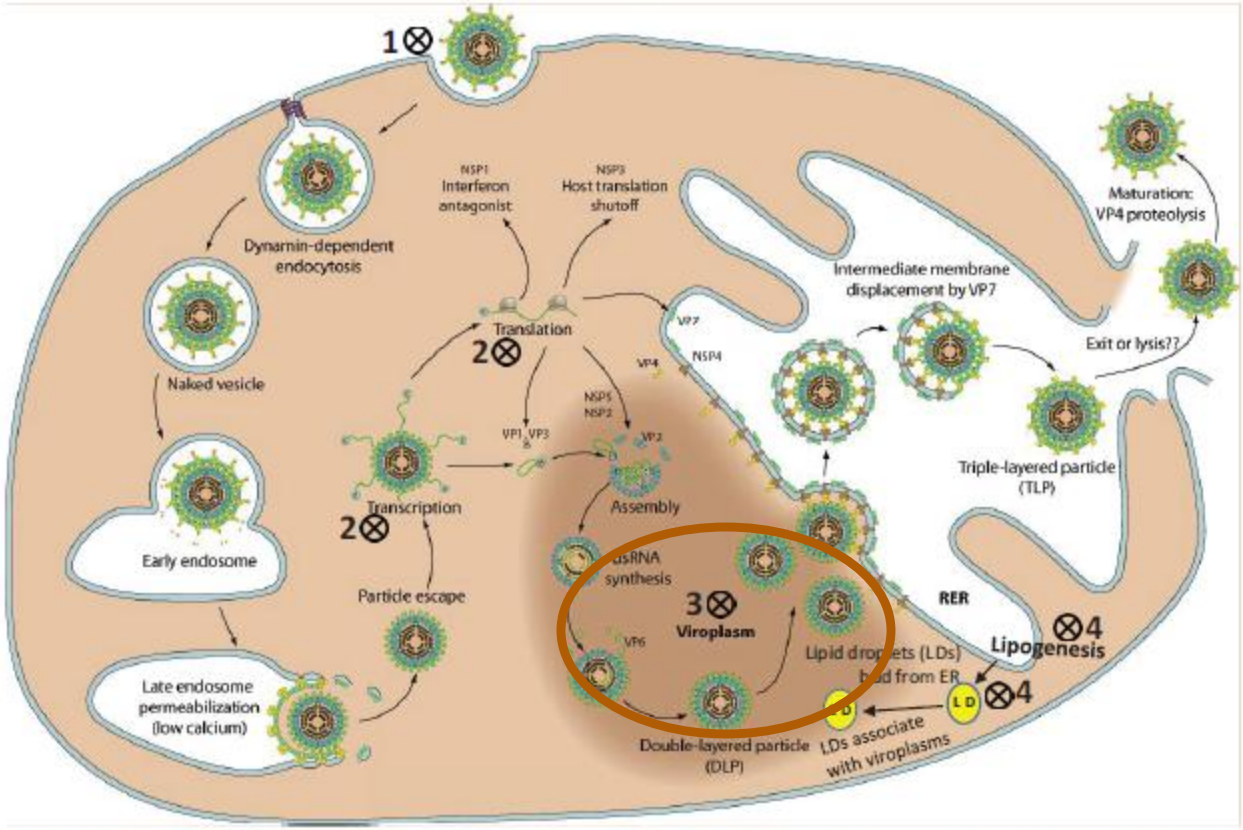
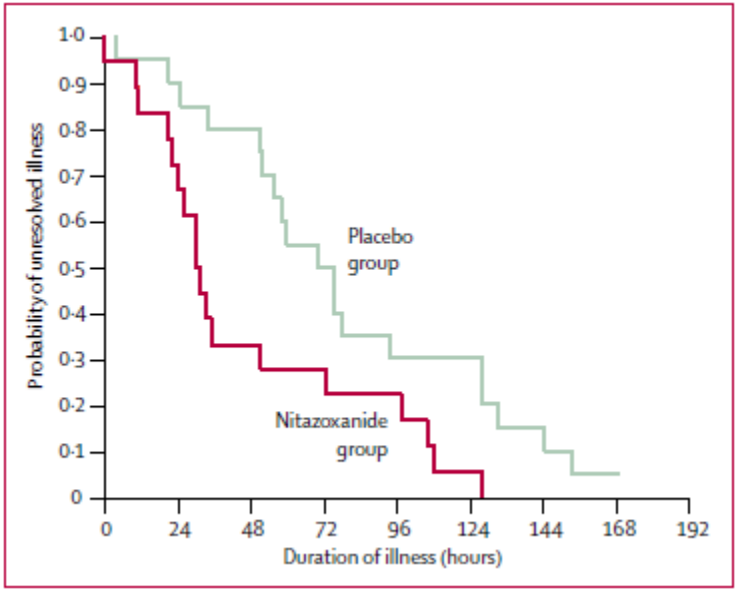
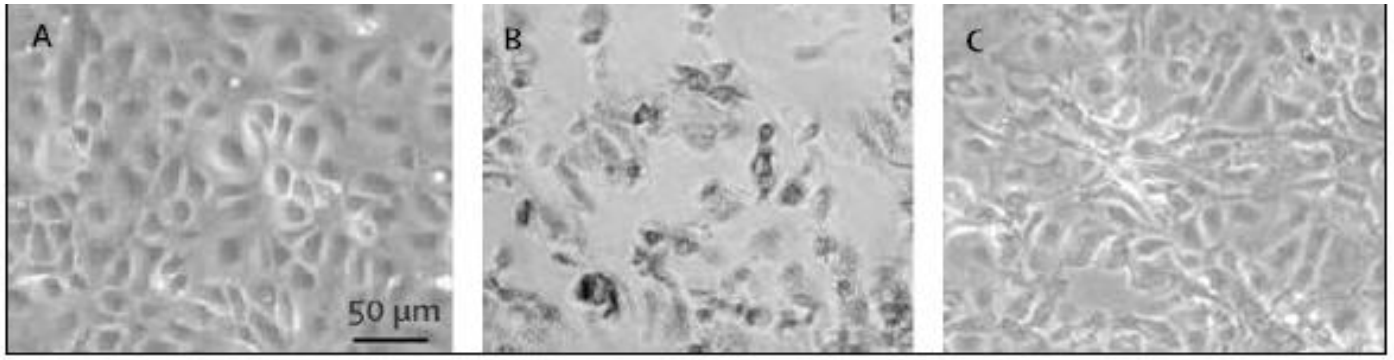


Fig. (2). Replication of rotavirus in host cell. Potential anti-rotaviral targets have been shown with symbol ⊗ ⊗ **1.** Blocking virus attachment and entry into host cells: sialylmimetics, lactadherin-derived peptides, neoglycolipid receptor mimetics, and membrane-impermeant thiol/disulfide-blockers. ⊗ **2.** Inhibition of viral RNA and/or protein synthesis: genistein, phosphonoformic acid [foscarnet, PFA], ribavirin and other nucleoside analogs, 3-deazaguanine (3-DG), neomycin and other aminoglycosides, actinomycin D, mycophenolic acid, isoprinosine, viscogens (glycerol), and siRNA. ⊗ **3.** Inhibition of viroplasm formation: nitazoxanide. ⊗ **4.** Suppression of virus replication, and/or virus maturation through inhibition of host cell lipid metabolism pathways and/or homeostasis of lipid droplets (LD): bile acids and farnesoid X receptor (FXR) agonists, 5-(tetradecyloxy)-2-furoic acid (TOFA), triacsin C, isobutylmethylxanthine (IBMX) + isoproterenol, stilbenoids, lovastatin, and cyclooxygenase inhibitors. Lipogenesis and its role in rotavirus replication has been excellently reviewed by Lever and Desselberger, 2016 [169]. This image has been modified with permission from the original source: ViralZone www.expasy.org/viralzone, © SIB Swiss Institute of Bioinformatics [297]. RER, rough endoplasmic reticulum.

Ghosh Current Drug Metabolism 2018; 19: 170-91

Nitazoxanide for rotavirus infection





Rossignol Lancet 2006; 368: 124-9

Rossignol Aliment Pharmacol Ther 2006; 24; 1423-30

- Noroviruses are genetically and antigenically very diverse, with more than 25 genotypes. Across three genogroups infecting humans. GII.4 is the most prominent norovirus genotype worldwide.
- Norovirus immunity is not well understood and there is currently no single well established correlate of protection that can be used in vaccine trials.
- Two vaccines currently in human clinical trials include a bivalent GI.1/GII.4 intramuscular VLP vaccine in phase IIb and a monovalent GI.1 oral pill recombinant adenovirus vaccine in phase I trials.
- Cost effectiveness is a key aspect of acceptability of a norovirus vaccine
- Public awareness of norovirus is relatively low, suggesting need for public outreach and education to maximize uptake of future vaccines.
- A licensed norovirus vaccine has the potential to save lives and prevent a significant proportion of diarrheal illnesses worldwide.

Key issues in the development of norovirus vaccine

Mattison Expert rev Vaccines 2018; 17: 773-84
Cortes-Penfield Clin Ther 2017; 39: 1537-49

Conclusions

- Viral gastroenteritis- major public health concern
- Global societal and economic burden
- RV and NoV- important in children
- NoV- implicated in gastroenteritis outbreaks in semiclosed communities
- Leading cause of foodborne gastroenteritis
- The revolution of the RV vaccines