
NOROVIRUS GASTROENTERITIS: EPIDEMIOLOGY, CLINICAL MANIFESTATIONS, INFECTION CONTROL ISSUES

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Disclosure: Clorox

GASTROENTERITIS

- Toxin mediate (watery stools)
 - Viruses: Noroviruses, rotaviruses, astroviruses, adenoviruses
 - Bacteria: *Bacillus cereus*, *Clostridium perfringens*, *S. aureus*, *E. coli* (ETEC), *Vibrio cholerea*
- Invasive microbes (bloody stools)
 - Bacteria: *E. coli* (EHEC, EPEC, EIEC), *Salmonella*, *Campylobacter*, *Shigella*, *Clostridium difficile*
 - Parasites: *Giardia*, *Entamoeba histolytica*
- Penetrating microbes (systemic infection)
 - Bacteria: *Salmonella* (typhoid, paratyphoid), *Yersinia enterocolitica*

GASTROENTERITIS: HISTORY

- Exposure to ill persons: Norovirus, *Shigella*, EHEC
- Underlying diseases: IBS, host defense abnormalities
- Recent antibiotics (30 days): *C. difficile*
- Travel outside of US (dates, locales): *E. coli*, *Salmonella*, *Giardia*
 - Cruise ships: *Norovirus*
- Animal exposure (e.g., camping, occupation): *Salmonella*, EHEC, *Giardia*
- Water exposure (swimming in pools or lakes): Cryptosporidia, EHEC
- Food exposure (cooking, unpasteurized products): *Salmonella*

GASTROENTERITIS: PATHOGENESIS - DIAGNOSIS

Infecting Dose (# organisms)

- Norovirus: 10-100
- *Cryptosporidia*: 10 - 100
- *Shigella*: 10 - 100
- EHEC: 10 - 100
- *Campylobacter*: 10^4 - 10^6
- *Salmonella*: 10^5 - 10^8
- *Vibrio cholerae*: 10^5 - 10^8
- ETEC: 10^8
- *Yersinia*: 10^9

Stool culture

- *Campylobacter*: 2.33%
- *Salmonella*: 1.82%
- *Shigella*: 1.06%
- EHEC: 0.39% (7.75% if stool visibly bloody)

Slutsker L, et al. Ann Intern Med 1997;
126:505-13

VIRUSES IN THE HUMAN GUT

Gastroenteritis:

- Rotavirus (gp A, gp C)
- Adenovirus (Ty 40 / 41)
- Astrovirus

Caliciviridae:

- Norovirus
- Sapovirus

Torovirus
Aichi virus
Picobirna virus

Hepatitis:

- Hepatitis A
- Hepatitis E

Other illness:

- Enteroviruses (poliovirus, coxsackievirus, ECHO)
- TBEV (Flaviviridae)
- Cytomegalovirus (Herpesviridae)
- Parvoviruses

Family Caliciviridae

Genus	Lagovirus (rabbit, hare)
Genus	Vesivirus (cat, pig, sea lion, other)
Genus	Norovirus (human, bovine, swine, mouse)
Genus	Sapovirus (human, swine)

Morphology: Virions (35 -40 nm) nonenveloped and icosahedral
Genome: Linear positive sense RNA of 7.4 - 7.7 kb
Proteins: Virions are constructed from 90 VP1 dimers (+VP2)

Cell culture: no (human strains)
Animal model: no (chimpanzees)
Virus detection: RT-PCR, (ELISA), Electron Microscopy

NOROVIRUS: HISTORY

- In 1929, Zahorsky proposed the name “winter vomiting disease” to describes outbreaks of presumed viral gastroenteritis
- In the 1940s, Gordon demonstrated that pooled stool filtrates obtained from patients in an institutional outbreak of nonbacterial gastroenteritis could infect inoculated volunteers
- In 1968, CDC investigated an outbreak of vomiting disease in an elementary school in Norwalk OH: 50% of students and teachers developed gastroenteritis
- Kaplan used immune electronmicroscopy to identify viral particles in the stools of volunteers infected with the “Norwalk” strain
- Virus initially classified as small round viruses, later reclassified as caliciviruses when genome cloned

NOROVIRUS: MICROBIOLOGY

- Classified as a calicivirus
 - Five genogroups: I, II, and IV contain human strains
- Single-stranded RNA genome
- Non-enveloped
- Environmentally stable (due to capsid): Resists heating to 60 °C
- Human noroviruses cannot be grown in cell culture so feline calicivirus used as a surrogate

CHALLENGES TO STUDING NOROVIRUSES

- Infection and disease are limited to humans
- No small-animal model
- No cell culture system

NOROVIRUS: EPIDEMIOLOGY

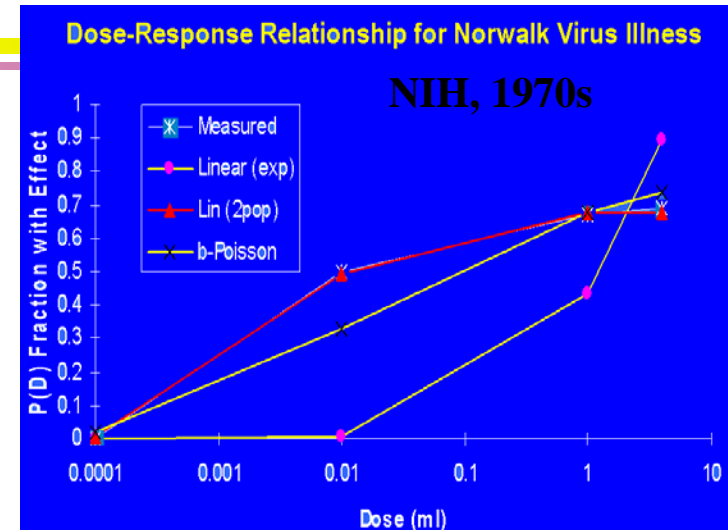
- Prevalence
 - Causes an estimated 23 million infections per year in the US
 - Causes ~60% of illness due to known
 - Accounts for 70-95% of gastroenteritis outbreaks
- Infectious dose: 10-100 viruses
- Fecal-oral transmission (shedding for up to 2-3 weeks)
- Droplet transmission? (via ingestion of airborne droplets of virus-containing particles)
- Common cause of traveler's diarrhea
- May cause chronic infection in transplant recipients

NOROVIRUS: EPIDEMIOLOGY

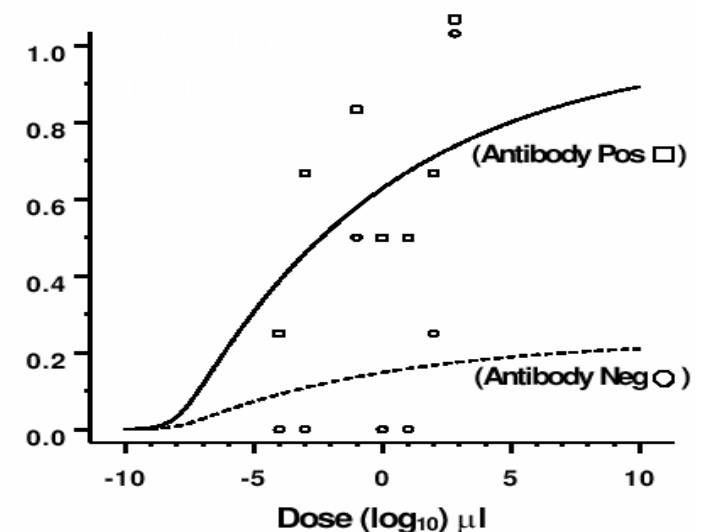
- Increase in norovirus activity reported in Europe (9 of 11 countries) in 2006 compared to 2004-05. *Eurosurv* 2006;11
- 81% of 226 GE outbreaks in US (2000-2004) caused by calicivirus, group II NoV was most common (79%), then Group I NoV (19). *JID* 2006;193:413
- Widespread outbreak of norovirus gastroenteritis among evacuees of hurricane Katrina. Yee et al. *Clin Inf Dis* 2007;44:1032
 - Crowding, close contact among evacuees with potentially soiled fomites (cots), in sufficient sanitation in lavatories, lack of HH facilities, delays in cleaning

Norovirus Human Infectivity

- Norovirus is infectious at low dose
- As few as 10-100 virions may be a 50% human infectious dose (ID_{50})
- Data from early (1970s) and recent studies document low ID_{50}
- Immunity is short-lived and strain-specific; little cross-protection
- Virus levels in feces and vomitus are high enough to cause high risk of human infection from exposure



Norwalk Virus Dose-Response:
Two populations; Beta-Poisson Model; Moe



NOROVIRUS INFECTION: CLINICAL FEATURES

- Incubation period: 24-48 hours (range, 18-72 hours)
- Onset: Gradual or abrupt
- GI symptoms: Nausea, vomiting, abdominal pain, non-bloody diarrhea (4-8 stools per day); only upper GI or lower GI symptoms may be present
- Systemic symptoms: Myalgias, malaise, headache, fever 38.3-38.9 °C (~50%)
- Second only to rotavirus for causing severe disease in young children
- Duration: 12-72 hours

Response of Human Volunteers to Norwalk Virus Infection via the Oral Route

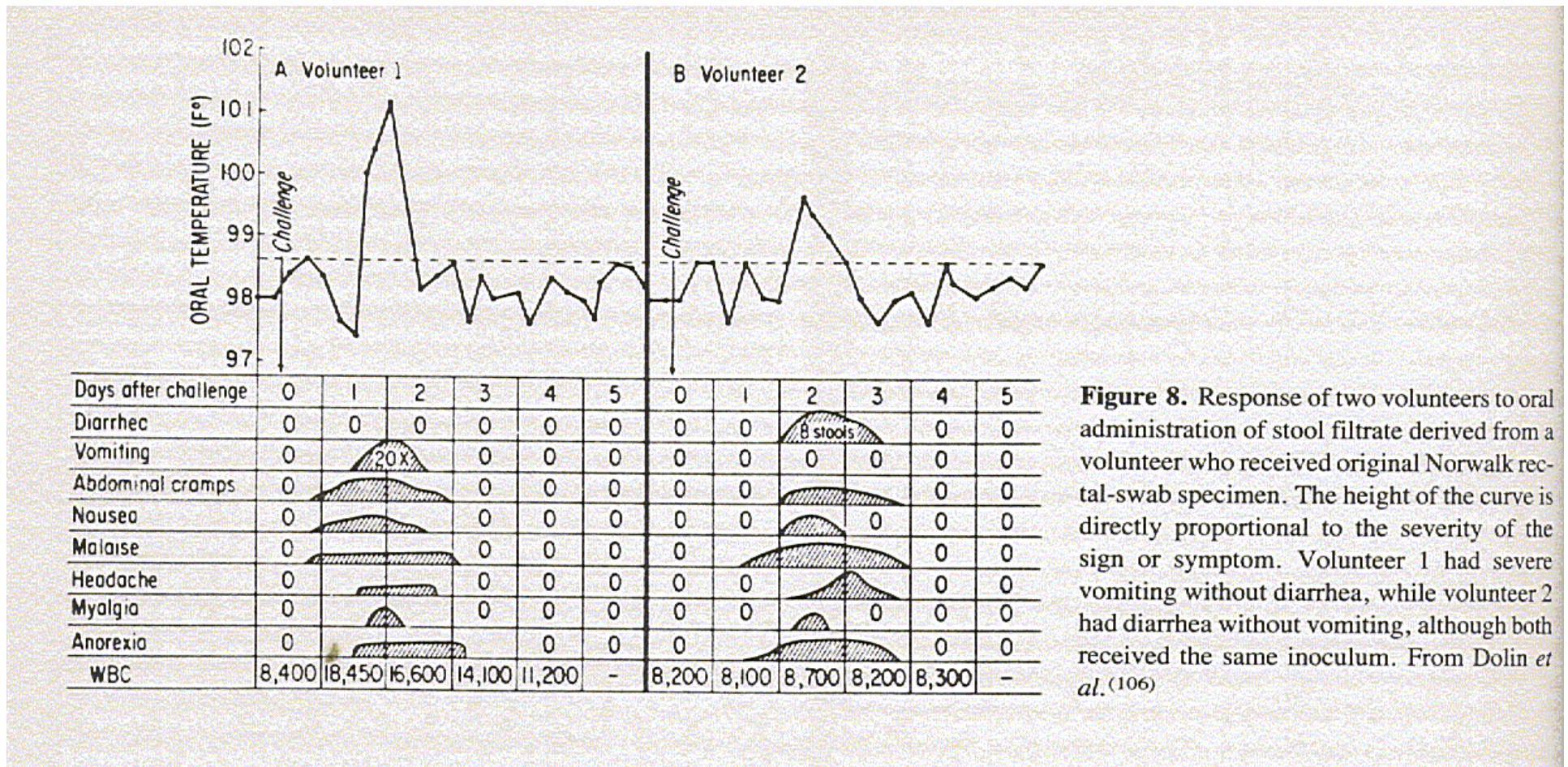


Figure 8. Response of two volunteers to oral administration of stool filtrate derived from a volunteer who received original Norwalk rectal-swab specimen. The height of the curve is directly proportional to the severity of the sign or symptom. Volunteer 1 had severe vomiting without diarrhea, while volunteer 2 had diarrhea without vomiting, although both received the same inoculum. From Dolin *et al.* (106)

NOROVIRUS INFECTION: IMMUNOLOGY

- Predominant type I immune response to norovirus infection
- Susceptibility based on an individual's histo-blood group antigens
 - Primary receptor in the gut = H type 1
- Only short term immunity

NOROVIRUS: DIAGNOSIS

Diagnosis

- WBC: normal or slightly elevated
- Stool = nonbloody
- Electron microscopy (EM) and immune EM (insensitive)
- Immune assays for virus Ag in stool (insensitive)
- Serology
- RT-PCR (method of choice)

Outbreak criteria (Kaplan)

- Bacterial infection excluded
- Vomiting \geq 50% of cases
- Mean/median incubation period: 24-48 hours
- Mean/median duration of illness: 12-60 hours

NOROVIRUS: DIAGNOSIS

- Clinical
 - Acute onset diarrhea \pm vomiting
 - Stool = nonbloody
 - WBC: normal or slightly elevated
- Laboratory
 - Electron microscopy (EM) and immune EM (insensitive, require $>10^6$ particles/mL)
 - Immune assays for virus Ag in stool (insensitive; too specific due to viral diversity)
 - Serology
 - RT-PCR (method of choice)

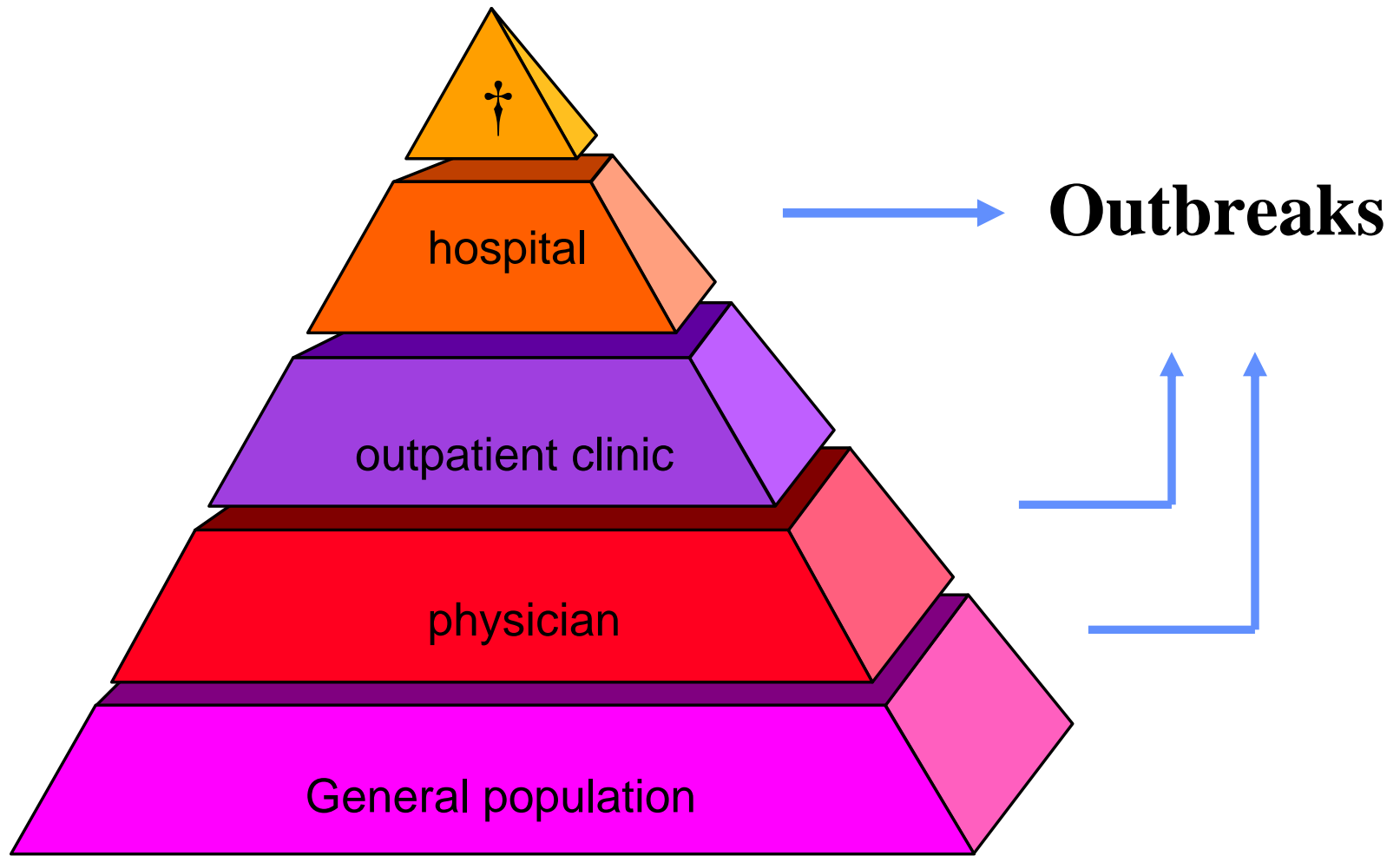
NOROVIRUS: DIAGNOSIS

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 - Bacterial infection excluded
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WHY NOROVIRUS INFECTION IS SO COMMON

- Small infectious dose (secondary attack rate >30%)
- Environmentally stable
- Large human reservoir
- High numbers of susceptible persons
- Asymptomatic infection may occur
- Limited immunity (genetically variability in strains)
- Prolonged shedding
- Multiple routes of transmission (persons-to-person, food, water, aerosol?)
- Resistant to commonly used disinfectants

Studies of disease estimates: We detect the tip of the iceberg



OUTBREAKS

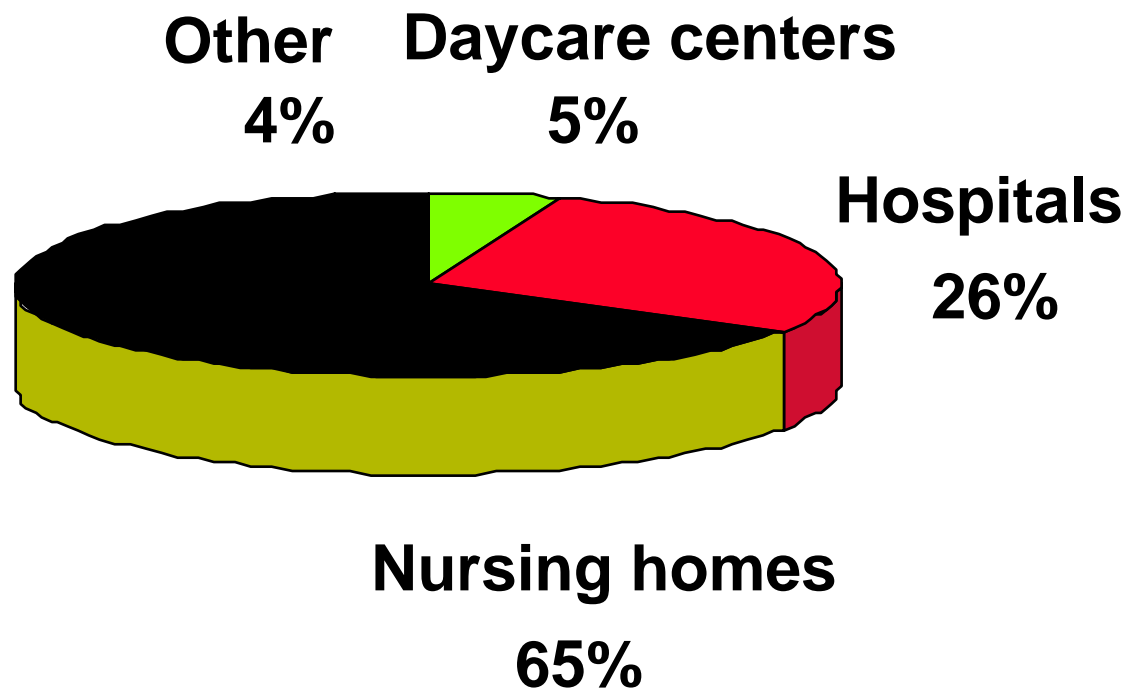
Locations

- Cruise ships
- Day care centers
- Extended care facilities
- Hospitals
- Hotels
- Military camps and facilities
- Restaurants
- Schools
- Summer camps

Sources

- Food
 - Shellfish
- Water
 - Ice
 - Potable
 - Recreational

INSTITUTIONAL OUTBREAKS

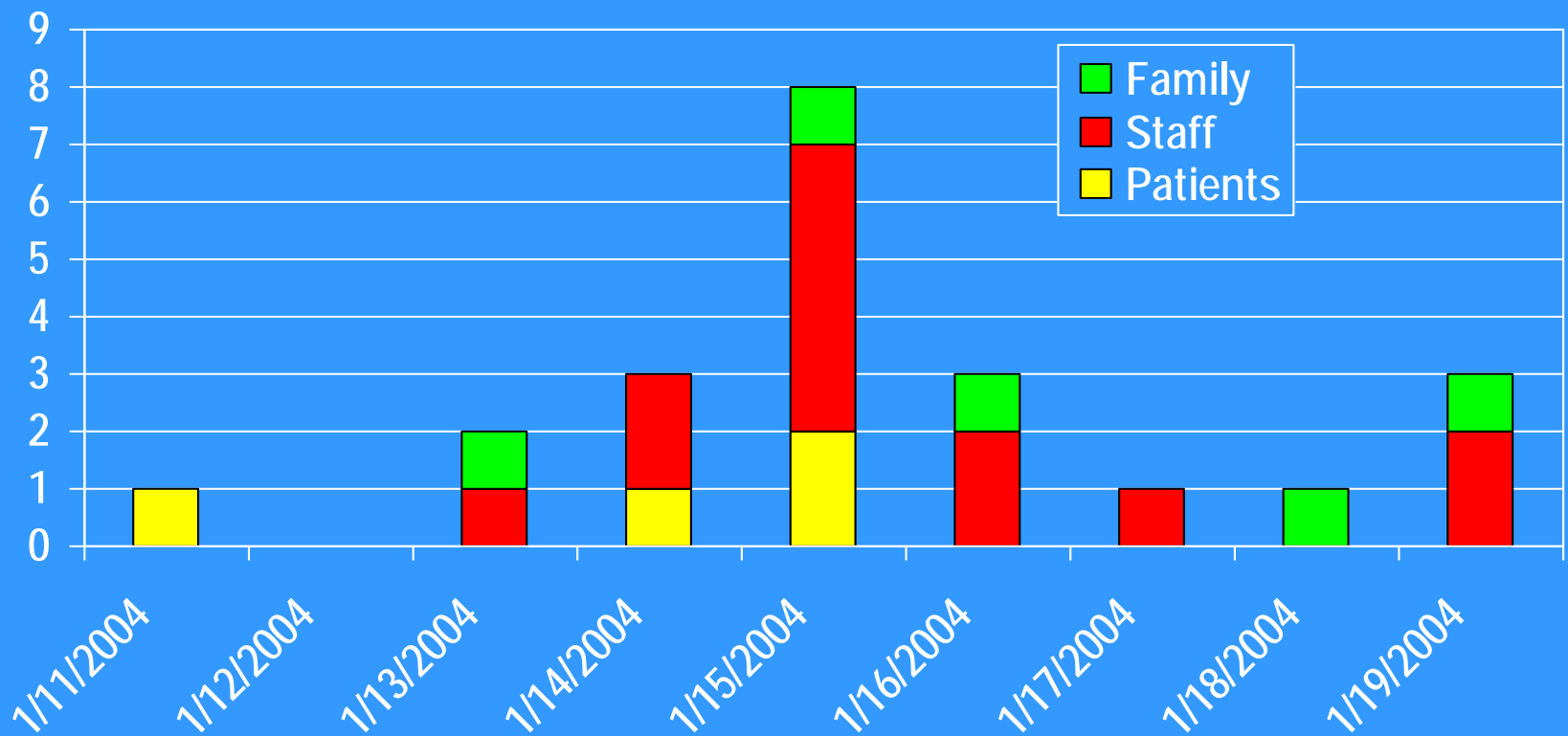


Vinje J, *et al.*, 1997

NOROVIRUS OUTBREAK, UNC 2004: TIMELINE

- 1/11 – Index case admitted to locked pediatric psych unit
- 1/11 – Index case develops nausea and vomiting
- 1/13 – First 2^o case
- 1/15 – Hospital Epidemiology contacted
- 1/16 – Control interventions initiated
- 1/19 – Onset of symptoms of last 2^o case
- 1/24 – Unit re-opened for admission

OUTBREAK CURVE, PSYCH UNIT



Attack rate: patients 75% (3/4); staff (assigned) 26% (10/38);
staff (temporary): ?% (3/?); family: ?% (5/?)

OUTBREAK STRAIN, PSYCH UNIT

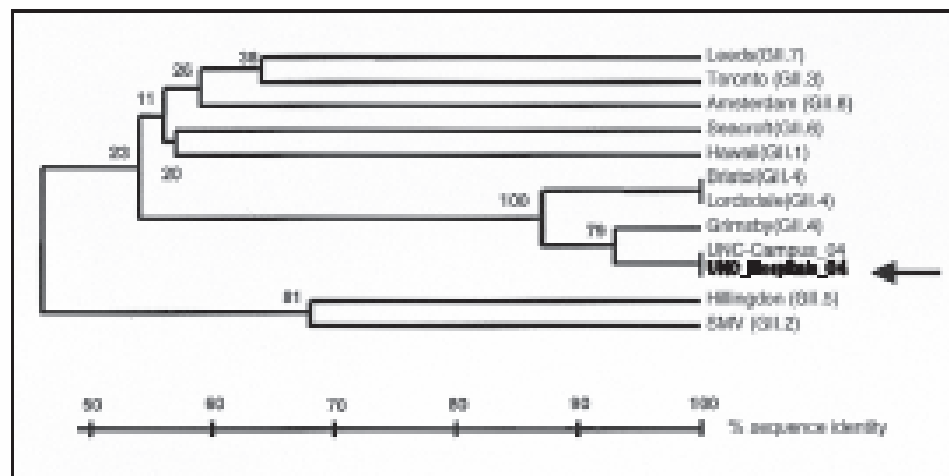


FIGURE 2. Phylogenetic analysis of norovirus GII region D nucleotide sequences including sequences of University of North Carolina (UNC) Hospitals and UNC Campus outbreak and norovirus prototype strains previously submitted to GenBank (Leeds, AJ277608; Toronto, U02030; Amsterdam, AF195848; Seacroft, AJ277620; Hawaii, U07611; Bristol, X76716; Lordsdale, X86557; Grimsby, AJ004864; Hillingdon, AJ277607; and Snow Mountain virus [SMV], U75682). Bootstrap values are given for each node. Norovirus strains are classified according to the most recent norovirus genotype nomenclature.⁴ The arrow indicates the strain that caused the outbreak.

OUTBREAK INTERVENTIONS

- Stool from ill staff and patients obtained for routine bacteria, cryptosporidia, norovirus
- Potential ill staff contacted; instructed to remain home for 48 hours after symptoms resolve (Ill staff seen in OHS)
- Psych unit closed for admissions
- Entire unit placed on Contact Precautions
- Staff eating with patients curtailed
- Enhanced environmental cleaning with diluted bleach 1:10 initiated

UNC OUTBREAK

(Simultaneous With Psych Unit Outbreak)

- Outbreak in UNC student
 - ~300 students ill
 - 2^o transmission noted
 - Source/reservoir unknown
 - 5/9 stool samples for students norovirus+
- Case control study
 - Interviewed 154 students: 91 cases, 63 controls
 - OR 5.4 – ate at Top of Lenoir dormitory on Jan 19, 2004
 - ◆ OR 4.3 – ate off of salad bar

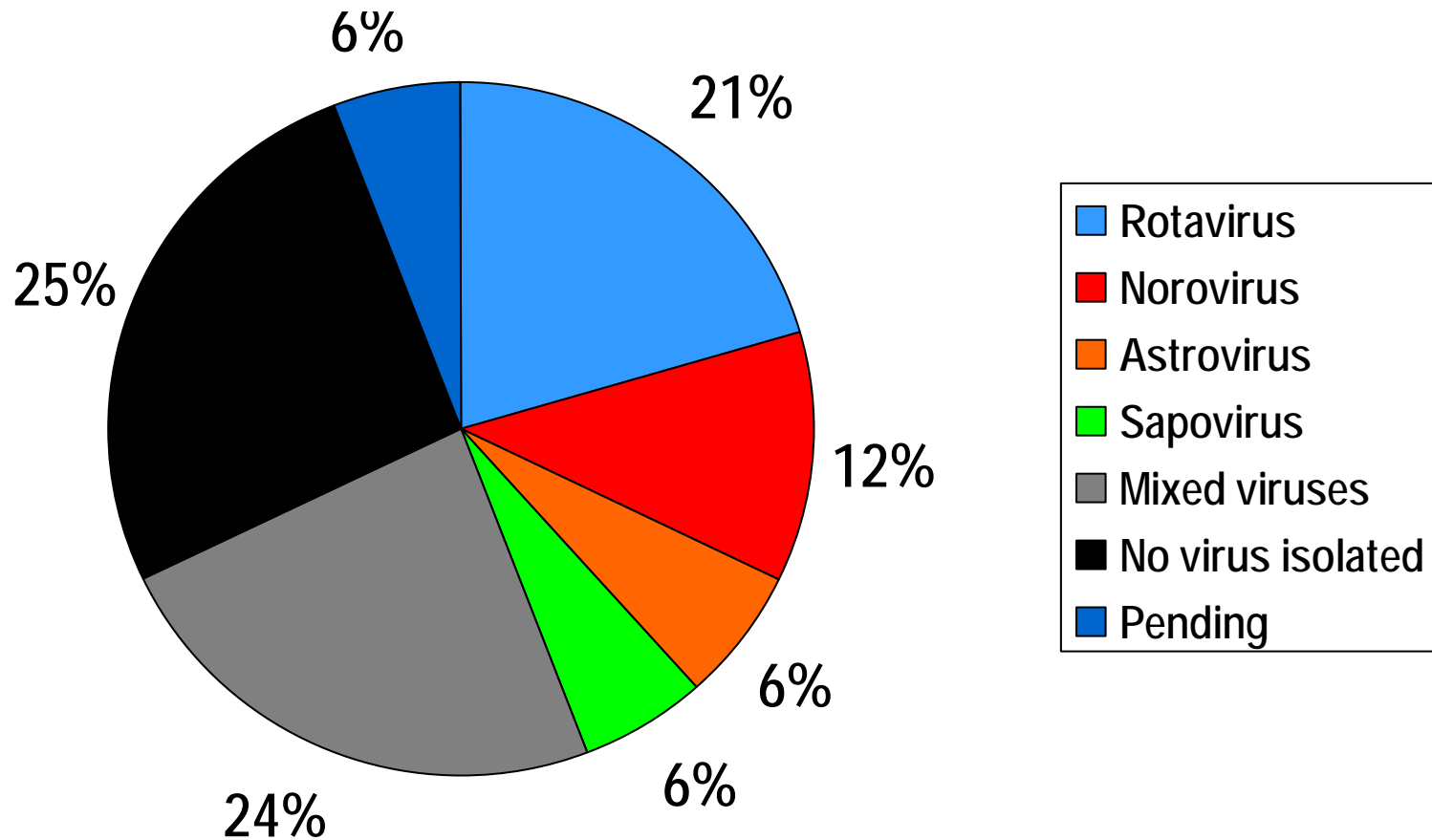
CLINICAL COMPLICATIONS OF NOROVIRUS INFECTION

- Study: Outbreak investigation
- Site: 5 hospital wards (1 Nov 2002 – 31 Jan 2003)
 - Source of infection: Hospital 72, community 12
- Impact
 - Patient attack rate = 38% (72/219)
 - Nurse attack rate = 76% (60/79)
 - 45% of patients required intravenous hydration
 - 22 patients had elevated creatinine (3 required hemodialysis)
 - 3 patients developed ventricular tachycardia (1 needed cardioversion)
 - 2 patients s/p renal transplant required D/C of immunosuppressives

IMPACT OF NOROVIRUS INFECTION ON HOSPITAL RESOURCES

- Study: Matched case-control study and microbiological investigation of norovirus outbreak
- Site: 2 internal medicine wards (7-21 Jan 2003)
- Impact
 - Patient attack rate = 13.9% (16/115)
 - HCW attack rate = 29.5% (26/88)
 - Increased nursing time = 74.3 vs 41.9 min day ($P < 0.05$)
 - Total direct costs = \$40,675 (lost revenue = \$37,969)

DAY CARE CENTER OUTBREAKS, NC, 2006-07



Weber DJ, Kotch J, et al. Personal Communication

NOROVIRUS: THERAPY

- Therapy
 - Supportive
 - Fluid replacement
- Prevention
 - Prevent contamination of food and water
 - Disinfection of environmental surfaces
 - Hand hygiene
- Key = prevent transmission in closed populations

NOROVIRUS

- Healthcare epidemiology
- Disinfection and antisepsis
- Control measures

disinfectionandsterilization.org

NOROVIRUS: EPIDEMIOLOGY

- Prevalence
 - Causes an estimated 23 million infections per year in the US
 - Causes ~60% of illness due to known enteric pathogens
 - Accounts for 70-95% of gastroenteritis outbreaks
- Infectious dose: 10-100 viruses
- Fecal-oral transmission (shedding for up to 2-3 weeks)
- Droplet transmission? (via ingestion of airborne droplets of virus-containing particles)
- Outbreaks have been reported in hospitals, homes, camps, schools, restaurants, hotels, rehabilitation centers and cruise ships
- Common cause of traveler's diarrhea
- May cause chronic infection in transplant recipients

NOROVIRUS: EPIDEMIOLOGY

- Increase in norovirus activity reported in Europe (9 of 11 countries) in 2006 compared to 2004-05. *Eurosurv* 2006;11
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EPIDEMIOLOGY: NOROVIRUS

- Hospital-62% (13/21) for patients and 46% (16/35) for staff. Green et al. J Hosp Infect 1998;39:39
- Hospital-77 persons (28 patients and 49 staff) Leuenberger et al. Swiss Med Weekly 2007;137:57
- Hospital-21% (20 of 92) of all patients admitted to the pediatric oncology unit. Simon et al. Scand J Gastro 2006;41:693.
- Hospital-75% (3 of 4) of patients and 26% (10 of 38) staff. Weber et al. ICHE 2005;26:841

NOROVIRUS: MICROBIOLOGY

- Classified as a calicivirus (*Caliciviridae*)
 - Five genogroups: I, II, and IV contain human strains
- Single-stranded RNA genome
- Non-enveloped
- Environmentally stable (due to capsid): Resists heating to 60°C
- Human noroviruses cannot be grown in cell culture so feline calicivirus used as a surrogate

ROLE OF THE ENVIRONMENT IN TRANSMISSION

Pathogens implicated in transmission via contaminated noncritical surfaces

- Bacteria
 - Oxacillin-resistant *Staphylococcus aureus*
 - Vancomycin-resistant *Enterococcus spp.*
 - *Clostridium difficile*
 - *Acinetobacter* and *P. aeruginosa*
- Viruses
 - Rotavirus
 - Norovirus
 - SARS coronavirus

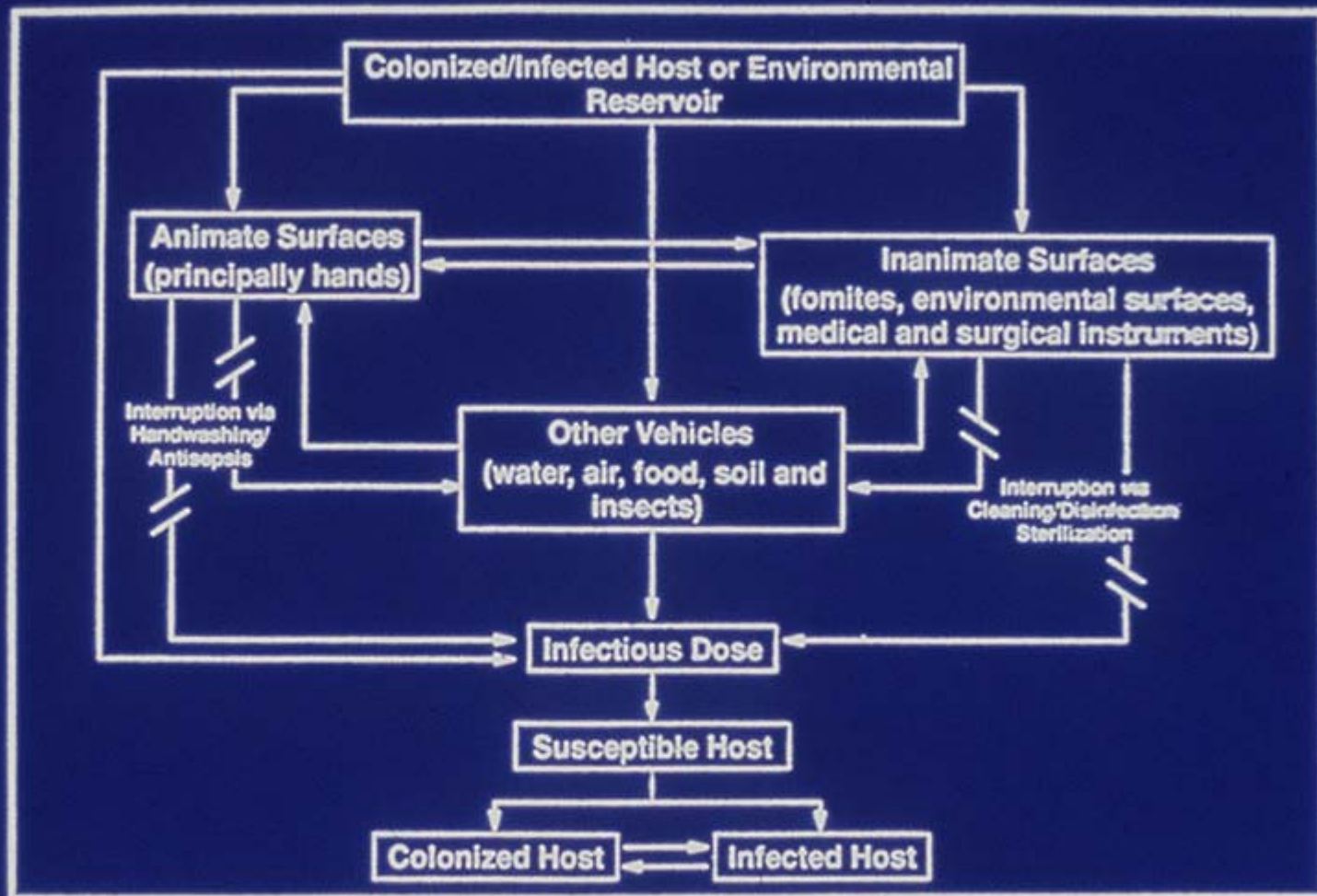


FIGURE. Transmission of infectious agents via animate and inanimate surfaces (modified from reference 25).

ENVIRONMENTAL CONTAMINATION

- Hospital-11/36 (31%) environmental swabs were positive by RT-PCR. Positive swabs were from lockers, curtains and commodes and confined to the immediate environment of symptomatic patients. Green et al. *J Hosp Infect* 1998;39:39.
- Hotel-61/144 (42%) were positive for NLV RNA. Cheesbrough et al. *Epid. Infect* 2000;125:93.
- Rehabilitation Center-Norovirus detected from patients and three environmental specimens (physiotherapy instrument handle, toilet seat (2-room of symptomatic guest, public toilet) RT-PCR. Kuusi et al. *Epid Infect* 2002;129:133-138.
- LTCF-5/10 (50%) of the environmental samples were positive for norovirus by RT-PCR. Wu et al. *ICHE* 2005;26:802.

Some positive PCR results may represent non-infectious virus.

ENVIRONMENTAL SURVIVAL

- Distilled water or saline: Survival 0-2 days West AP, et al. J Clin Path 1992;48:228
- Sterile river water: Survival 2 to 20-30 days Shahamat M, et al. Appl Environ Micro 1993;59:1231
- Tap water at 4°C: 4 days Fan EG, et al. J Gastroenterol Hepatol 1998;13:1096
- At 20°C a 9-log₁₀ reduction of FCV between 21-28 days in a dried state Doultree et al. J Hosp Infect 1999;41:51
- At 20°C a 9-log₁₀ reduction of FCV between 14-21 days in suspension Doultree et al. J Hosp Infect 1999;41:51
- 1 log reduction of HCV on telephone is 12-24 hours. Clay et al. AJIC 2006;34:41
- At 20°C a 3-log₁₀ reduction in infectivity (two animal caliciviruses) occurred in 1 week. Duizer et al. Appl Env Micro 2004;70:4538.

ROLE OF THE ENVIRONMENT

1. Prolonged outbreaks on ships suggest norovirus survives well
2. Outbreak of GE affected more than 300 people who attended a concert hall over a 5-day period. Norwalk-like virus (NLV) confirmed in fecal samples by RT-PCR. The index case was a concert attendee who vomited in the auditorium. GI illness occurred among members of 8/15 school parties who attended the following day. Disinfection procedure was poor. Evans et al. *Epid Infect* 2002;129:355
3. Extensive environmental contamination of a hospital ward.

Suggest transmission most likely occurred through direct contact with contaminated fomites.

INACTIVATION OF FELINE CALICIVIRUS

Sattar SA. J Hosp Infect 2004;56:S64

Disinfectant	Log Reduction	Contact Time (min)
Accel HP (5000 ppm)	>4.7	3
Chlorine dioxide (1000 ppm)	4.5	1
Chlorine (1000 ppm)	>4.5	1
QUAT	4.0	10
75% Ethanol	4.7	10

INACTIVATION OF FELINE CALICIVIRUS

Doultree et al. J Hosp Infect 1999;41:51

Disinfectant	Log Reduction	Contact Time
Glutaraldehyde, 0.5%	5	1
Hypochlorite, 1000 and 5000 ppm	5	1
QUAT	0	1
Iodine, 0.8%	5	1
Ethanol, 75%	1.25	1

INACTIVATION OF MURINE AND HUMAN NOROVIRUSES

Rutala WA, Folan MP, Tallon LA, Lyman WH, Park GW, Sobsey MD, Weber DJ. 2007

- 25 germicides were evaluated for their ability to inactivate human norovirus on contaminated non-porous inanimate surfaces
- Used a quantitative RT-PCR assay to quantify human norovirus reduction
- As no cell culture model is currently available for human norovirus, we chose a murine norovirus as a surrogate model for human norovirus
- 10 μ l inoculum of virus was placed on SS disk, allowed to dry, 50 μ l of the germicide applied, the virus-germicide mixture was neutralized and assayed for infectivity and by RT-PCR.

INACTIVATION OF MURINE AND HUMAN NOROVIRUES

Rutala WA, Folan MP, Tallon LA, Lyman WH, Park GW, Sobsey MD, Weber DJ. 2007

Disinfectant, 1 min	MNV Log ₁₀ Reduction	HNV Log ₁₀ Reduction
2% Glut	>4	0.9-1.6
Chlorine (19,000ppm)	>3	3.8
70% Ethanol	>4 (3.3 at 15sec)	2
65% Ethanol + QUAT	>2	3.6
Chlorine (5000ppm)	4	3

INACTIVATION OF MURINE AND HUMAN NOROVIRUSES

Rutala WA, Folan MP, Tallon LA, Lyman WH, Park GW, Sobsey MD, Weber DJ. 2007

Disinfectant, 1 min	MNV Log ₁₀ Reduction	HNV Log ₁₀ Reduction
70% Isopropyl alcohol	4.2	2.2
0.5% Accel H ₂ O ₂	3.9	2.8
79% Ethanol + QUAT	3.4	3.6
Chlorine (24,000ppm)	2.4	4.3
Phenolic, QUAT, Ag, 3% H ₂ O ₂	≤1	≤1 (2.1 QUAT)

INACTIVATION OF MURINE AND HUMAN NOROVIRUES

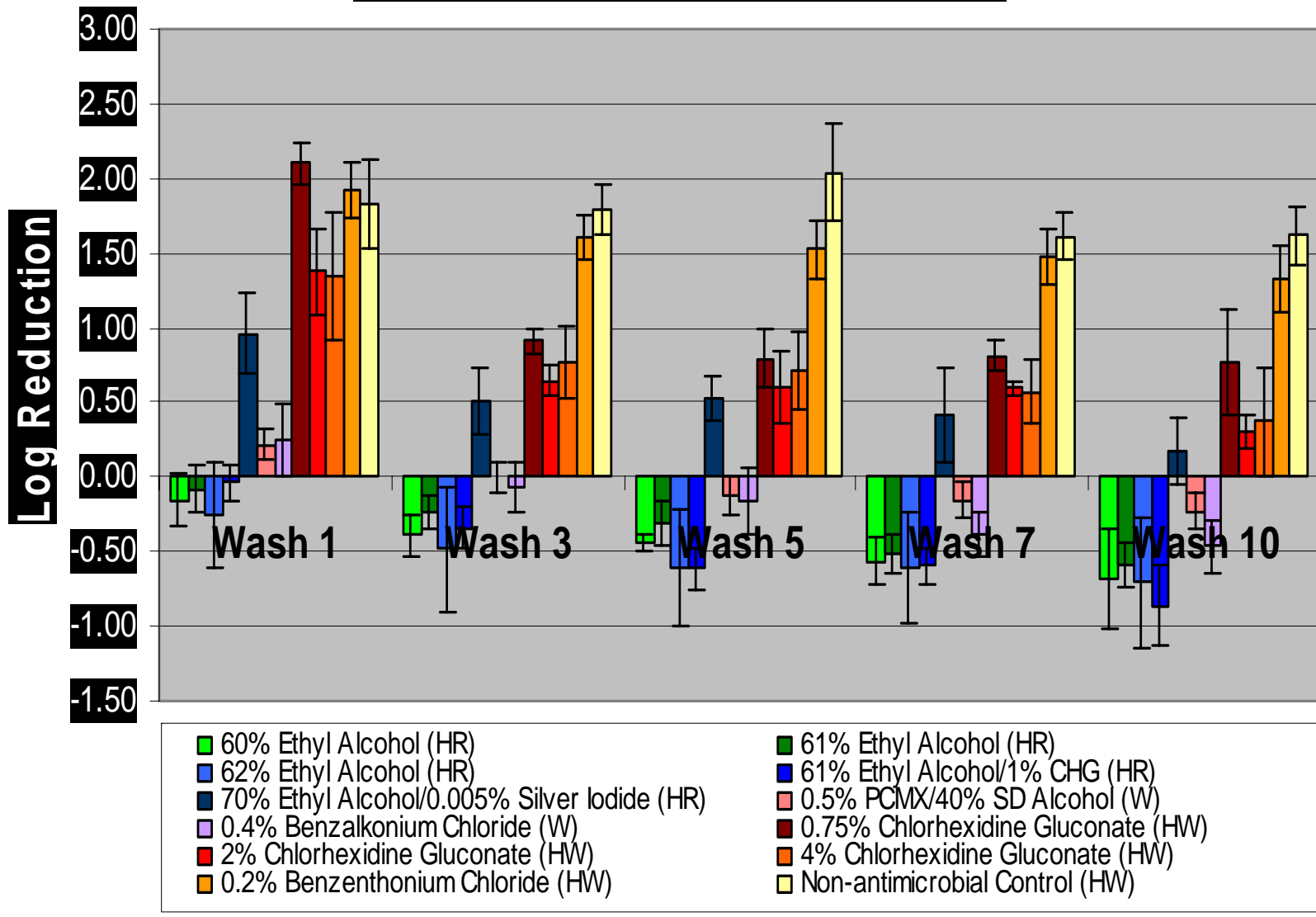
Rutala WA, Folan MP, Tallon LA, Lyman WH, Park GW, Sobsey MD, Weber DJ. 2007

Antiseptic, 1 min	MNV Log ₁₀ Reduction	HNV Log ₁₀ Reduction
Ethanol Hand Spray	3.2	0.4
Ethanol Based Rub	1.9	2.1
Iodophor (10%)	0.8	0.5
4% CHG	0.1	0.3
0.5% Triclosan	1.3	0.2
1% PCMX	0	2.4

SURFACE DISINFECTION

- School outbreak of NLV-cleaning with QUAT preparations made no impact on the course of the outbreak. The outbreak stopped after the school closed for 4 days and was cleaned using chlorine-based agents. Marks et al. *Epid Inf* 2003;131:727
- Detergent-based cleaning to produce a visibly clean surface consistently failed to eliminate norovirus contamination. A hypochlorite/detergent formulation of 5000 ppm chlorine was sufficient to decontaminate surfaces. Barker et al. *J Hosp Infect* 2004;58:42.

Summary of Log Reductions of MS2 Bacteriophage



ALCOHOL-BASED HAND RUBS

- Ethanol-based hand rub had superior efficacy against feline calicivirus than propanol. A higher ethanol concentration (2.17-95% ethanol, 1.56-70%, 30 sec) in hand rubs was associated with better efficacy against FCV using a fingerpad method. Kampf et al. J Hosp Infect 2005;60:144

ALCOHOL-BASED HAND RUBS

- A new formula with reduced ethanol content (55%) in combination with other alcohols and 0.7% phosphoric acid exhibited activity ($>3 \log_{10}$) against four non-enveloped viruses (HAV, polio, rotavirus, FCV) in 30s using a suspension test.
- In fingerpad tests, 70% ethanol produced a 0.68 \log_{10} reduction with FCV (new formulation 2.38).
Kramer et al. J Hosp Infect 2006;62:98

CONTROL MEASURES

- Containment of infectious persons
- Symptomatic staff instructed to remain home for 48 hours after symptoms resolve
- Rigorous/enhanced environmental cleaning procedures; terminal cleaning of the unit and then daily cleaning (or twice daily)
- Implementation of strict contact precautions; keep on isolation until patient asymptomatic for 48 hours
- Soap and water for hand hygiene should be considered rather than alcohol-based hand rubs
- During clusters, surfaces should be disinfected with an agent shown to have efficacy (e.g., hypochlorite)

CONTROL MEASURES

Carling PC et al, SHEA, 2007

- Assess patient area cleaning/disinfecting activities in twenty hospitals
 - Used invisible fluorescent targeting method to assess thoroughness of terminal room cleaning of high touch objects (959 rooms, 11,370 objects, 20 hospitals)
 - Mean proportion of objects cleaned was 48.4%
 - Successful surface disinfection is dependent of “practice not product”. When VRE, norovirus, or MRSA recovered from a surface not due to a failure of the disinfectant but rather a failure to wipe all surfaces leads to continued contamination

CONTROL MEASURES

- When fecal soiling (vomit) present, wipe the surface clean using a soaked cloth before applying disinfectant
- Use of masks when assisting vomiting patients (vomit- 10^5 to 10^6 viruses) or cleaning soiled fomites
- Carpets (harbor virus for 12 days, detergent cleaning and vacuuming will not remove all virus), which cannot tolerate chlorine, should be steam cleaned
- Ward closed to admissions (possibly-44% closure rates in norovirus outbreaks); entire ward placed on Contact Precautions.

CONTROL MEASURES

- Restrict visitors to two persons at a time and screen for signs of gastroenteritis
- No symptomatic patients transferred to other units
- Cohort nursing: all symptomatic patients were cared for in one unit; staff not allowed to work in unaffected area

NOROVIRUS

- Healthcare epidemiology
- Disinfection and antisepsis
- Control measures

Thank you

REFERENCES

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- Estes MK, et al. Noroviruses everywhere: has something changed: *Curr Opin Infect Dis* 2006;19:467-464.
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