Norovirus Epidemiology:
Burden, Attribution, and Surveillance

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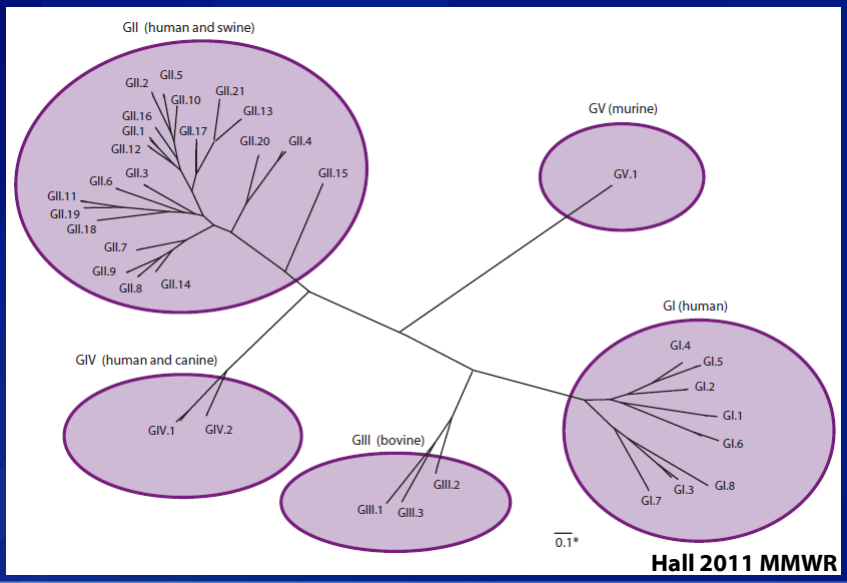
National Center for Immunization & Respiratory Diseases
Division of Viral Diseases

Presentation Outline

- Norovirus 101
- Disease burden
- Outbreak surveillance
- Attribution
- Prevention and control

NOROVIRUS 101

Norovirus Classification



Hall 2011 MMWR

Emergent GII.4 Norovirus Variants

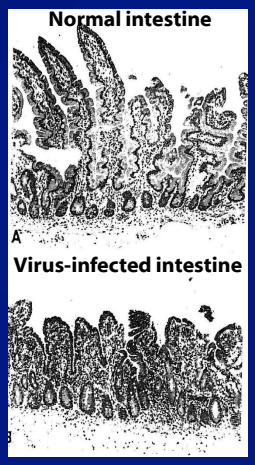
Variant	Years of Circulation	Pandemic Season	Other Names
95/96-US	1995–2002	1995–1996	Grimsby
Farmington Hills	2002–2005	2002–2003	2002
Hunter	2003–2006	None	2004
Yerseke	2006–2008	2006–2007	Laurens, Nijmegen, 2006a
Den Haag	2006–present	2006–2007	Minerva, 2006b
New Orleans	2009–present	None*	

*Based on data available as of September 2010, the New Orleans GII.4 variant has not been associated with an increased number of norovirus outbreaks in the U.S.

Hall 2011 MMWR

Clinical Disease

- Incubation period: 12-48 hours
- Acute-onset vomiting and/or diarrhea
  - Watery, non-bloody stools
  - Abdominal cramps, nausea, low-grade fever
- Most recover after 12-72 hours
  - 10-12% seek medical attention; some require hospitalization and fluid therapy
  - More severe illness and death possible in elderly and those with other illnesses
- 30% of infections are asymptomatic



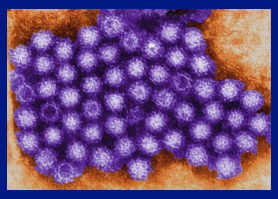
Hall 2011 EID
Phillips 2010 Am J Epid
de Wit 2001 Am J Epid

Laboratory Diagnostics

- No cell culture or animal model available
- Real-time RT-PCR
  - Quantitative assay provides estimate of viral load
  - Available in public health laboratories and research facilities
- Conventional RT-PCR
  - Sequence analysis used for genotyping
  - Capsid gene (regions C and D)
- Enzyme immunoassays (EIA)
  - Complicated by antigenic diversity
  - Currently inadequate sensitivity for clinical use in diagnosing sporadic cases

Viral Shedding

- Primarily in stool, but also vomitus
- Occurs for at least 2-3 weeks
- Peaks 4 days after exposure
  - 10^5-10^{11} viral copies/gram feces
  - May persist after resolution of symptoms



- Infectious dose: ≥18 viral particles
- Infectivity of shed virus and role of asymptomatic shedding in transmission is unknown

Atmar 2008 EID
Aoki 2010 J Hosp Infect
Teunis 2008 J Med Virol

Treatment

- No specific antiviral agents or vaccines currently available
- Supportive care for dehydration, primarily oral or IV fluid therapy
- Antibiotics, antiemetics, antimotility agents generally not recommended

Immunity and Genetic Susceptibility

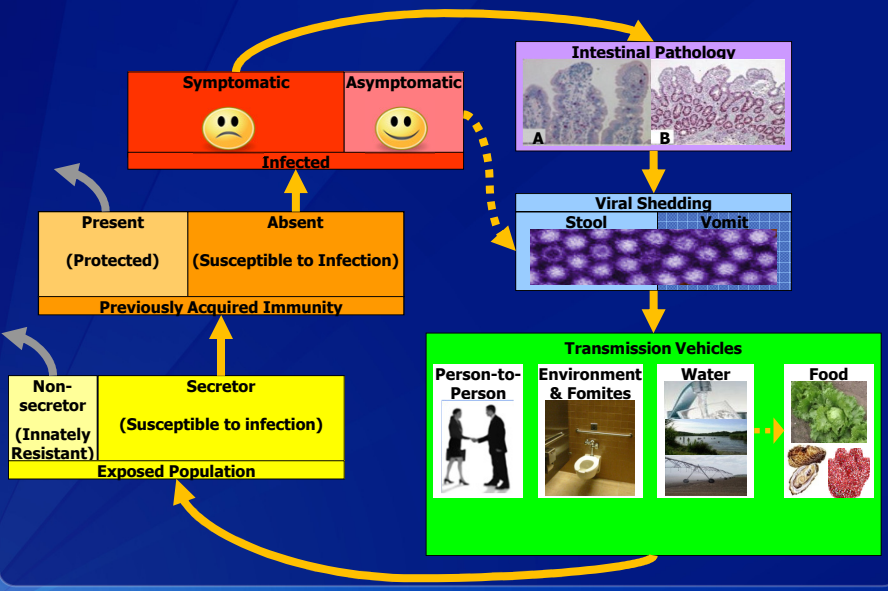
- Human volunteer studies demonstrated short-term homologous immunity (<6-12 mos)
- Little persistent cross-protective immunity
- Genetic susceptibility/resistance
  - Histo-blood group antigens
  - Secretor status (FUT2 gene)

Johnson 1990 JID
Lindesmith 2003 Nat Med

Transmission

- Person to person
  - Direct fecal-oral
  - Ingestion of aerosolized vomitus
  - Indirect via fomites or contaminated environment
- Food
  - Contamination by infected food handlers
  - During production of shellfish and produce
- Recreational and Drinking Water
  - Well contamination from septic tank
  - Chlorination system breakdown

Norovirus Transmission Cycle



DISEASE BURDEN

Burden of Foodborne Norovirus in the United States

- Causes 58% of all domestically-acquired foodborne illness from known agents
  - #1 cause of illness
  - #2 cause of hospitalization
  - #4 cause of death
- Costs $2 billion per year in medical care services and lost productivity

Scallan 2011 EID
Batz 2011

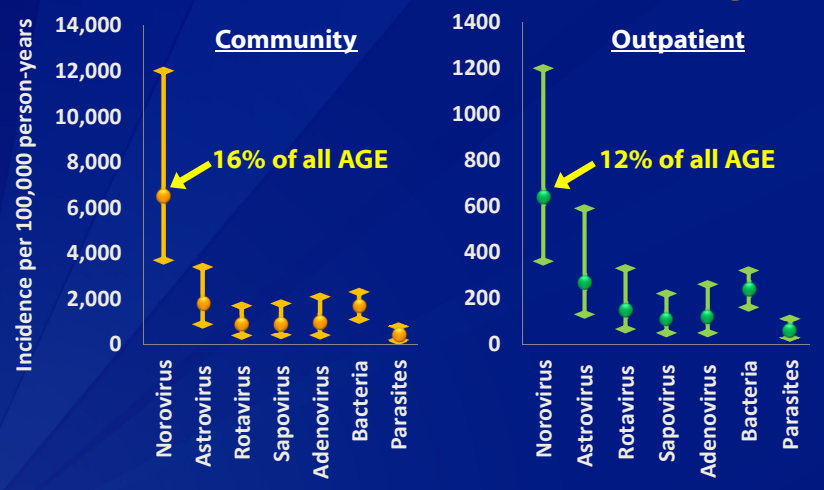
Challenges to Estimating Norovirus Disease Burden

- No national case-based reporting
- No rapid, sensitive clinical assays widely available
- Most AGE patients do not seek medical care and even fewer submit stool specimens
- Coding for most viral AGE pathogens in administrative data is insensitive and unreliable
- Limited laboratory-based data available on role of viruses in sporadic AGE

Laboratory-Based Approach to Estimating Incidence

- Collaborate with clinical laboratories with known population catchments (e.g., HMO)
- Sample stools submitted for routine clinical diagnostics (i.e., bacterial culture)
- Perform molecular diagnostics for norovirus
- Extrapolate detection rates to incidence using healthcare utilization rates

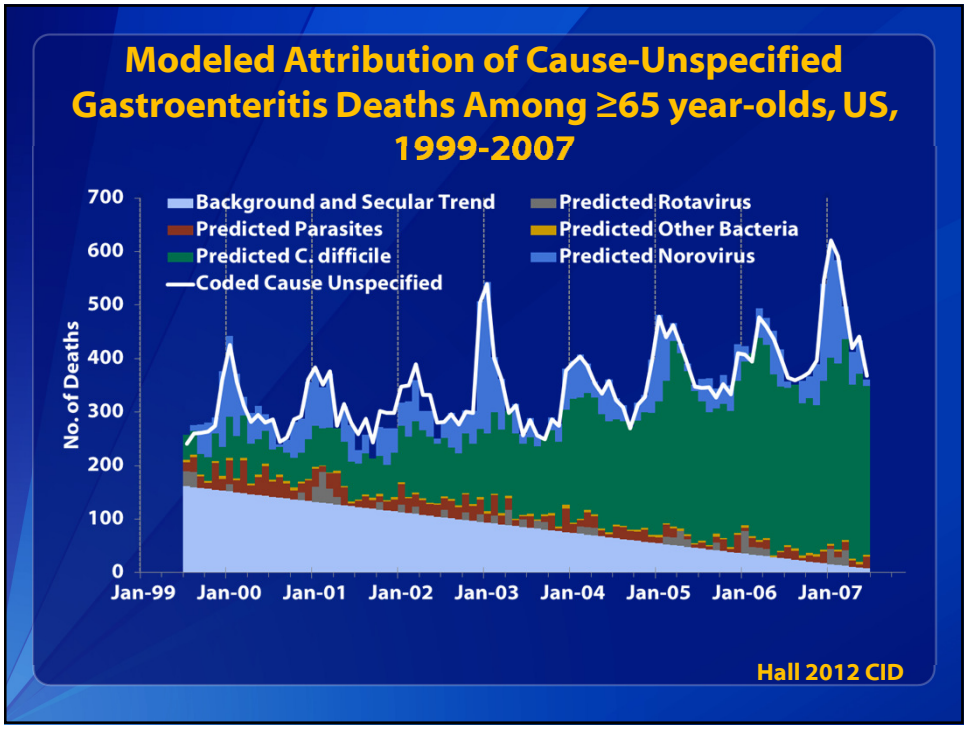
Incidence of AGE by Etiology, Kaiser Permanente of Georgia

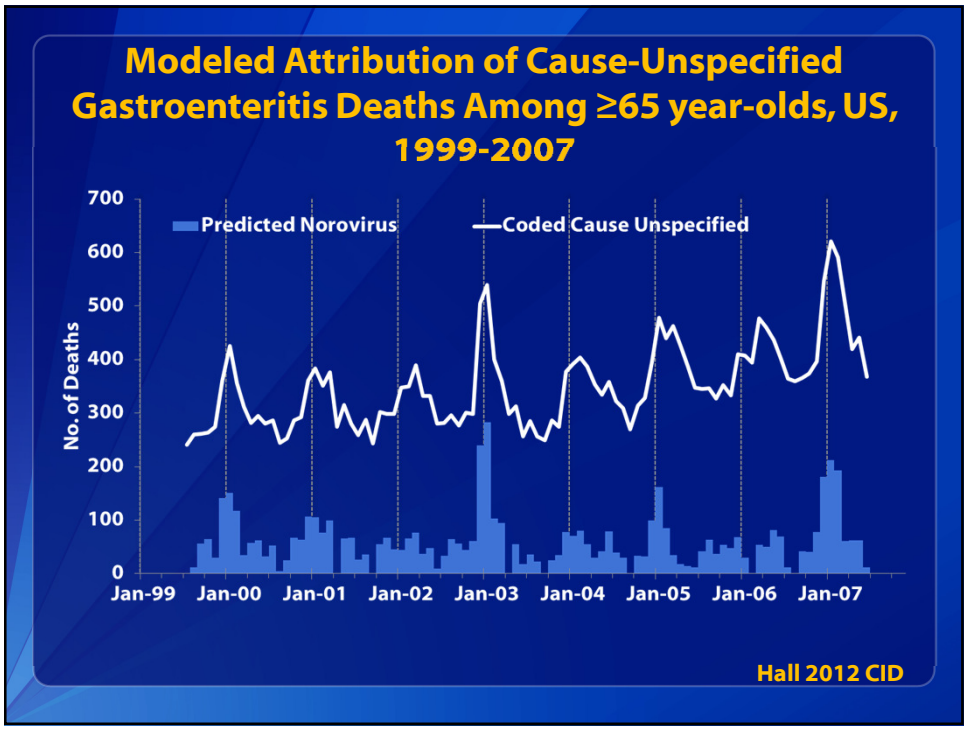


Hall 2011 EID

Indirect Modeling Approach to Estimating Incidence

- Utilize national or nationally-representative administrative datasets
  - Deaths
  - Hospitalizations
  - Emergency department and outpatient visits
- Develop time-series regression models to identify proportion of cause-unspecified gastroenteritis likely due to specific causes
- Analyze model residuals to estimate norovirus-associated burden


Modeled Attribution of Cause-Unspecified Gastroenteritis Deaths Among ≥65 year-olds, US, 1999-2007
Background and Secular Trend
Predicted Rotavirus
Predicted Parasites
Predicted Other Bacteria
Predicted C. difficile
Predicted Norovirus
Coded Cause Unspecified
No. of Deaths
700
600
500
400
300
200
100
0
Jan-99
Jan-00
Jan-01
Jan-02
Jan-03
Jan-04
Jan-05
Jan-06
Jan-07
Hall 2012 CID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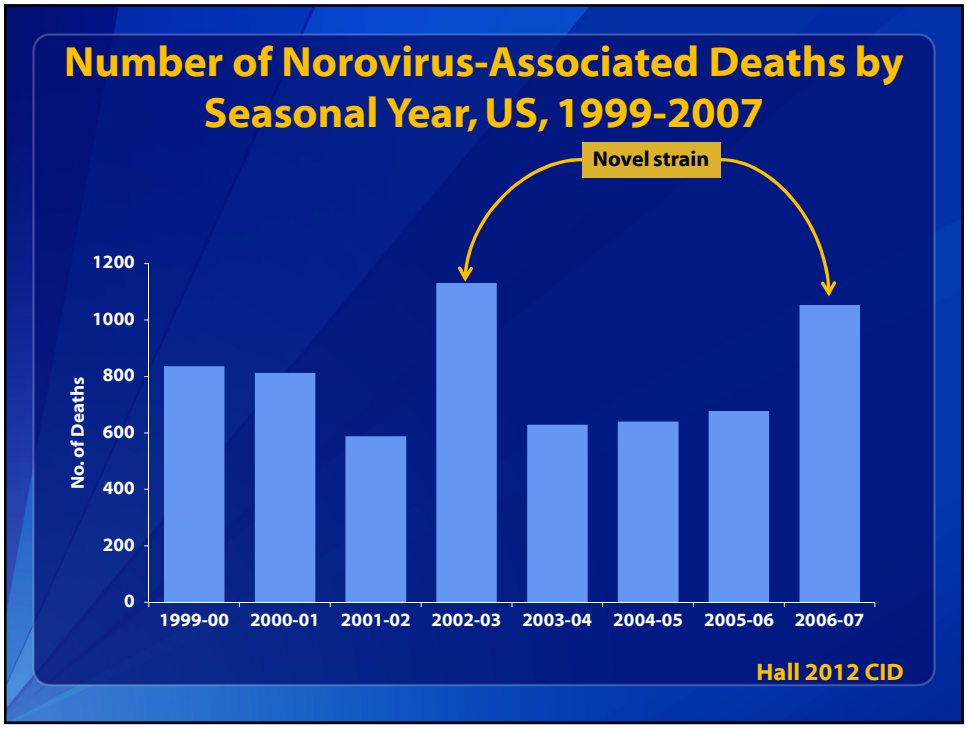
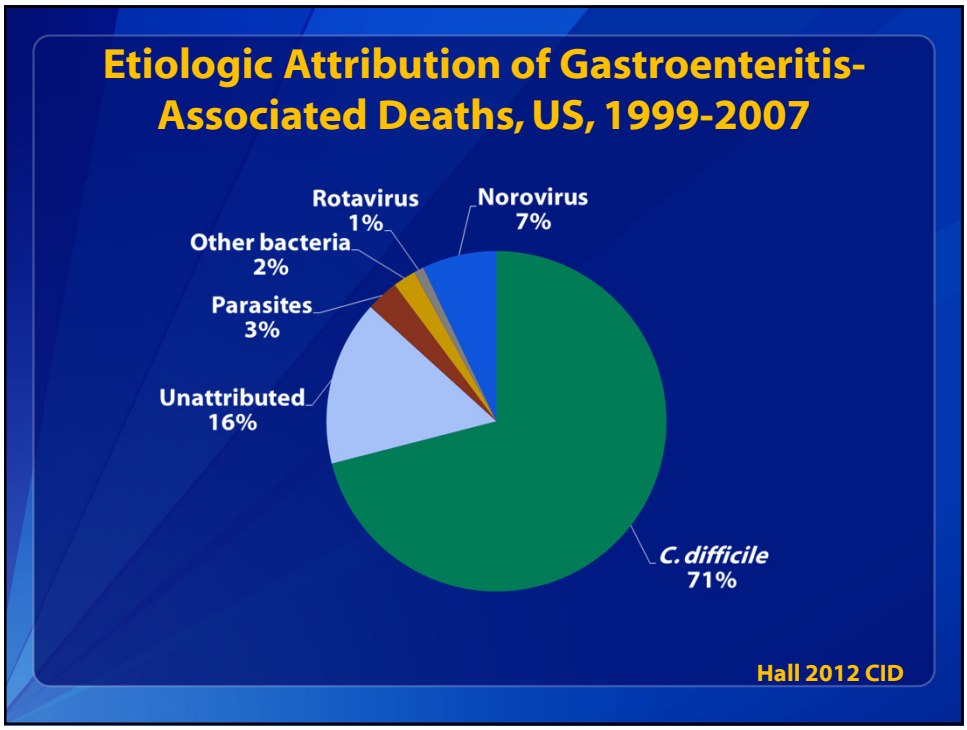
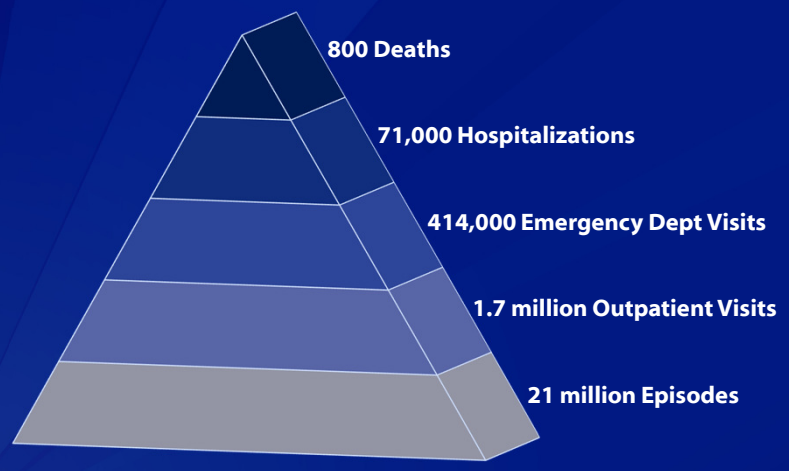

Number of Norovirus-Associated Deaths by Seasonal Year, US, 1999-2007
Novel strain
No. of Deaths
1200
1000
800
600
400
200
0
1999-00
2000-01
2001-02
2002-03
2003-04
2004-05
2005-06
2006-07
Hall 2012 CID


Etiologic Attribution of Gastroenteritis-Associated Deaths, US, 1999-2007
Rotavirus 1%
Norovirus 7%
Other bacteria 2%
Parasites 3%
Unattributed 16%
C. difficile 71%
Hall 2012 CID

Summary of Findings from Indirect Incidence Analyses

- Severe norovirus-associated disease has been previously underestimated
- Greatest burden and highest rates of severe disease and death are in the elderly (≥65 years)
  - Burden in young children (<5 years) is comparable to that of rotavirus prior to vaccine program
- Pronounced winter seasonality with peaks during December-February
- Surges by up to 50% during epidemic years associated with emergence of new variants

Annual Burden of Norovirus Disease in the United States



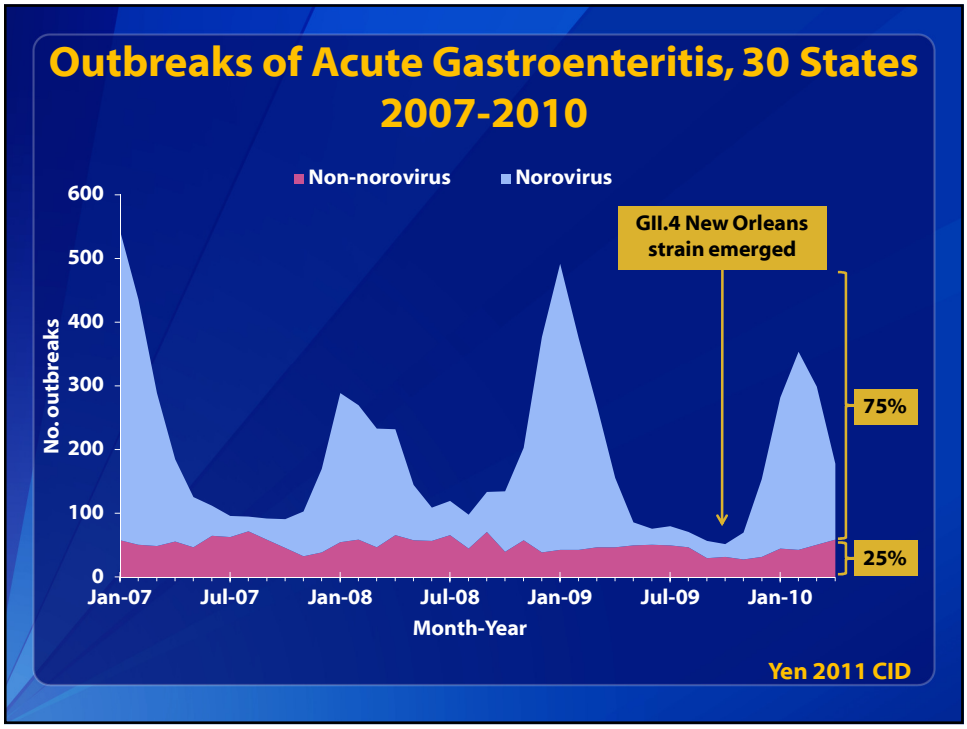
Hall 2012 CID; Lopman 2011 CID; Gastañaduy 2012 EIS; Hall 2011 EID; Scallan 2011 EID

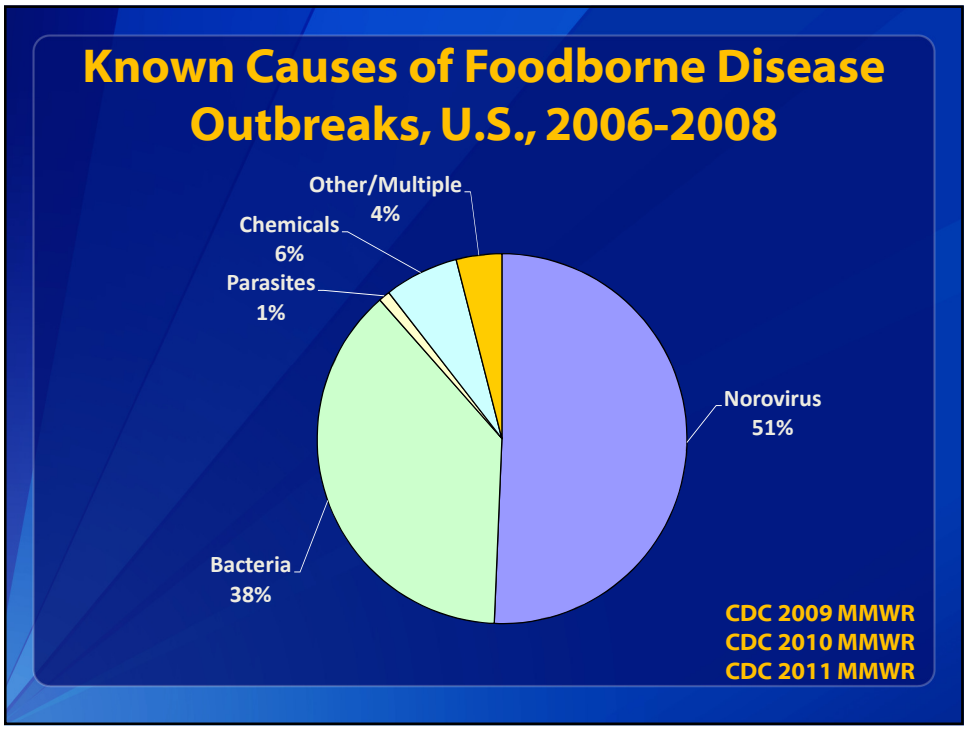
OUTBREAK SURVEILLANCE

Norovirus Outbreaks

- Leading cause of epidemic gastroenteritis
  - 50% of all cause gastroenteritis outbreaks worldwide
  - 50% of all foodborne disease outbreaks in the United States due to known etiologies
- Occur year round, although peak activity during winter months
- Periodic emergence of new variants sometimes associated with increased number of outbreaks

Patel 2009 J Clin Virol
CDC 2009, 2010, 2011 MMWR


Outbreaks of Acute Gastroenteritis, 30 States 2007-2010
Non-norovirus
Norovirus
GII.4 New Orleans strain emerged
75%
25%
No. outbreaks
600
500
400
300
200
100
0
Jan-07
Jul-07
Jan-08
Jul-08
Jan-09
Jul-09
Jan-10
Month-Year
Yen 2011 CID


Known Causes of Foodborne Disease Outbreaks, U.S., 2006-2008
Other/Multiple 4%
Chemicals 6%
Parasites 1%
Norovirus 51%
Bacteria 38%
CDC 2009 MMWR
CDC 2010 MMWR
CDC 2011 MMWR

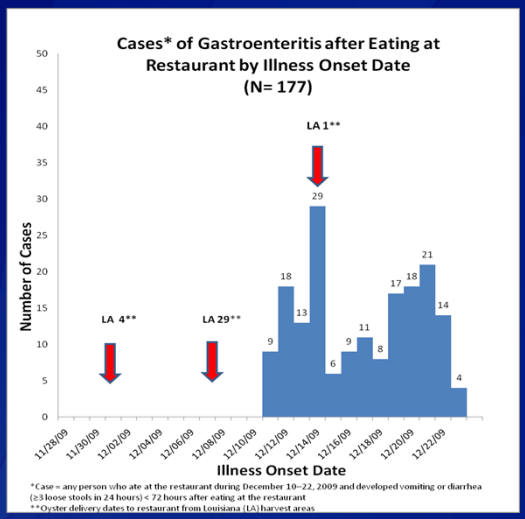
CDC Role During Outbreaks

- Consultation and assistance from NCIRD Division of Viral Diseases
  - Epidemiology: Viral Gastroenteritis Team
  - Laboratory: National Calicivirus Laboratory
- Coordination of multi-state outbreaks
- Special studies to elucidate transmission dynamics
  - Secondary household attack rates and risk factors
  - Immunologic, genetic, and environmental factors
- National outbreak surveillance
  - NORS
  - CaliciNet

State and Regulatory Partner Roles During Outbreaks

- State and local health departments
  - Lead agencies in most norovirus outbreak investigations
  - Interview patients, collect stool specimens, perform clinical diagnostic testing
- Regulatory agencies
  - Collaborate when epidemiologic link established between food and illnesses
  - Coordinate recalls of implicated foods including trace-back and trace-forward
  - Perform food sample diagnostic testing, depending on specific food matrix (e.g., oysters)

Restaurant-associated GII.12 Norovirus Outbreak, North Carolina, 2009



- Involved county, state, CDC, FDA, & academia
- Associated with steamed oysters (OR=12)
- LDHH closed growing area and issued recall
- Recalled product distributed to ≥11 states
- Secondary cases in 20% of households

Alfano-Sobsey 2011 Epid Infect

Norovirus Infections Associated with Frozen Raw Oysters, Washington, 2011

- 3 of 7 diners consumed raw oyster dish at local restaurant
  - All 3 developed gastroenteritis 18-36 hours later lasting 24-48 hours
  - One tested positive for norovirus 17 days after onset
- Internationally distributed product with 2-year shelf life
  - Harvested 7 months before being consumed by WA cluster
  - Imported from Korea and distributed to 8 US states; subsequently recalled
  - Tested positive for norovirus by FDA Gulf Coast Seafood Laboratory

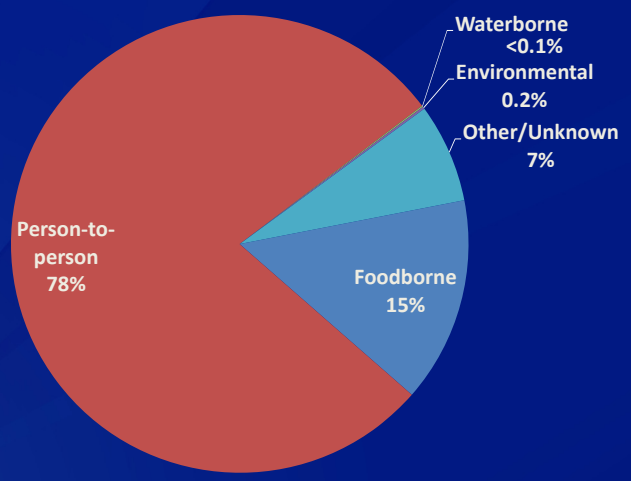
CDC 2012 MMWR

National Outbreak Reporting System (NORS)

- Comprehensive national surveillance system for all US enteric disease outbreaks
- Launched February 2009
- Assess the national burden and temporal trends of outbreaks
- Identify priority settings and populations for interventions
- Characterize outbreaks, e.g.:
  - Pathogen
  - Setting
  - Mode of transmission

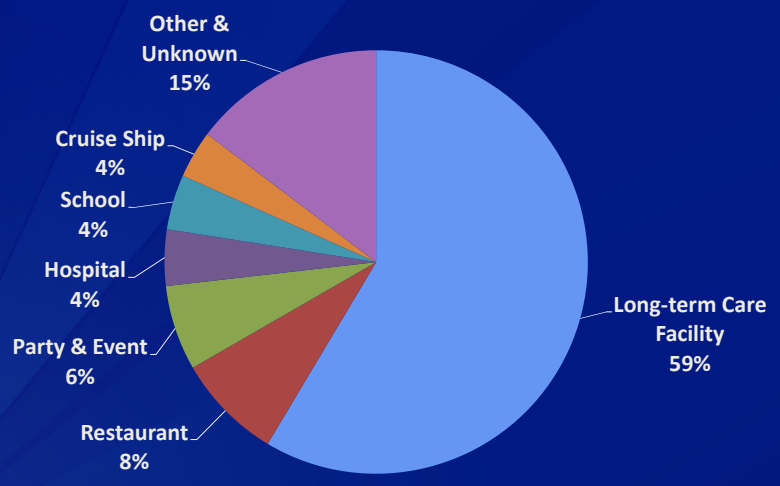
NORS
National Outbreak Reporting System

Mode of Transmission in Norovirus Outbreaks, 20 States, 2009 (N=613)



Preliminary CDC data

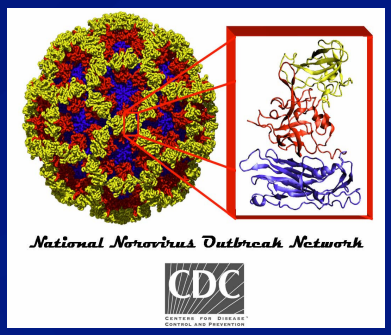
Setting of Confirmed Norovirus Outbreaks, U.S., 2010-2011 (N=1518)



Preliminary CDC data

CaliciNet

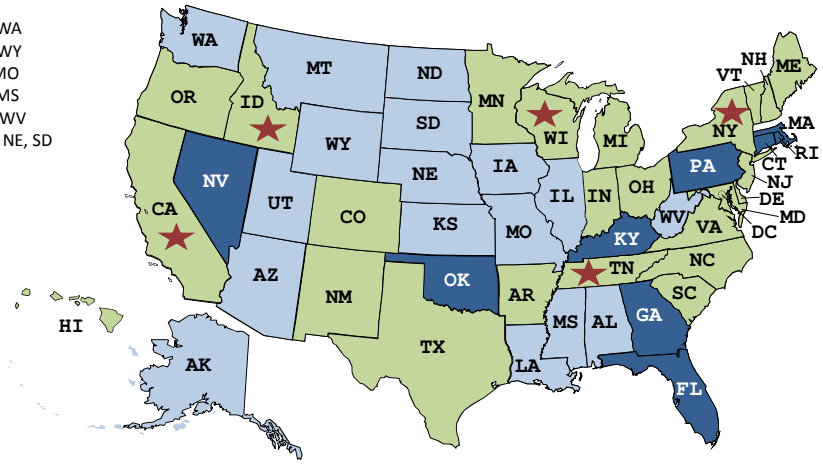
- Molecular norovirus genotyping network (similar to PulseNet)
- Data shared between public health labs and CDC
- Link outbreaks and identify common sources
- Identify emergent variants
- Implemented March 2009
- Currently 25 states certified



CaliciNet: Participating States and OSC

★ CN-Outbreak Support Centers

CA: AZ, UT, WA
ID: AK, MT, WY
WI: IA, KS, MO
TN: AL, LA, MS
NY: MA, RI, WV
CDC: IL, ND, NE, SD



CaliciNet: initiated March 2009
CN-Outbreak Support Centers: November 2010
Data exchange: Bionumerics v 5.1 and higher

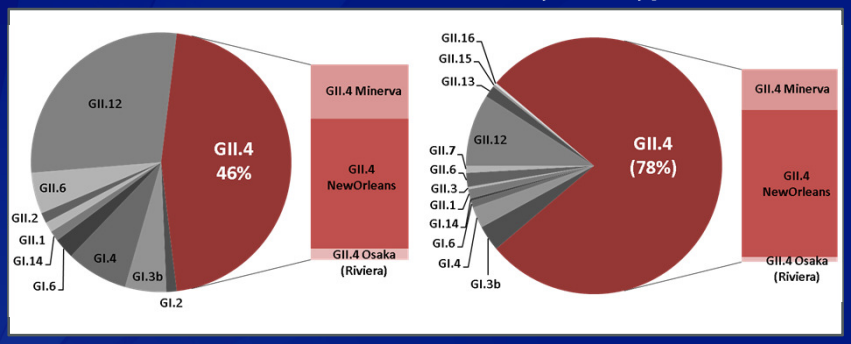
State and Local laboratories certified (n = 25)
State and Local laboratories pending certification
State and Local laboratories submitting to CN-OSC

Updated: 11/08/11

Correlation Between Transmission Route and Genotype, CaliciNet, March 2009-May 2010

Foodborne Outbreaks by Genotype (n = 78)

Person-to-Person Outbreaks by Genotype (n = 340)



Odds ratio: 4.1 (2.5–6.9), p<0.0001

Preliminary CDC data

ATTRIBUTION

Rationale for Attribution Analyses

- Despite demonstrated burden, few evidence-based interventions exist
- Attribution to specific foods can help identify targets for interventions
- Improve understanding of role of food workers and contamination pathways

Foodborne Norovirus Outbreaks Reported to CDC, 2001–2008 (N=2922)

- Average 365 outbreaks annually (1.2 outbreaks/1,000,000 persons)
  - 58% laboratory confirmed
  - 26% included genogroup information
    - 78.0% Genogroup II
    - 18.5% Genogroup I
    - 3.5% both GI/GII
- Outbreaks reported by all 50 states and DC
  - 10% involved residents of multiple states/counties
  - 2% involved exposures in multiple states/counties

Hall 2011 IAFP

Foodborne Norovirus Outbreak-Associated Illnesses by Age and Outcome, 2001-2008

Characteristic	Estimated Average Annual Illnesses (%)[a]	Annual Incidence per 1,000,000 persons[b]
Age group (years)		
<5	215 (2)	10.6
5 to 19	1,827 (18)	30.3
20 to 49	4,923 (48)	39.8
50+	3,359 (33)	37.7
Outcome		
Healthcare Provider Visit	1,247 (12)	4.3
Hospitalization	156 (1.5)	0.5
Death	1 (0.01)	0.002
Total Illnesses	10,324 (100)	35.2

[a] Proportions among illnesses with age and outcome data extrapolated to all illnesses
[b] Incidence calculated using U.S. census data for study period midpoint (2004)

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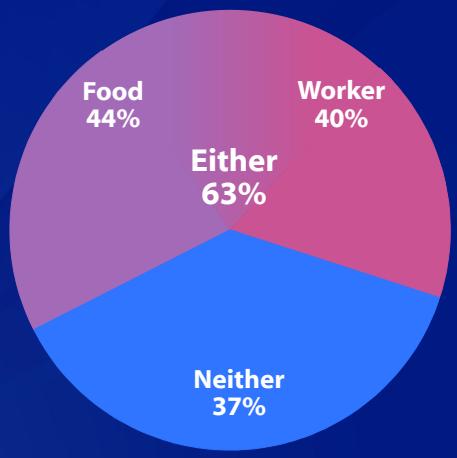
Setting of Foodborne Norovirus Outbreaks Reported to CDC, 2001-2008

Location of Food Preparation[a]	Outbreaks No. (%)	Illnesses per Outbreak Median (Range)
Restaurant or Deli	1824 (62)	12 (2-811)
Private Home or Event[b]	754 (26)	18 (2-400)
School or Daycare	95 (3)	43 (7-425)
Nursing Home	66 (2)	35 (4-160)
Other	598 (20)	28 (2-1200)
Total	2922 (100)	15 (2-1200)

[a] Multiple locations may be implicated in a given outbreak
[b] Includes church, caterer, grocery store, private home, or picnic

Hall 2011 IAFP

Identification of Implicated Source(s) in Foodborne Norovirus Outbreaks Reported to CDC, 2001-2008



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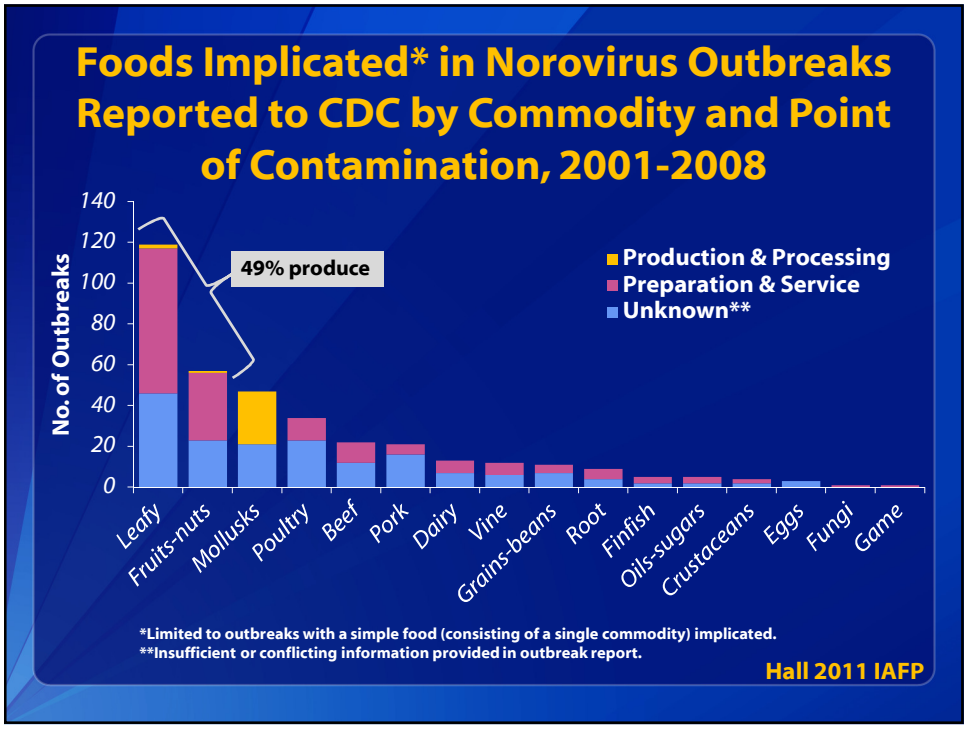
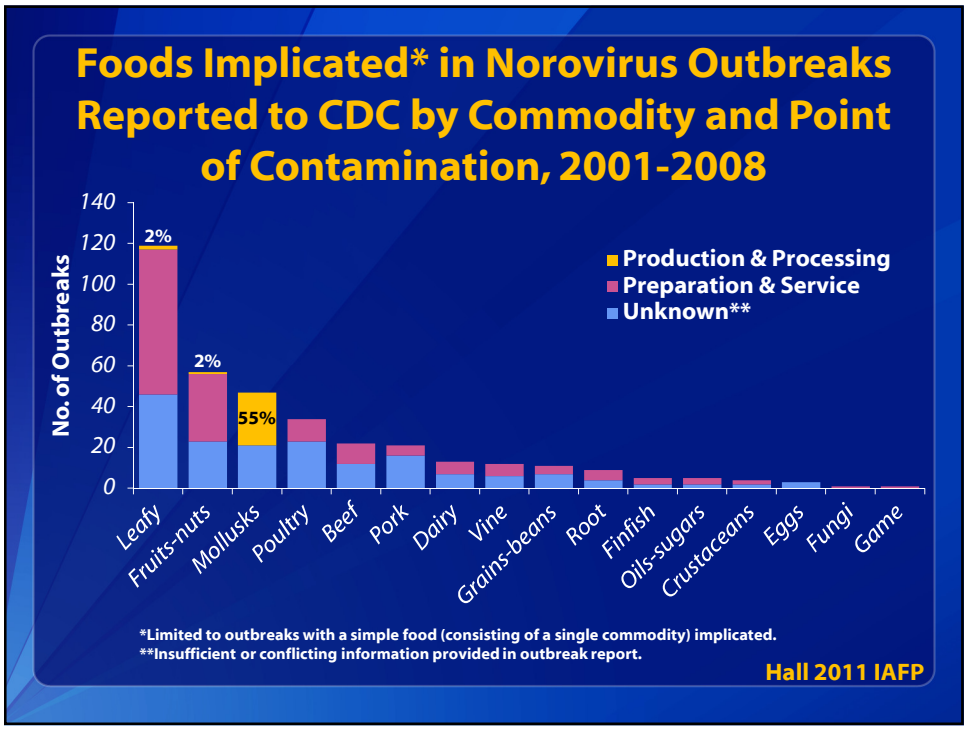

Foods Implicated* in Norovirus Outbreaks Reported to CDC by Commodity and Point of Contamination, 2001-2008
No. of Outbreaks
140
120
100
80
60
40
20
0
49% produce
Production & Processing
Preparation & Service
Unknown**
Leafy
Fruits-nuts
Mollusks
Poultry
Beef
Pork
Dairy
Vine
Grains-beans
Root
Finfish
Oils-sugars
Crustaceans
Eggs
Fungi
Game
*Limited to outbreaks with a simple food (consisting of a single commodity) implicated.
**Insufficient or conflicting information provided in outbreak report.
Hall 2011 IAFP


Foods Implicated* in Norovirus Outbreaks Reported to CDC by Commodity and Point of Contamination, 2001-2008
No. of Outbreaks
140
120
100
80
60
40
20
0
2%
2%
55%
Production & Processing
Preparation & Service
Unknown**
Leafy
Fruits-nuts
Mollusks
Poultry
Beef
Pork
Dairy
Vine
Grains-beans
Root
Finfish
Oils-sugars
Crustaceans
Eggs
Fungi
Game
*Limited to outbreaks with a simple food (consisting of a single commodity) implicated.
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Summary of Attribution Analyses

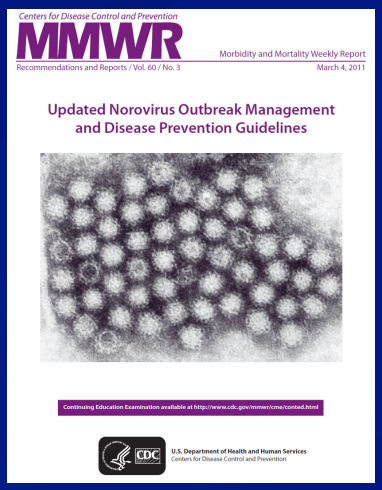
- On average, at least one foodborne norovirus outbreak occurs every day in the United States
- Most common scenario: Ready to eat foods prepared in commercial settings where food handler contact contributed to contamination
- Nearly all commodities have been implicated
  - Those typically eaten raw are most common (leafy greens, fruits, mollusks)
  - Most contamination occurs at point of preparation/service, except with mollusks
  - Production-level contamination of produce identified rarely, but likely under-recognized

PREVENTION AND CONTROL

Updated CDC Guidelines

http://www.cdc.gov/mmwr/pdf/rr/rr6003.pdf

- Developed by CDC based on literature review and unpublished data from outbreak investigations
- Input from state and local health departments and regulatory partners
- Reviews advances since previous guidelines (2001)
- Provides recommendations for general outbreak management and disease prevention
- Published March 2011


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 60 / No. 3
March 4, 2011

Updated Norovirus Outbreak Management and Disease Prevention Guidelines

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/conhed.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Prevention and Control

- Rapid reporting, response, and investigation
  - Identify mode of transmission and source of contamination
  - Collect appropriate specimens

Prevention and Control

- Rapid reporting, response, and investigation
  - Identify mode of transmission and source of contamination
  - Collect appropriate specimens
- Promote appropriate hand hygiene
  - Wash with soap and water ≥ 20 seconds
  - Alcohol-based hand sanitizers?

Prevention and Control

- Rapid reporting, response, and investigation
  - Identify mode of transmission and source of contamination
  - Collect appropriate specimens
- Promote appropriate hand hygiene
  - Wash with soap and water ≥ 20 seconds
  - Alcohol-based hand sanitizers?
- Prompt and thorough disinfection
  - Bleach solution for contaminated surfaces
  - Other EPA-approved disinfectants?

Prevention and Control

- Rapid reporting, response, and investigation
  - Identify mode of transmission and source of contamination
  - Collect appropriate specimens
- Promote appropriate hand hygiene
  - Wash with soap and water ≥ 20 seconds
  - Alcohol-based hand sanitizers?
- Prompt and thorough disinfection
  - Bleach solution for contaminated surfaces
  - Other EPA-approved disinfectants?
- Manage and exclude ill persons
  - ≥ 24-72 hrs after symptom resolution
  - Accommodating sick pay/leave policies for staff

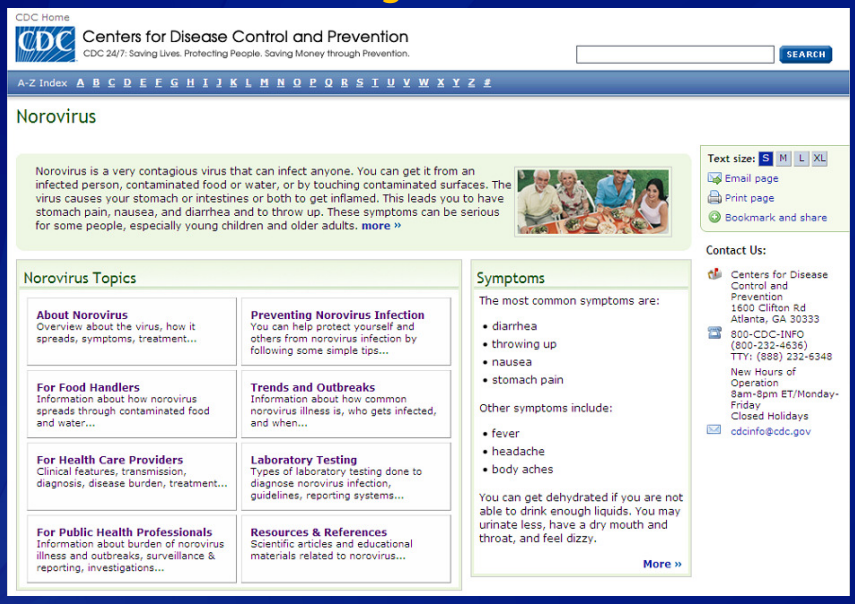
The NEW ENGLAND JOURNAL of MEDICINE

Norovirus Vaccine against Experimental Human Norwalk Virus Illness

- Randomized double blind placebo-controlled multicenter trial with healthy adults 18-50 years old
- Safety, immunogenicity, and efficacy of intranasally delivered norovirus VLP vaccine after homologous challenge with Norwalk virus (genotype GI.1)
- Vaccine protected against illness (~50%) and decreased infection frequency (~25%)
- First demonstration that a norovirus vaccine can prevent disease
- Key questions remaining: duration of immunity, cross-protection, other formulations, other age groups

Atmar 2011 NEJM

Acknowledgments

- NCIRD / Division of Viral Diseases
  - Viral Gastroenteritis Team
    - Ben Lopman
    - Mary Wikswo
    - Scott Grytdal
    - Catherine Yen
    - Rishi Desai
    - Paul Gastañaduy
    - Tarak Trivedi
    - Manish Patel
    - Dan Payne
    - Umesh Parashar
  - National Calicivirus Lab
    - Jan Vinjé
    - Leslie Barclay
    - Nicole Gregoricus
    - GeunWoo Park
    - Verónica Costantini
    - Everardo Vega
- NCEZID / Division of Foodborne, Waterborne & Environmental Diseases
  - Hannah Gould
  - Jonathan Yoder
  - Olga Henao
  - Virginia Roberts
  - Karunya Manikonda
  - Magdalena Kendall
- NCEZID / Division of Healthcare Quality Promotion
  - Tara MacCannell
  - Cliff McDonald
- State, Local, and Regulatory Partners
- USDA-NIFA Food Virology Collaborative (NoroCORE)

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