Update on Rotavirus and Other Viral Causes of Acute Gastroenteritis

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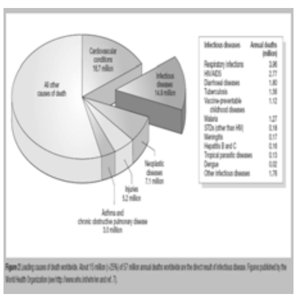
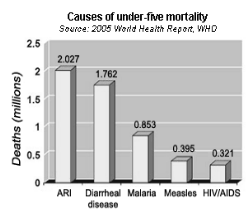
Update on Rotavirus and Other Viral Causes of Acute Gastroenteritis -Objectives-

- Updated information about norovirus and rotavirus
- Public health impact of rotavirus vaccination program
- Current epidemiological trends
- Importance of public health surveillance systems

Global Impact of Gastroenteritis (Diarrheal Diseases)

www.who.int/vaccine_research/diseases/diarrhoeal/en/print.html





United States Impact of Gastroenteritis

- Estimates of foodborne illness in the U.S.
  http://www.cdc.gov/foodborneburden/index.html
  - Each year:
    - 48million people (1 in 6) get sick
    - 128,000 hospitalized
    - 3000 die
  - Estimates can be compounded by community spread
- Only the common cold reported more often than GE of all cases

FOODBORNE GASTROENTERITIS

www.cdc.gov/ncidod/dbmd/diseaseinfo/foodborneinfections_g.htm

Bacterial Agents
- **Campylobacter spp.**
- **Salmonella spp.**
- **E. coli STEC, ETEC, Other**
- Shigella spp.
- S. aureus
- C. perfringens
- C. botulinum
- L. monocytogenes
- V. cholerae
- V. parahemolyticus
- V. vulnificus
- Vibrio spp.
- B. cereus
- Y.enterocolitica
- Strep spp., Grp A
- Brucella spp.

Viral Agents
- **Norovirus**
- Hepatitis A
- **Rotavirus**
- Sapovirus
- Astrovirus
- Other ???

Protozoan Agents
- Giardia intestinalis
- Cryptosporidium parvum
- Cyclospora cayatenensis
- Toxoplasma gondii
- Trichinella spp

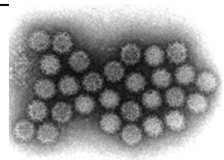
Noroviruses 2011

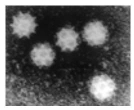
http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus.htm
New Engl J Med 2009;361:1776-85

A nasty bug and getting nastier
- New pandemic strain identified
- Immunity strain-specific and non-enduring
- Highly contagious; environmentally stable
- Food-borne and community-acquired
- Targets restaurants, schools, chronic care facilities, and cruise ships
- Critical need for personal hygiene!

Norovirus
Virology

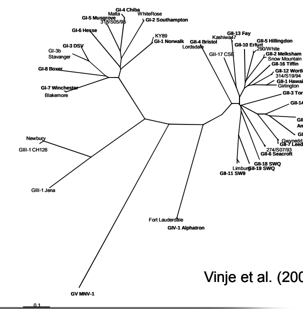
- Family *Caliciviridae*----ssRNA, non-enveloped, 26-34nm viruses
- 4 genera:
  - *Lagovirus*
  - *Vesivirus*
  - ***Sapovirus***
  - ***Norovirus***
    - 5 *genogroups*
      - GI, GII, GIV---humans
      - GIII---pigs and cows
      - GV---mice
    - ≥ 25 *genotypes (genetic clusters)*
    - Ongoing emergence (drift) resulting in *strains* among *genotypes*
    - GII.4 *strains* currently predominate worldwide





Norovirus
Antigenic Diversity

GI: human



GII: human

Vinje et al. (2009)

Norovirus
Clinical Features

- Incubation period----10-51hr
- Duration of illness---24-72 hours
- Clinical effects across the age spectrum
  - Acute onset of nausea and cramping
  - Vomiting (more prevalent among children) and moderate diarrhea (more prevalent among adults) are hallmarks
  - Low-grade fever in up to 50% of cases
  - Variable constitutional symptoms (e.g., chills, malaise, headache, myalgia)
- Dehydration is most common complication
  - May require i.v. replacement fluids
- Most patients recover without incident; fatalities rare

Norovirus
Pathogenesis and Immunity

- Exact mechanism of diarrhea and vomiting unknown
- Observation: asymptomatic infection may occur in 30% of infections
  - Susceptibility to infection and illness severity genetically determined
    - Link to ABH histo-blood group antigens
  - Role for asymptomatics in transmission?
- Recent GII.4 strains cause more severe disease
  - More intense symptoms, more fever, longer illness duration (3-4d); greater transmissability
- Immunity strain-specific, but short-lived (months?)
  - Re-infection common

Norovirus
Epidemiology(I)

Reservoir

- Humans are only known reservoir for human infection

Modes of Transmission

- High levels of virus found in stool and vomit
- Transmission via:
  - Food
  - Water
  - Direct person-to-person contact
    - 2° and 3° cases following point-source outbreak
  - Contact with contaminated object or surface
  - Airborne via aerosolization of vomitus

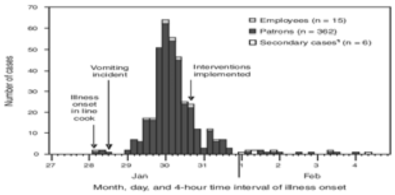
Norovirus
Epidemiology(II)

Characteristics That Facilitate Spread:

- Low infectious dose (<10-100 viral particles)
- Prolonged (up to 4w or more) viral shedding even in asymptomatic (>90%)
  - Increased risk from infected food handlers
  - Viral shedding vs. infectivity
- Environmental stability and persistence
  - Survives:
    - up to10 ppm chlorine
    - freezing
    - up to 60°C
    - use of many routine disinfectants

Norovirus
Transmissibility

FIGURE 1. Number of cases of norovirus illness among patrons and employees* of a restaurant,† by 4-hour time interval§ of illness onset — Eaton County, Michigan, January 28–February 4, 2006



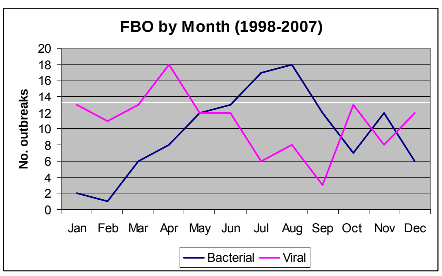
* Cases among patrons defined as illness with vomiting or diarrhea, with an incubation period of 10–50 hours. Cases among employees defined as illness with vomiting or diarrhea during January 19–February 3, regardless of incubation period.
† The first two employees in whom cases were identified (onset dates January 19 and 21) and the first two patrons in whom cases were identified (onset dates January 23) are not included.
§ Time intervals: 1) 12:00 a.m. to 3:59 a.m.; 2) 4:00 a.m. to 7:59 a.m.; 3) 8:00 a.m. to 11:59 a.m.; 4) 12:00 p.m. to 3:59 p.m.; 5) 4:00 p.m. to 7:59 p.m.; and 6) 8:00 p.m. to 11:59 p.m.
¶ Cases in persons who had not eaten at the restaurant but became ill after contact with a patron or employee in whom a case was identified.

MMWR (2007) Norovirus Outbreak Associated with Ill Food-Service Workers --- Michigan, January--February 2006 56(46).

Outbreaks of Acute Gastroenteritis
Settings in the U.S.- 2006

Setting	Number of Outbreaks
Cruise ships	37
Long-term care facilities	37
Restaurants	13
Hospitals	7
Colleges	3
Parties	3
Other:Schools,daycare,etc.	26
Total	**126**

Norovirus
Epidemiology (III) - *Seasonality*



Source: WI Dept. of Public Health

Norovirus
Prevention and Control

Prospects for a vaccine

- The clinical and public health motivation is present
- Significant obstacles
  - Is morbidity /mortality severe enough?
  - Lack of *in vitro* propagation methods
  - Lack of long-term protective immunity
    - A local infection
  - Antigenic diversity:
    - multiple genotypes, strains
    - "influenza-like" drift
    - Pandemic-like global spread of new strains

Norovirus
Prevention and Control

Recommended Measures

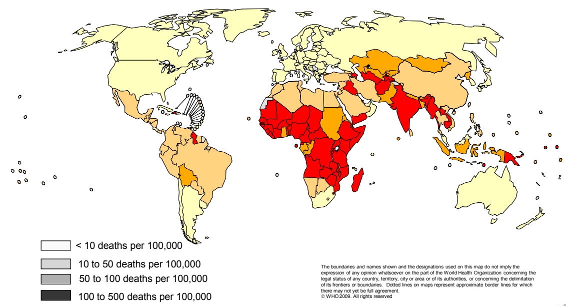
- Practice good hand hygiene
- Aggressive disinfection of contaminated surfaces
- Do not return to work or school until 24-72h after symptoms resolve
  - Particularly important with food handlers
- Aggressive measures for outbreak control in healthcare and LTCFs

Rotavirus
www.cdc.gov/rotavirus/index.html

ROTAVIRUS
Public Health Importance

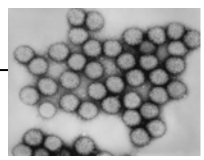
- Most important cause of severe, dehydrating GE in children <5y in all socioeconomic groups in all regions of the world
- Responsible for ~ 6% of all mortality in children < 5y
  - Mortality predominately in developing world
    - > 500,000 deaths annually; >2,000,000 hospitalized
    - Malnutrition, less access to Rx, synergy with other pathogens
- However, the story is changing

Mortality Rate per 100,000 Child Deaths due to Rotavirus Disease



Source: WHO/IVB database, 193 WHO Member States. Data as of July 2009
Date of slide: September 2009

Rotavirus
Virology



- Family: *Reoviridae*
  - dsRNA, 11 segments, non-enveloped
- 7 serogroups A-G; only A, B, C infect humans
- Many serotypes within serogroup A
  - 4 responsible for 90% of pediatric cases worldwide. However…
  - Serotype prevalence varies geographically
  - Reassortment and antigenic drift occur

Rotavirus
Clinical Features

- Incubation period----24-72 h
- Duration of illness---- 3 to 8d
- Most severe illness in infants 6m – 2yrs
  - Fever, **vomiting,** diarrhea
  - Dehydration with severe electrolyte abnormalities
- Exacerbating factors: malnutrition, immunodeficiency & poor sanitation
- Decrease in illness severity with age

Rotavirus
Pathogenesis and Immunity

- Mechanisms of diarrhea and vomiting complex and incompletely understood
- As many as 50% infections subclinical
- Complex immune response
  - Innate, cellular, and humoral mechanisms
  - Re-infections common throughout life; succeeding illnesses milder
    - This is the case even if initial infections asymptomatic

Rotavirus
Epidemiology

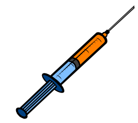
- Human reservoir
- Transmission: person-to-person
  - fecal - oral; very rarely waterborne, foodborne
  - respiratory?
- Characteristics that facilitate spread
  - Virus shed in very large amounts; prolonged shedding
  - Small infectious dose
  - Environmental stability
- Seasonality (“back in the day”)
  - Marked Winter-Spring peak in temperate climates

ROTAVIRUS
Prevention and control

- Vaccine represents the most promising public health control measure
  - Natural infection provides protection against disease
  - Treatments not readily available
  - Transmission unaffected by improvements in sanitation and hygiene
  - Cost effective

Rotavirus
Vaccines

- RotaTeq®
  - Pentavalent vaccine containing G1, G2, G3, G4, P[8]
  - Licensed by FDA in 2006
  - ACIP recommendations in 2006
- Rotarix®
  - Monovalent contains genotype G1P[8]
  - Relies on heterotypic immunity
  - Licensed by FDA in 2008
  - Widely used in Brazil



Rotavirus
Vaccines

- Uptake nationally: >70% in 6 of 8 states (MMWR, 2010).
- Uptake in WI: 80% had received at least one dose of vaccine (MMWR, 2010).

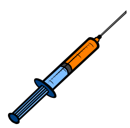
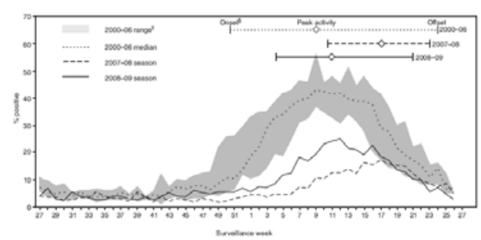
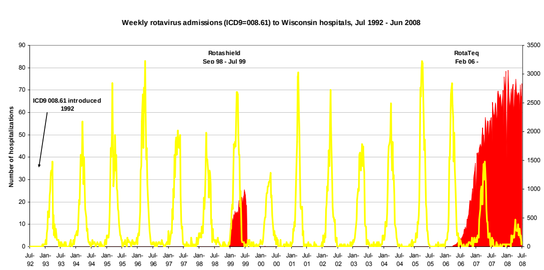


FIGURE. Percentage of rotavirus tests with positive results, by surveillance week --- participating laboratories, National Respiratory and Enteric Virus Surveillance System (NREVSS), United States, July 2000--June 2009*

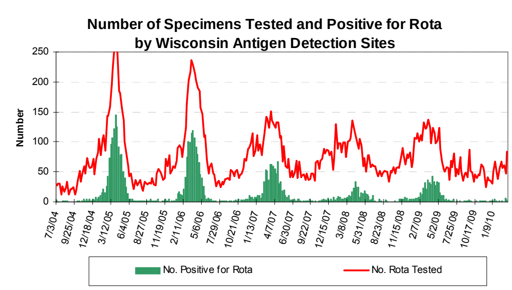


MMWR, Oct 23, 2009/ 58(41);1146

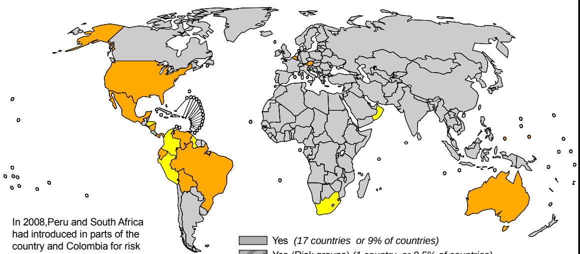
Early Returns in the Wisconsin are Promising As Well (I)



Early Returns in the Wisconsin are Promising As Well (II)



Countries Using Rotavirus Vaccine in National Immunization Schedule, 2008



In 2008,Peru and South Africa had introduced in parts of the country and Colombia for risk groups

Source: WHO/IVB database, 193 WHO Member States. Data as of July 2009. 2009 data is provisional
Date of slide: September 2009

Rotavirus Vaccines
Prospects for Global Success

Recent successes: 2006-07 N Engl J Med 362;4 1/28/10
- Mexico
- Africa

Anticipated challenges
- How reproducible are results in other countries
- Storage and shipment requirements
- Narrow window for vaccine administration*
  - 1st dose between 6-15 weeks and 3rd dose no later than 32 weeks
- Cost of vaccine in the U.S.
- Past experience with oral vaccines in developing countries
- Antigenically changeable virus - will immunization drive evolution?
  - Need to maintain/expand surveillance

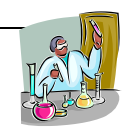
Norovirus vs. Rotavirus
An interesting public health comparison

One on the rise

vs.

One on the decline

Norovirus:
Laboratory methods

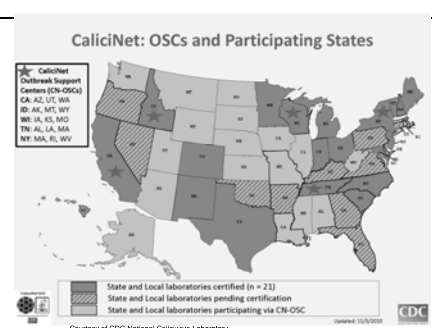


- Cell culture
- RT-PCR
  - High sensitivity, specificity, throughput, same day results.
  - Limitations: Infectious virus, inhibitors
- EIA
  - Sensitivity =55% compared with RT-PCR (Moe, 2004).
  - Specificity =83 to 96% (Gray, et al., 2007)

Norovirus:
National Surveillance

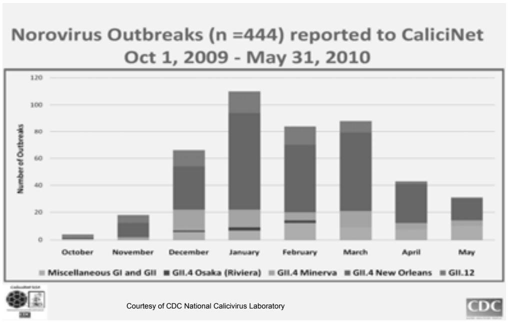
- CaliciNet
  - 17 states certified March 2010
  - Wisconsin one of 5 SPHL selected
  - Specimens received from 3 Midwest states
  - Sequences deposited in national database
  - Objectives:
    - Improve surveillance
    - Real-time data exchange
    - Linking clusters of illness
    - Monitor for emerging strains

CaliciNet: Geographical representation

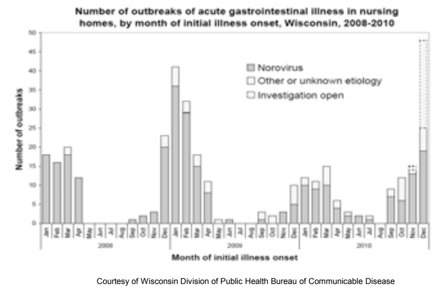


Courtesy of CDC National Calicivirus Laboratory

Norovirus diversity

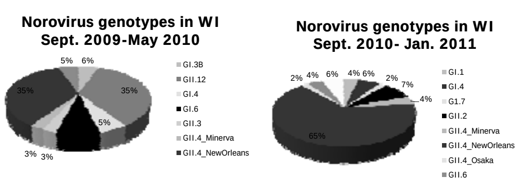


Norovirus
WI Surveillance



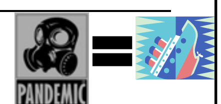
Norovirus
WI Surveillance

- Wisconsin strain surveillance



Norovirus
Epidemiology

PANDEMICs occur every 2-4 years!



Source: www.stuffwelike.com/.../2009/11/Pandemic.jpg

- Emergence of novel GII.4
  - Possess different epidemiological profile
    - ↑ Attack rate
    - Vomiting & diarrhea
    - Duration of illness
- **2002 GII.4_Farmington Hills**
- **2006 GII.4_Minerva**
  - **WDPH investigated 106 AGE v. 23 in 2005!**
- **2010 GII.4_New Orleans**
  - **WDPH investigated 37 outbreaks in December 2010!**

Norovirus Summary

- Genetically diverse
- Antigenic drift
- GII.4 pandemic potential
- National and community impact uncertain
- Vaccine faces many challenges
- Knowledge base continues to expand

Rotavirus
Laboratory methods

- EIA* Sensitivity >90%
  - BioRad Pathfinder, Vidas, Rotaclone, etc…
  - Limitations:
    - NPV high
    - PPV low
    - GrpA specific

- RT-PCR
- Sequencing

Rotavirus
Molecular Epidemiology

- US Rotavirus strain surveillance data: 2005-2008 (Hull et al., 2011)

Year	Genotypes
2005-2006	G1 predominate
2006-2007	G1 predominate
2007-2008	G1 & G3 predominate, G2, G9

Rotavirus vaccine: Impact on strain diversity and age distribution

- Key findings (Hull J et al., 2011)
  - Reports from Brazil & Australia described changes in genotype prevalence post-vaccine
  - US: G3 emerged as predominate rotavirus genotype in some sentinel sites (2007-2008)
  - G3 predominated in states primarily using RotaTeq® (natural fluctuation vs. vaccine driven)
  - Mean age of rotavirus patients increased from
    - 13 to17.8 months in 2007-2008.

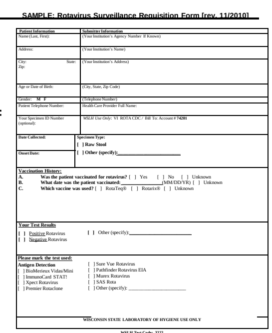
Is diversity natural fluctuation or vaccine driven??

Rotavirus surveillance--Wisconsin

- Collaboration between CDC/WSLH/WI Clinical Laboratories
- Aim is to assist CDC with national strain surveillance
  - ➢Monitor for emerging strains
  - ➢Change in genotype prevalence
  - ➢Ensure vaccines are effective

Rotavirus specimen submission

- Please send **ALL** rotavirus positive specimens to WSLH
- **NO cost** for shipping if using Dunham
- Specimens can be sent weekly (refrigerated)
- Sent with Flu surveillance specimens
- Raw stool or VTM acceptable



Rotavirus
Summary

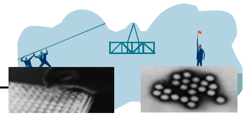
- Diverse genome
- Vaccine impact on morbidity & prevalence
- Vaccine impact on strain evolution (genotypes G&P included in vaccine)
  - Brazil and US noted a shift in prevalence of other genotypes following vaccination (Gentsch et al., 2009). Natural fluctuation or vaccine driven?

⇨ Importance of monitoring viral genotype prevalence.

Future Concerns

- Monitoring for emerging strains of *norovirus* and *rotavirus*.
- No national surveillance system for norovirus
  - Difficult to assess public health impact
- Emergence of *sapovirus*
  - Studies have concluded that sapovirus infections are increasing in Europe (Svraka et al., 2010).
- What is the significance of other viral etiologies?
  - Adenovirus 40/41, astrovirus, sapovirus, unknown

Diagnostic gap



- What role do viruses other than *norovirus* play in outbreaks and AGE morbidity in the US?
  - Etiologies unknown in 12-41% of outbreaks (Lyman et al., 2009 & Finkbeiner et al., 2009).
- WI NFBO investigation data:

Year	NV	Unknown	%	Other
2006	61	11	15.3	
2007	41	12	22.6	
2008	90	5	5.3	
2009	102	21	17.1	Sapovirus
2010	110	27	19.7	

Courtesy of John Archer WI Division of Public Health (2010)

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