Norovirus
Highly Infectious and Seemingly Ubiquitous...
But Soon To Be Vaccine-Preventable?

BEN LOPMAN, PhD MSc
Associate Professor, Department of Epidemiology
Emory University, Rollins School of Public Health
CDC Division of Viral Diseases

Georgia Emerging Infections Program
24 March 2017
Outline

• Clinical features, virology, immunity and host susceptibility
• The disease burden and epidemiology
• Vaccines
Norovirus affecting more than 100 persons

Norovirus leading cause of gastroenteritis
• in low- to high-income settings
• #1 cause of diarrheal disease in community
• #1 cause of foodborne disease in U.S.
• Key health care-associated infection

By Sonam Vashi
Executive Editor
and
Dustin Slade
News Editor
Key features: clinical

• Short incubation period
  – 24-48 hours

• Acute-onset vomiting and/or diarrhea
  – Watery, non-bloody stools
  – Abdominal cramps, nausea, low-grade fever

• Most recover after 12-72 hours
  – ~10% seek medical attention; some require hospitalization and fluid therapy
  – Severe illness and death in elderly and those with underlying conditions

• 30% of infections are asymptomatic
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: 18-2,800 viral particles
• Infectivity of prolonged viral shedding and role in transmission is unknown

Atmar 2008 EID; Teunis 2008 JMV; Aoki 2010 J Hosp Infect; Atmar 2014 JID
Basic Virology

- Single stranded RNA virus
- Highly diverse
  - 2 genogroups mainly cause disease in humans
    - 30 genotypes
- GII.4 viruses cause >75% of disease
  - May cause more severe disease

Kroneman et al, Arch Virol 2013
Noroviruses are highly diverse and rapidly evolving

- GII.4 noroviruses undergo genetic shifts every 2-3 years.
- New emerging strains will replace previous strains.

Epochal evolution: new GII.4 variants emerge every 2-4 years

Noel et al., 1999, Widdowson et al., 2004, MMWR 2007, Siebenga et al., 2009, Yen et al., 2011, Leshem et al., 2013, Vega et al., 2014
What we know about immunity and genetic susceptibility

- Human volunteer studies demonstrated short-term immunity
  - <6 months - 2 years
  - Modeling studies suggest may be longer
- Little persistent cross-protective immunity
- Genetic susceptibility

Role of FUT2 “secretor” gene

- Histo-blood group antigens (HBGAs) are expressed by the alpha fucosyltransferase-2 (FUT2) gene
- HBGAs are a binding interface on the surface of mucosal epithelial cells
- If FUT2 gene is inactivated, noroviruses cannot bind to the HBGAs
- ~20% of European descendants are non-secretors:

In vitro studies suggest that ‘secretors’ are at risk.

Payne, Parashar, Lopman, Current Opinion in Pediatrics, 2015
Interaction of viral molecular epidemiology and human genetics

In vivo studies: secretor status determines susceptibility -- to GII.4 norovirus

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Secretors NV+</th>
<th>Secretors NV-</th>
<th>Non-Secretors NV+</th>
<th>Non-Secretors NV-</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currier, 2014</td>
<td>17</td>
<td>130</td>
<td>1</td>
<td>42</td>
<td>0.69 [0.31, 1.54]</td>
</tr>
<tr>
<td>Lopman, 2014</td>
<td>21</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>0.50 [0.19, 1.30]</td>
</tr>
<tr>
<td>Nordgren, 2010</td>
<td>956</td>
<td>17</td>
<td>1</td>
<td>2</td>
<td>0.71 [0.23, 2.18]</td>
</tr>
<tr>
<td>Rockx, 2005</td>
<td>10</td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>7.50 [0.93, 60.43]</td>
</tr>
<tr>
<td>Lindesmith, 2003</td>
<td>97</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>21 [4.16, 1252.98]</td>
</tr>
<tr>
<td>Nordgren, 2013</td>
<td>1757</td>
<td>591</td>
<td>0</td>
<td>183</td>
<td>4.88 [0.27, 87.33]</td>
</tr>
<tr>
<td>Bucardo, 2009</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0.62 [0.03, 12.48]</td>
</tr>
<tr>
<td>Hutson, 2005*</td>
<td>1850</td>
<td>1232</td>
<td>0</td>
<td>9</td>
<td>[18.05, 12855.02]</td>
</tr>
<tr>
<td>RE Model for Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.36 [0.68, 16.68]</td>
</tr>
<tr>
<td>GII non-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currier, 2014</td>
<td>17</td>
<td>85</td>
<td>1</td>
<td>21</td>
<td>1.79 [1.10, 2.89]</td>
</tr>
<tr>
<td>Van Trang, 2014</td>
<td>33</td>
<td>10</td>
<td>1</td>
<td>16</td>
<td>0.65 [0.23, 1.86]</td>
</tr>
<tr>
<td>Lopman, 2014</td>
<td>21</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>3.24 [1.13, 9.28]</td>
</tr>
<tr>
<td>Nordgren, 2013</td>
<td>9</td>
<td>130</td>
<td>1</td>
<td>42</td>
<td>5.40 [0.71, 42.52]</td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>15</td>
<td>87</td>
<td>1</td>
<td>21</td>
<td>3.62 [0.45, 28.97]</td>
</tr>
<tr>
<td>Le Guayner, 2010</td>
<td>18</td>
<td>7</td>
<td>1</td>
<td>16</td>
<td>17.50 [1.70, 160.02]</td>
</tr>
<tr>
<td>Lindesmith, 2005*</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>4.00 [0.27, 58.56]</td>
</tr>
<tr>
<td>Bucardo, 2009</td>
<td>12</td>
<td>123</td>
<td>0</td>
<td>8</td>
<td>1.72 [0.09, 31.61]</td>
</tr>
<tr>
<td>Tan, 2008</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>8.64 [0.35, 214.61]</td>
</tr>
<tr>
<td>Jin, 2013</td>
<td>18</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td>0.30 [0.01, 7.88]</td>
</tr>
<tr>
<td>RE Model for Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.25 [1.20, 4.16]</td>
</tr>
<tr>
<td>GII.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>17</td>
<td>85</td>
<td>1</td>
<td>21</td>
<td>2.40 [0.53, 33.37]</td>
</tr>
<tr>
<td>Nordgren, 2013</td>
<td>9</td>
<td>130</td>
<td>1</td>
<td>42</td>
<td>2.91 [0.36, 23.63]</td>
</tr>
<tr>
<td>Carlson, 2009</td>
<td>33</td>
<td>10</td>
<td>1</td>
<td>16</td>
<td>52.80 [6.21, 449.03]</td>
</tr>
<tr>
<td>French, 2012*</td>
<td>16</td>
<td>7</td>
<td>1</td>
<td>16</td>
<td>36.57 [4.02, 332.34]</td>
</tr>
<tr>
<td>Jin, 2013</td>
<td>49</td>
<td>20</td>
<td>4</td>
<td>1</td>
<td>0.61 [0.06, 5.82]</td>
</tr>
<tr>
<td>Currier, 2014</td>
<td>1756</td>
<td>591</td>
<td>0</td>
<td>183</td>
<td>109.51 [6.79, 1766.38]</td>
</tr>
<tr>
<td>Van Trang, 2014</td>
<td>22</td>
<td>184</td>
<td>0</td>
<td>26</td>
<td>6.46 [0.38, 109.73]</td>
</tr>
<tr>
<td>Lopman, 2014</td>
<td>21</td>
<td>136</td>
<td>0</td>
<td>21</td>
<td>6.77 [0.40, 115.98]</td>
</tr>
<tr>
<td>Tan, 2008</td>
<td>41</td>
<td>74</td>
<td>0</td>
<td>15</td>
<td>17.27 [1.01, 296.05]</td>
</tr>
<tr>
<td>Thorven, 2005</td>
<td>38</td>
<td>40</td>
<td>0</td>
<td>18</td>
<td>35.17 [2.05, 604.09]</td>
</tr>
<tr>
<td>Kindberg, 2007</td>
<td>29</td>
<td>23</td>
<td>0</td>
<td>9</td>
<td>23.85 [1.32, 431.31]</td>
</tr>
<tr>
<td>Bucardo, 2009</td>
<td>11</td>
<td>123</td>
<td>0</td>
<td>8</td>
<td>1.56 [0.09, 29.22]</td>
</tr>
<tr>
<td>RE Model for Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.89 [3.94, 24.84]</td>
</tr>
</tbody>
</table>

Kambhampati, Payne, Costantini, Lopman, *CID*, 2015
Progress in cell culture

• No small animal model
• Cell culture
  – Human B cells
    • Jones et al., 2014 Science
  – Human Intestinal enteroids
    • Ettayebi et al., 2016 Science
Outline

• Clinical features, virology, immunity and host susceptibility

• The disease burden and epidemiology
Global Burden of Norovirus

• WHO Foodborne Disease Burden Epidemiology Reference Group (FERG)

• Global and regional age-stratified estimates of illnesses, deaths, and DALYs

• Norovirus ranking as foodborne hazard:
  – #1 cause of foodborne illness
  – #4 cause of foodborne deaths
  – #5 cause of foodborne DALYs

• Total norovirus burden annually:
  – 685 million cases; 200 million in children <5
  – 212,489 deaths; 54,214 in children <5
  – 85% of illnesses and 99% of deaths occur in developing countries
  – $60 billion in direct health system costs and productivity loses

Challenges in estimating [global] burden of norovirus

<table>
<thead>
<tr>
<th>Diagnostics: availability</th>
<th>Diagnostics: interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not coded for in ICD-data</td>
<td>Sub-clinical cases</td>
</tr>
<tr>
<td>Little surveillance</td>
<td>Few community studies</td>
</tr>
</tbody>
</table>
Age Specific Clinical Outcomes of Norovirus in the United States

Hall, Curns, McDonald, Parashar, Lopman, 2012 CID
Lopman, Hall, Curns, Parashar, 2011 CID
Gastañaduy, Hall, Curns, Parashar, Lopman, 2013 JID
Norovirus disease burden in the United States

- **Deaths**: 800, Lifetime risk: 1 in ~6,000
- **Hospitalizations**: 71,000, Lifetime risk: 1 in ~60
- **Emergency department visits**: 400,000, Lifetime risk: 1 in ~9
- **Outpatient visits**: 1.8 million, Lifetime risk: 1 in ~2
- **Cases**: 19 to 21 million, Lifetime risk: 5 times

Hall, Lopman, Payne, Patel, Gastañaduy, Vinjé, Parashar, 2013 EID
Hall, Curns, McDonald, Parashar, Lopman, 2012 CID
Lopman, Hall, Curns, Parashar, 2011 CID
Gastañaduy, Hall, Curns, Parashar, Lopman, 2013 JID
Scallan et al, 2010 EID
Is norovirus a cause of death?

- Retrospective cohort
- All nursing homes in Oregon, Pennsylvania, and Wisconsin that reported at least one norovirus outbreak between January 1, 2009–December 31, 2010
- 307 Nursing homes
  - 407 outbreaks

Is norovirus a cause of death?

Decline in rotavirus and AGE hospitalizations following vaccine introduction in US

Leshem, Tate Steiner, Curns, Lopman, Parashar, JAMA 2015
Norovirus and Rotavirus Hospitalization, ED and outpatient rates
0 – 4 year olds
2009 to 2010

Payne et al, NEJM, 2013
National Rotavirus Vaccine Introductions: 81 Countries*

*As of May 2016
U.S. Norovirus Outbreak Surveillance

• **NORS**
  - Epidemiologic surveillance for all enteric disease outbreaks
  - Data on setting, transmission mode, exposures, demographics, outcomes

• **CaliciNet**
  - Laboratory surveillance using molecular genotyping of outbreak-associated specimens
  - Data on genotypes to identify new strains and potentially link outbreaks
Norovirus Outbreaks by Month, NORS, 2009-2012 (N=4,318)
Setting of Norovirus Outbreaks, NORS, 2009-2012 (N=3,243)

- Long-Term Care Facilities: 59%
- Restaurants: 17%
- Schools: 5%
- Caterer/Banquet Facility: 5%
- Hospitals: 3%
- Private Residence: 2%
- Daycares: 2%
- Other/Multiple: 7%

Note: Does not include 44 (1%) norovirus outbreaks meeting VSP posting criteria
Transmission Mode of Norovirus Outbreaks, NORS, 2009-2012 (N=4,318)

Person-to-person: 69%
Foodborne: 23%
Unknown: 7%
Environmental: 0.3%
Waterborne: 0.3%
Outline

• A rough guide to norovirus epidemiology and virology
• US burden of disease
• Global burden and why its so hard to estimate
• Vaccines
Norovirus vaccines showing promise

• A number of products being developed
  – virus-like particles (VLPs)
• The products with human efficacy data are being developed by Takeda Pharmaceuticals.
• Intranasal and intramuscular formulations tested in challenge studies
  – 47% (95% CI, 15%–67%) VE against norovirus gastroenteritis

Atmar et al. *NEJM*. 2011
Bernstein et al. *JID* 2014
Takeda Bivalent Norovirus VLP Vaccine

- GI.1
- GII.4 consensus
- Adjuvants
  - Alum
    - Aluminum hydroxide $\text{Al(OH)}_3$
  - MPL
    - 3-O-desacyl-4’ monophosphoryl lipid A

Lindesmith et al., PLOS Med 2015
Challenges for a norovirus vaccine

1. Role of prior infection history?
2. Duration of protection?
3. Protection against multiple genotypes?
4. Need to be updated to keep up with viral evolution?
5. Need for different vaccine formulation for certain groups?
6. Variation in human genetic susceptibility?

Mathematical models can:

- Quantify the key parameters that will govern vaccine impact
  - Which groups transmit disease
- Address public health-policy questions
  - Which age group(s) should be vaccinated?

Overall goal:
To identify optimal strategies for vaccination
Which age group should be vaccinated to maximize public health impact?
Vaccine Impact

Pediatric Immunization
50% VE; 90% Coverage

Elderly Immunization
50% VE; 65% Coverage

Steele, Remais, Gambhir, Glasser, Handel, Parashar, Lopman. *Epidemics, 2016*
Conclusions

• Noroviruses cause a tremendous burden in the US and globally
  – multiple ages affected
  – ~70,000 deaths
  – $60 Billion economic loss

• Norovirus vaccines are moving through the development pipeline

• Need for surveillance to monitor for emergence of new strains and their epidemiologic impacts
Acknowledgements and support

• CDC
  – John Glasser
  – Aron Hall
  – Anita Kambhampati
  – Daniel Payne
  – Umesh Parashar
  – Kirsten Simmons
  – Jackie Tate
  – Jan Vinjé

• Emory
  – Juan Leon
  – Karen Levy
  – Christine Moe
  – Molly Steele

• CMC
  – Gagandeep Kang
  – Sidharth Giri
  – Prasanna Premkumar

• Berkeley
  – Justin Remais

• Monash University
  – Manoj Gambhir