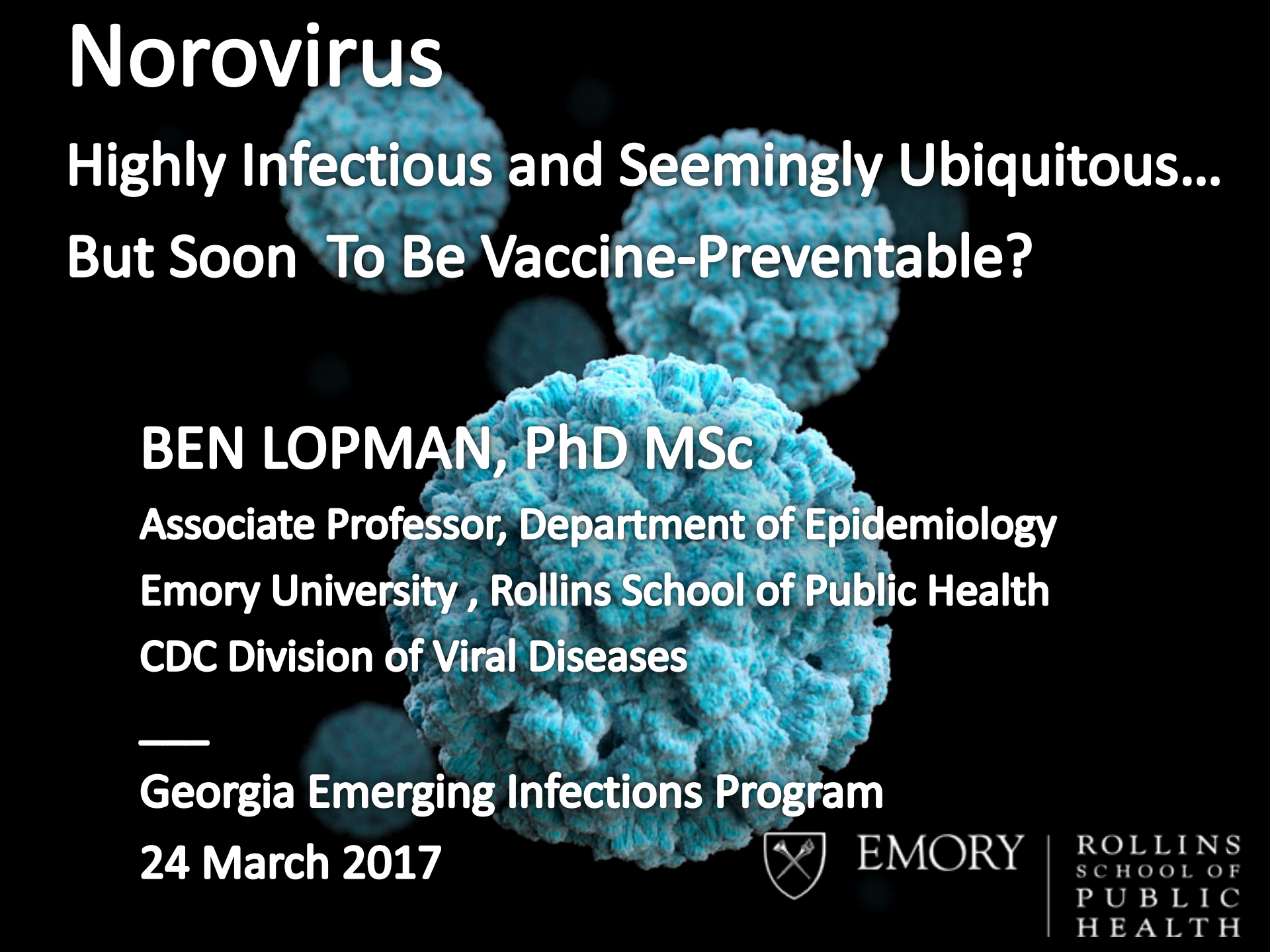
Norovirus

Highly Infectious and Seemingly Ubiquitous…

But Soon To Be Vaccine-Preventable?



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CDC Division of Viral Diseases

Georgia Emerging Infections Program

24 March 2017

EMORY | ROLLINS SCHOOL OF PUBLIC HEALTH

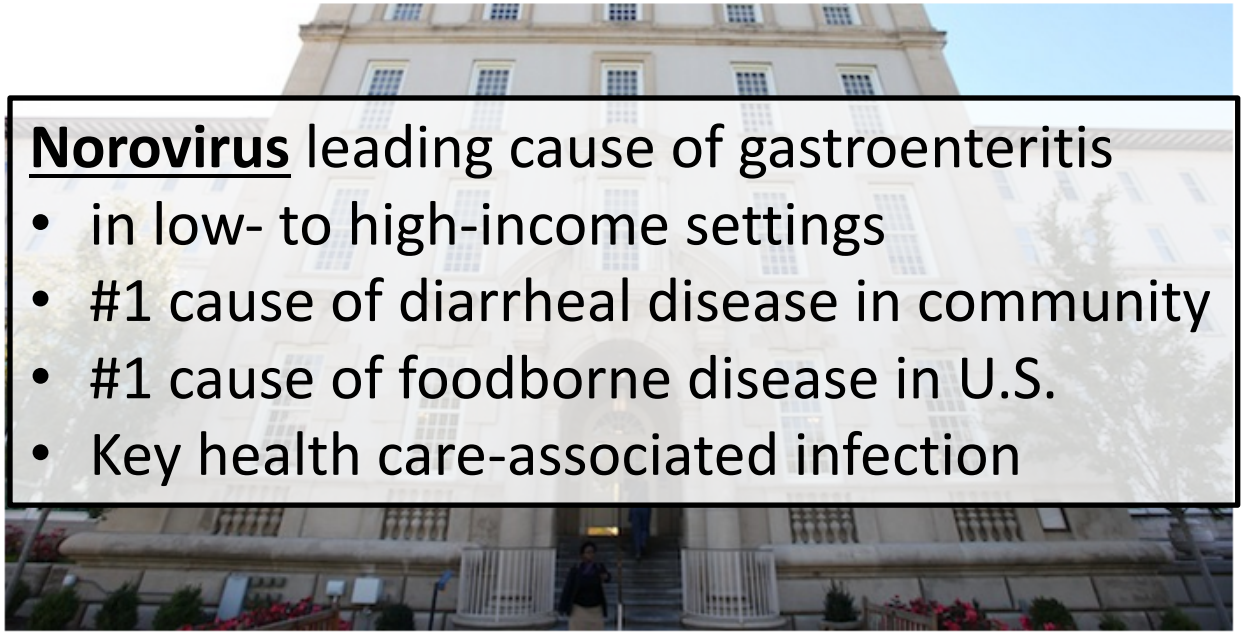
Outline

- Clinical features, virology, immunity and host susceptibility
- The disease burden and epidemiology
- Vaccines

THE EMORY WHEEL ONLINE

Norovirus Affects More Than 100

News Nov 18, 2014



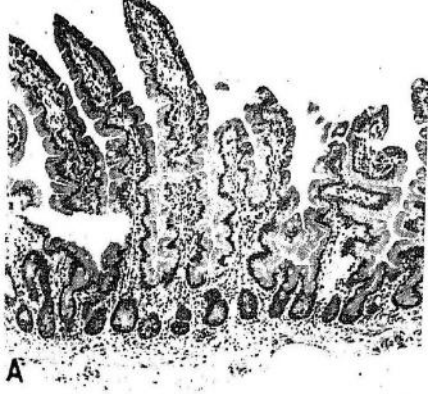
Emory University Hospital. Photo by Jason Oh.

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

Normal intestine

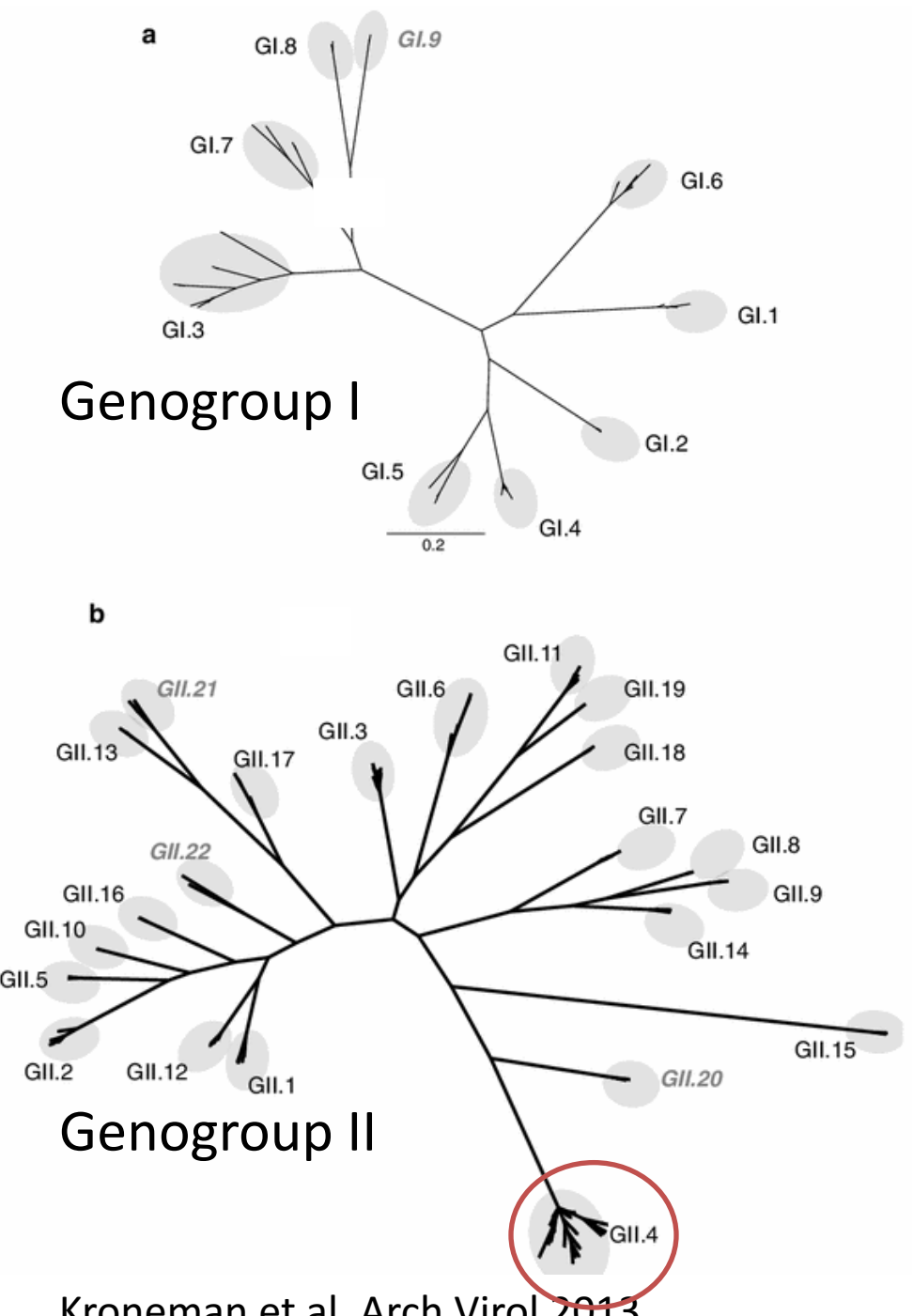


Virus-infected intestine

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



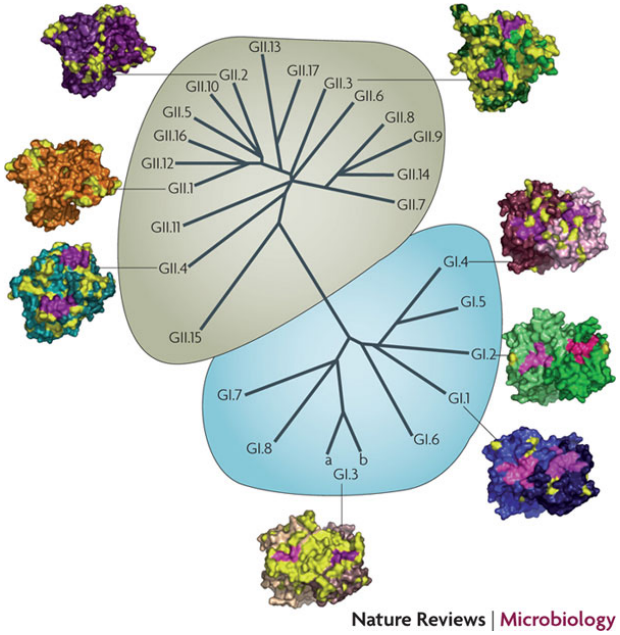
Kroneman et al, Arch Virol 2013

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

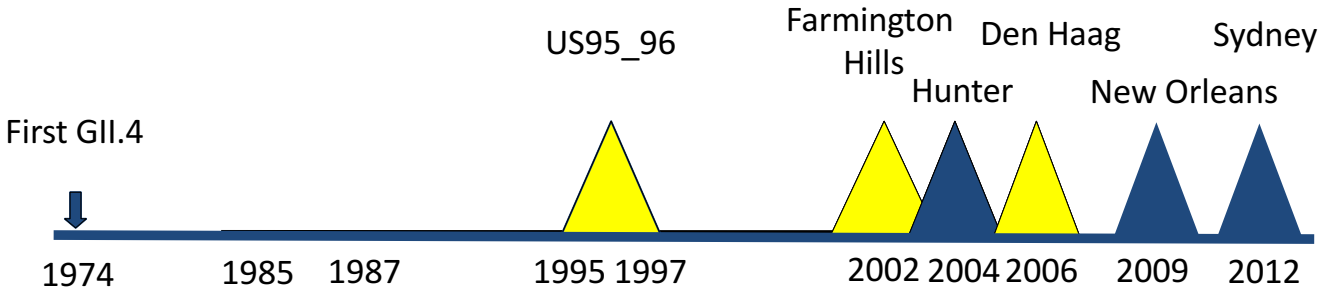
Noroviruses are highly diverse and rapidly evolving

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



Eric F. Donaldson, Lisa C. Lindesmith, Anna D. LoBue & Ralph S. Baric. 2010. Viral shape-shifting: norovirus evasion of the human immune system . Nature Reviews Microbiology 8, 231-241.

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

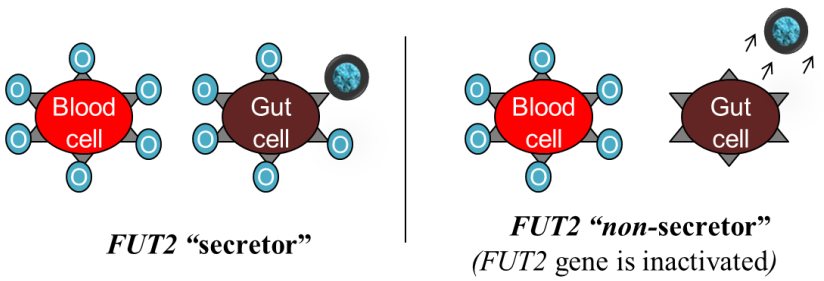
- Human volunteer studies demonstrated short-term immunity
  - <6months -2 years
  - modeling studies suggest may be longer
- Little persistent cross-protective immunity
- Genetic susceptibility

Payne, Parashar, Lopman, *Current Opinion in Pediatrics*, 2015

Role of FUT2 “secretor” gene

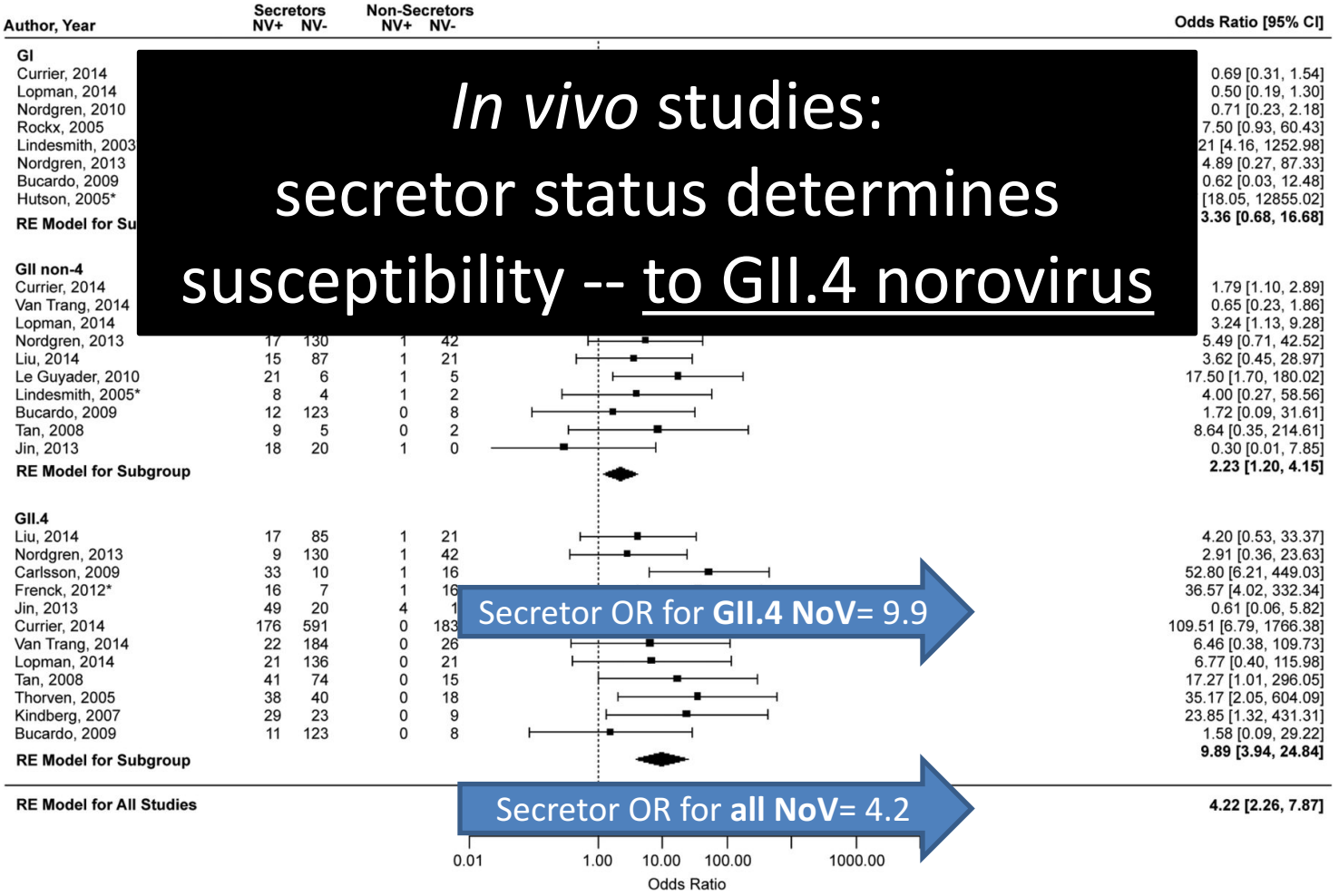
- Histo-blood group antigens (HBGAs) are expressed by the alpha fucosyltransferase-2 (*FUT2*) gene
- HBGAs are a binding interface on the surface of mucosal epithelia
- If *FUT2* g o the HBGA
- ~20% of European descendants are non-secretors:

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

Secretor OR for **GII.4 NoV**= 9.9

Secretor OR for **all NoV**= 4.2

Kambhampati, Payne, Costantini, Lopman, *CID*, 2015

Progress in cell culture

- No small animal model
- Cell culture
  - Human B cells
    - Jones et al., 2014 Science


NOROVIRUS

Science

Enteric bacteria promote human and mouse norovirus infection of B cells

Melissa K. Jones,[1*] Makiko Watanabe,[1*] Shu Zhu,[1] Christina L. Graves,[2,3] Lisa R. Keyes,[1] Katrina R. Grau,[1] Mariam B. Gonzalez-Hernandez,[4] Nicole M. Iovine,[5] Christiane E. Wobus,[4] Jan Vinjé,[6] Scott A. Tibbetts,[1] Shannon M. Wallet,[2,3] Stephanie M. Karst[1]†

  - Human Intestinal enteroids
    - Ettayebi et al., 2016 Science


INFECTIOUS DISEASE

Science

Replication of human noroviruses in stem cell–derived human enteroids

Khalil Ettayebi,[1*] Sue E. Crawford,[1*] Kosuke Murakami,[1*] James R. Broughman,[1] Umesh Karandikar,[1] Victoria R. Tenge,[1] Frederick H. Neill,[1] Sarah E. Blutt,[1] Xi-Lei Zeng,[1] Lin Qu,[1] Baijun Kou,[1] Antone R. Opekun,[2,3,4] Douglas Burrin,[3,4] David Y. Graham,[1,3,5] Sasirekha Ramani,[1] Robert L. Atmar,[1,2] Mary K. Estes[1,2]†

Outline

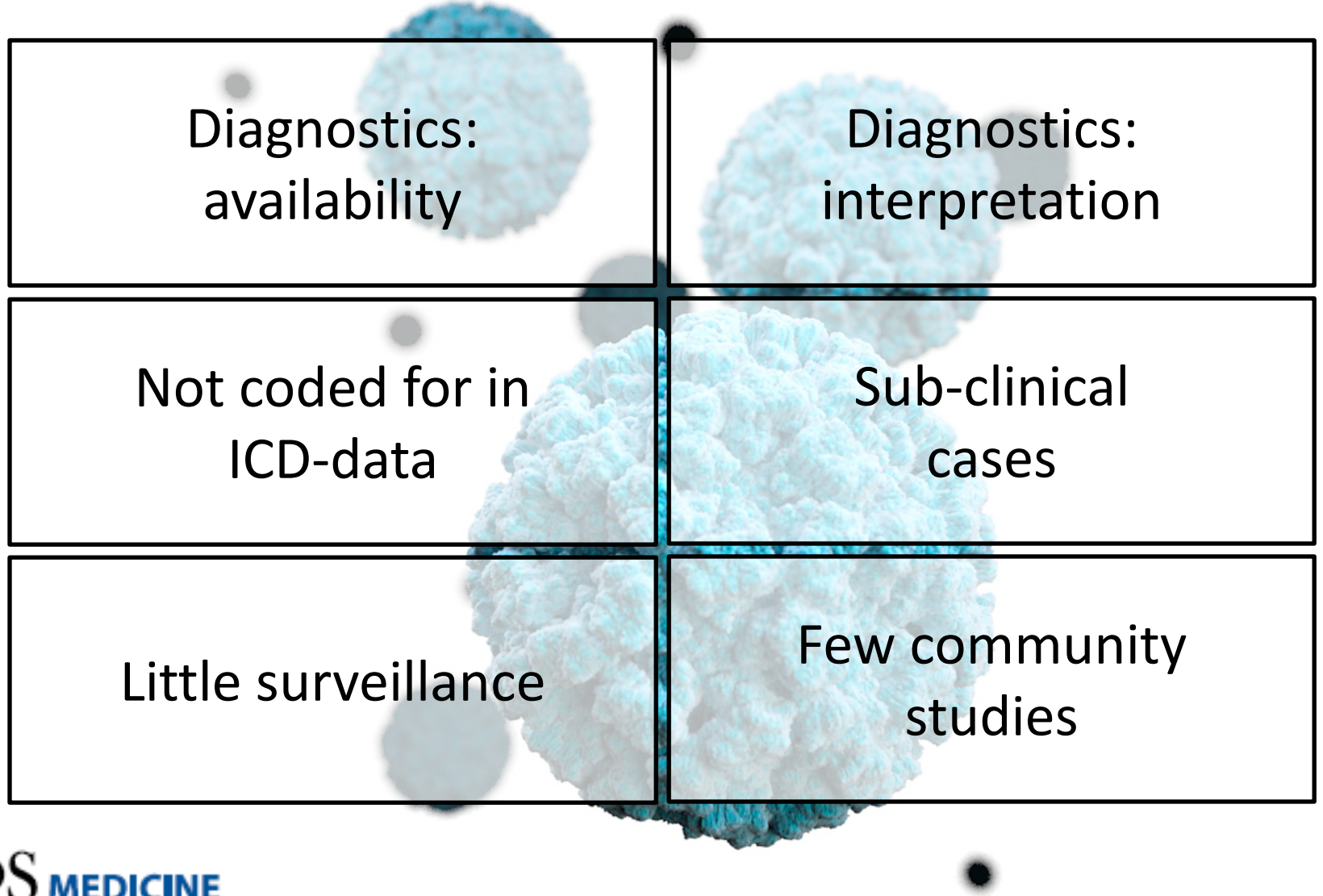
- Clinical features, virology, immunity and host susceptibility
- The disease burden and epidemiology

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

Pires 2015 PLoS One; Kirk 2015 PLoS Med; Bartsch 2016 PLoS One; Hall 2016 Exp Rev Vac

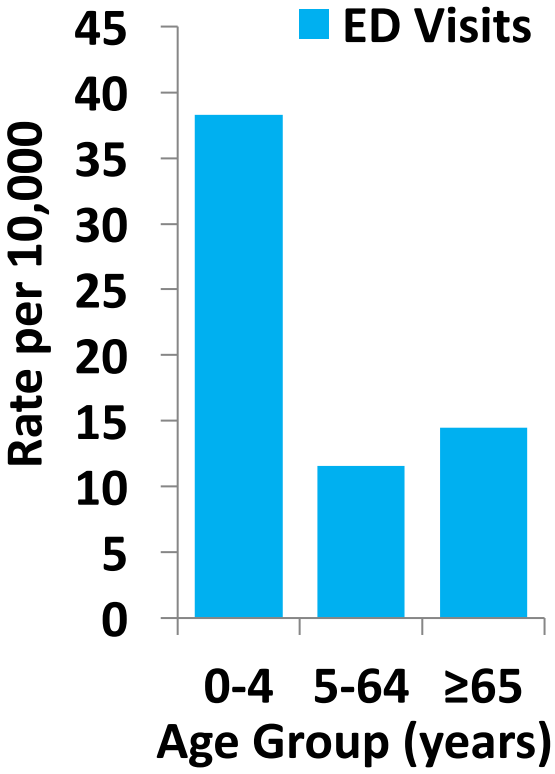
Challenges in estimating [global] burden of norovirus

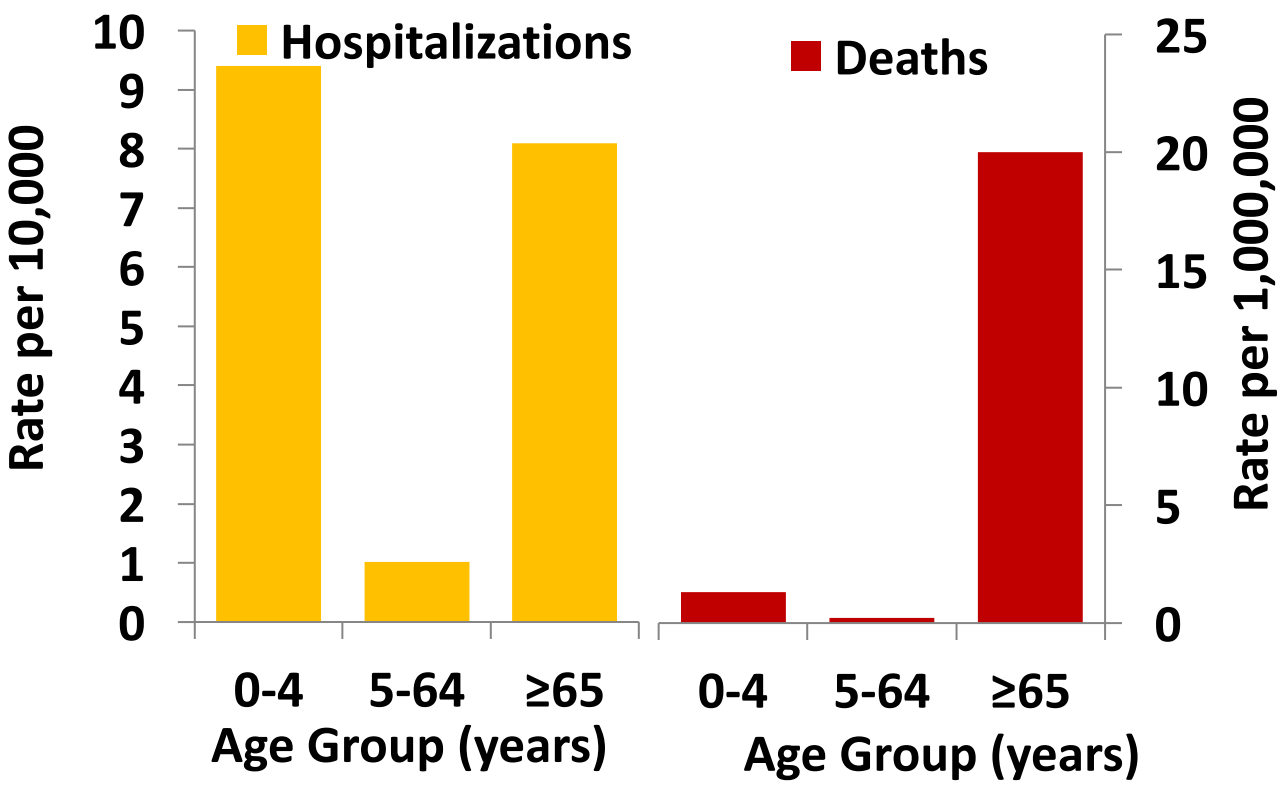


PLoS MEDICINE

Lopman, Steele, Parashar, PLOS Medicine, 2016

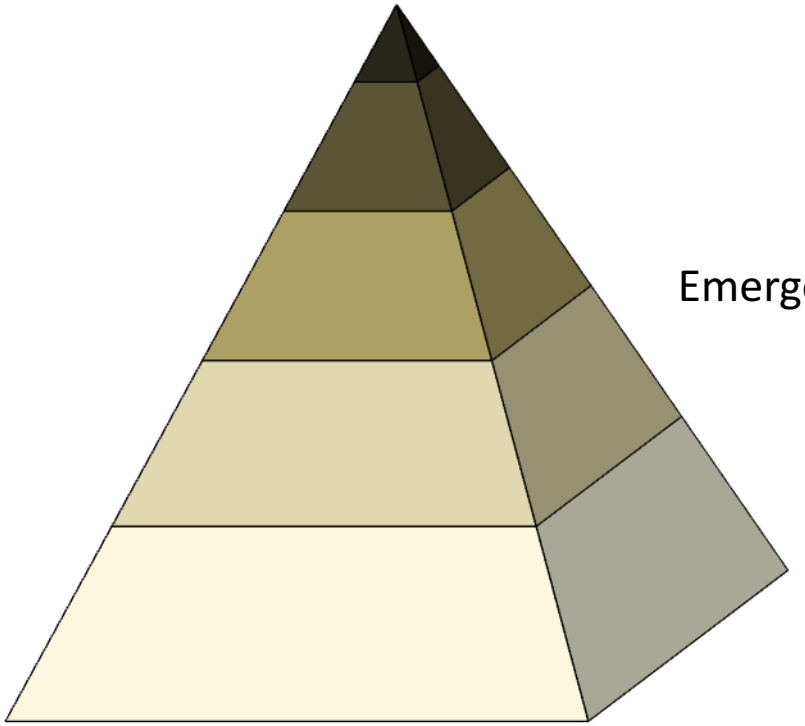
Age Specific Clinical Outcomes of Norovirus in the United States





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

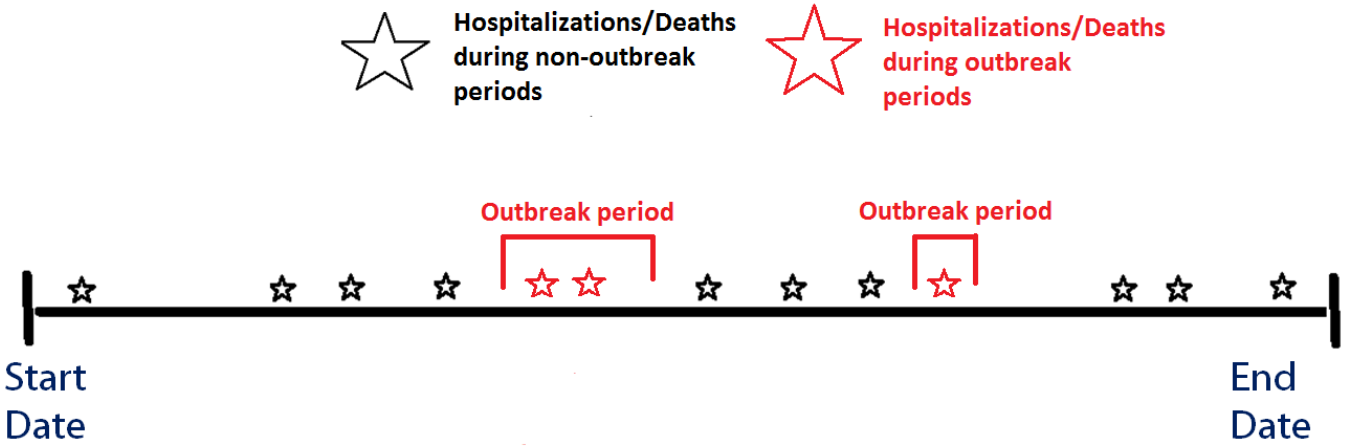


	Annual estimate	Lifetime risk
Deaths	800	1 in ~6,000
Hospitalizations	71,000	1 in ~60
Emergency department visits	400,000	1 in ~9
Outpatient visits	1.8 million	1 in ~2
Cases	19 to 21 million	5 times

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

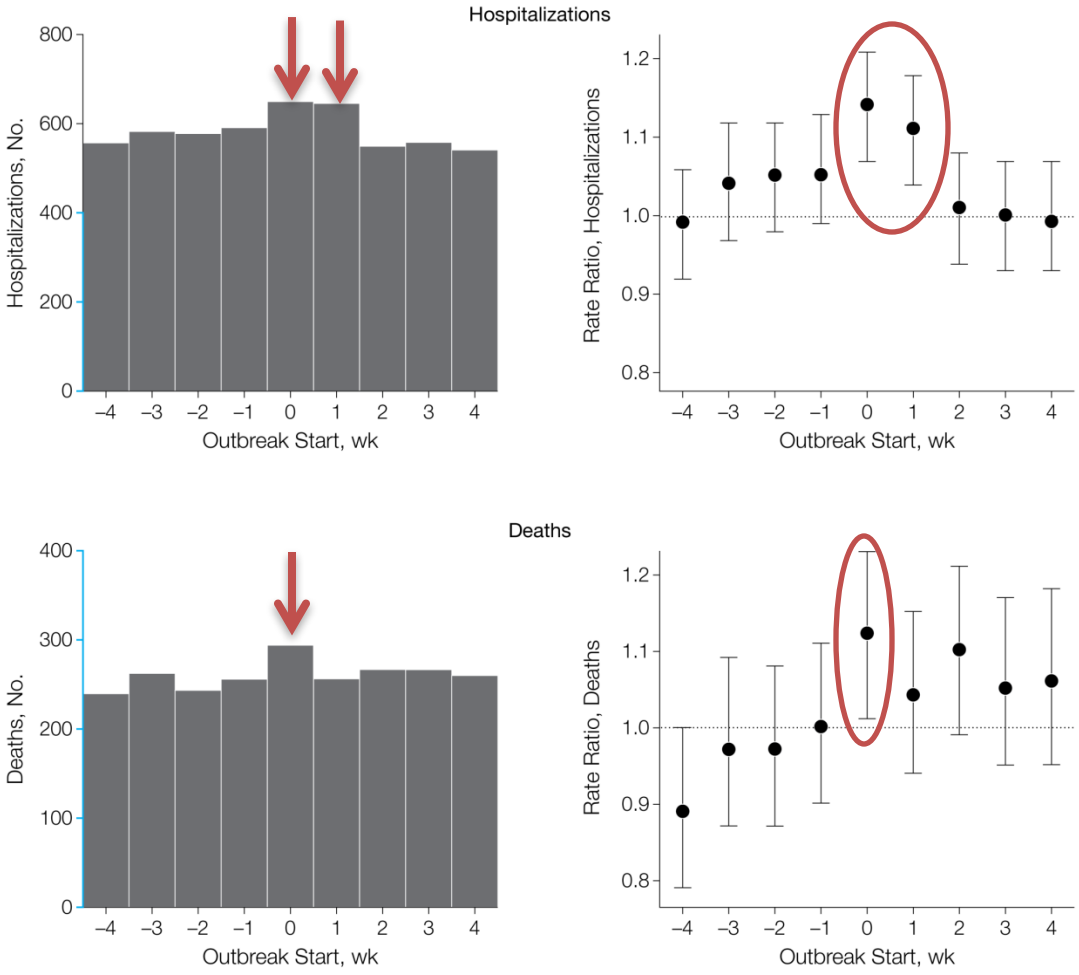
Is norovirus a *cause* of death?

- 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



Trivedi, DeSalvo, Lee, Palumbo, Lee, Moll, Curns, Hall, Patel, Parashar, Lopman, JAMA, 2012

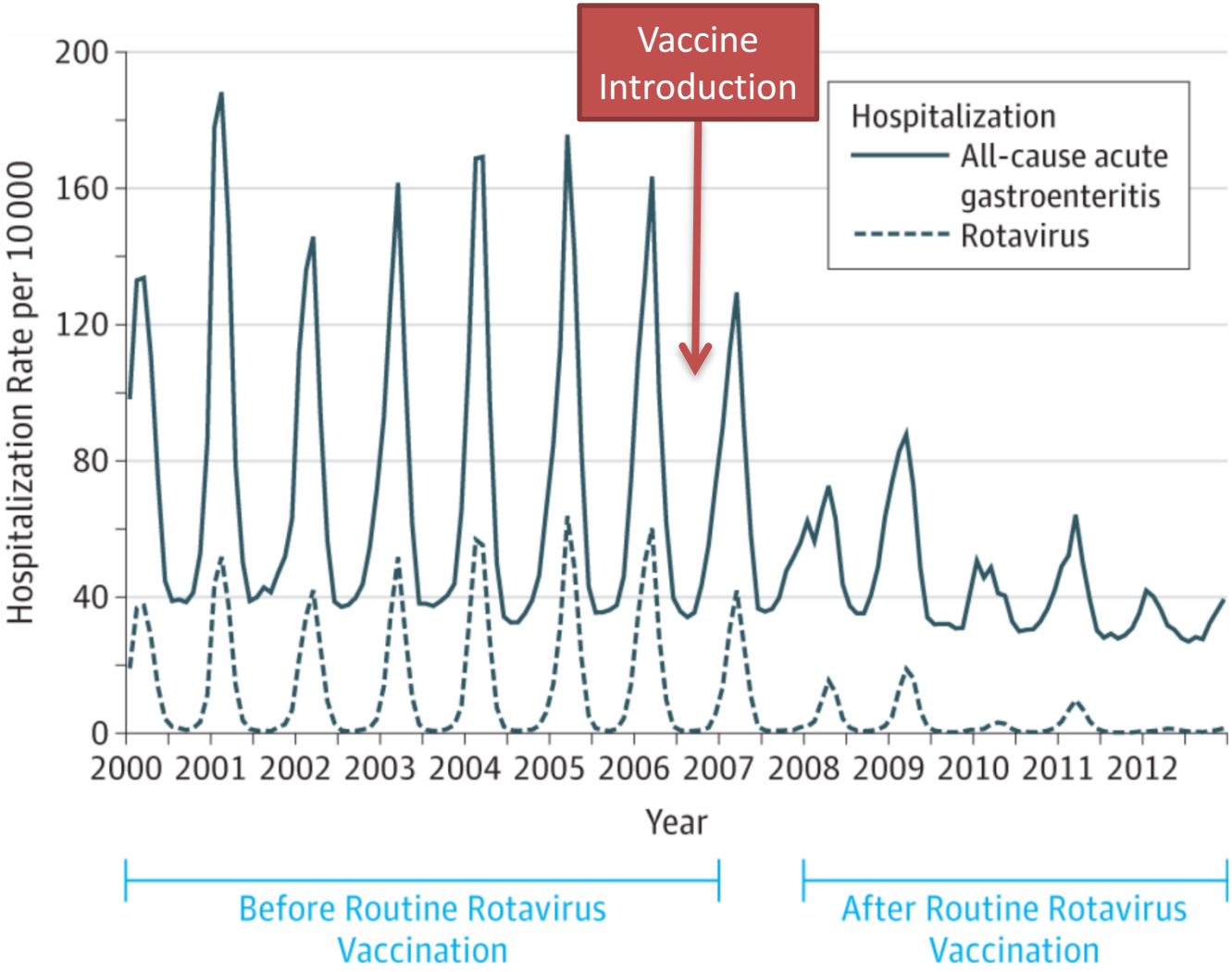
Is norovirus a *cause* of death?



Trivedi, DeSalvo, Lee, Palumbo, Lee, Moll, Curns, Hall, Patel, Parashar, Lopman, JAMA, 2012

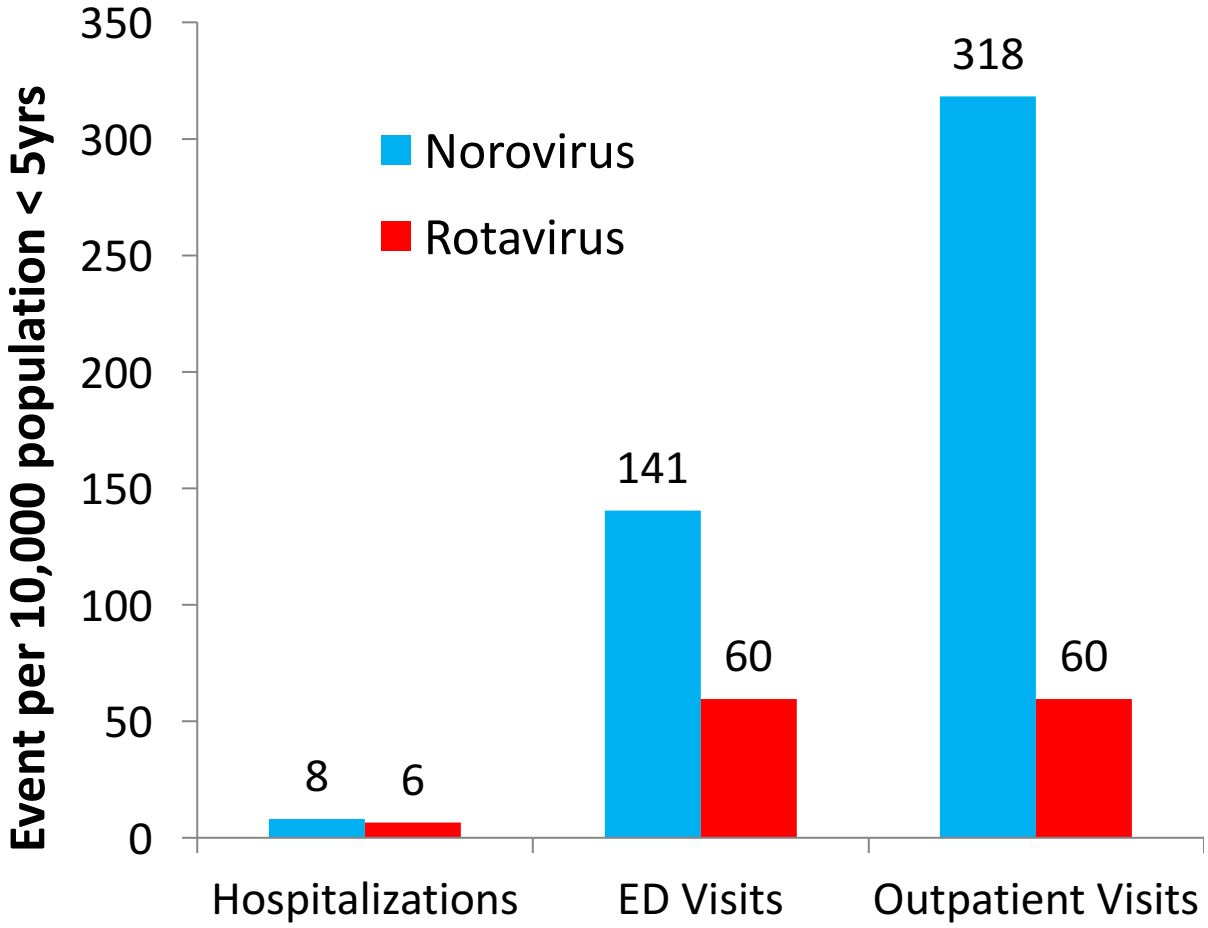
JAMA

Decline in rotavirus and AGE hospitalizations following vaccine introduction in US



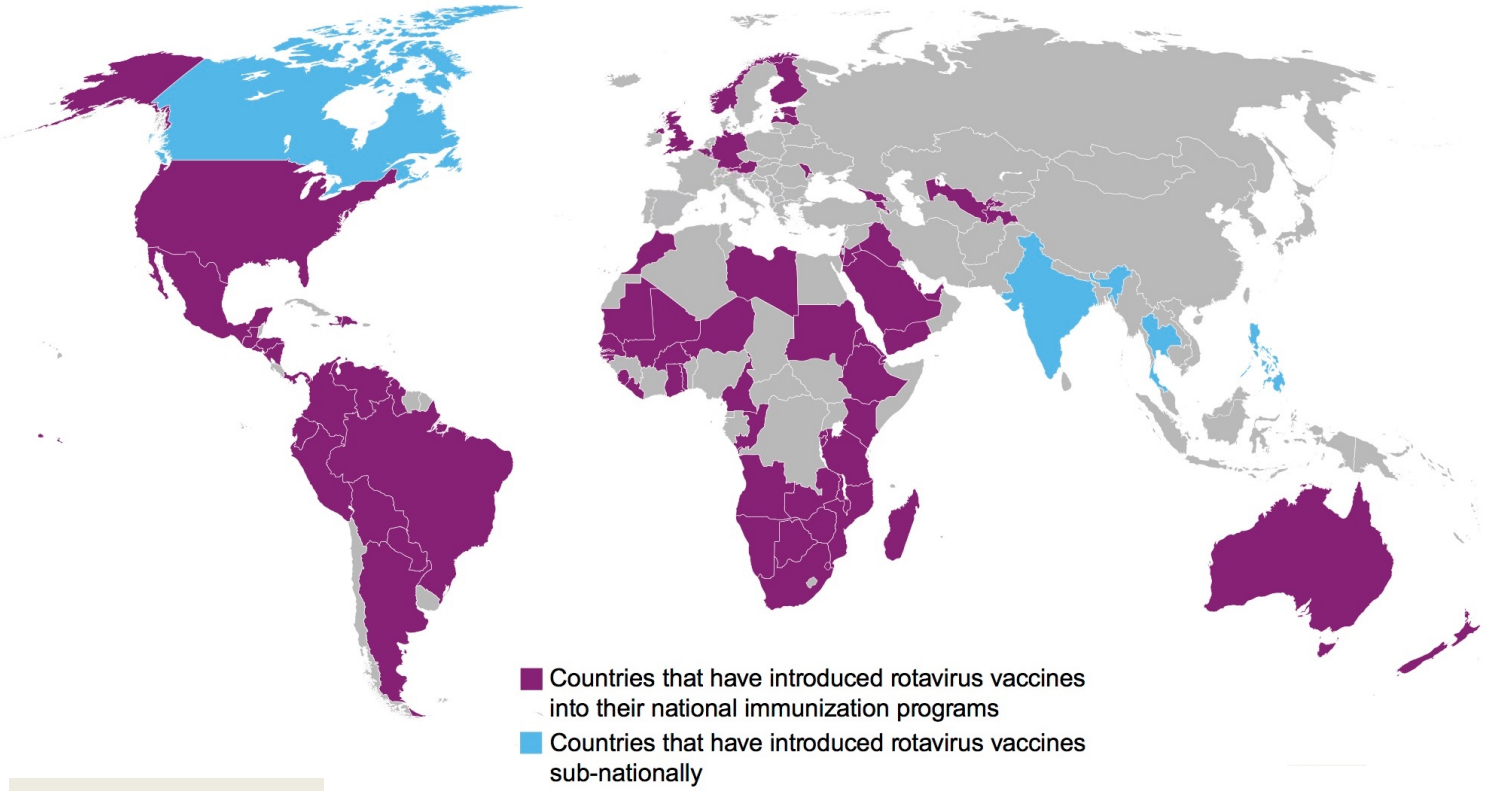
Leshem, Tate Steiner, Curns, Lopman, Parashar, *JAMA 2015*

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*



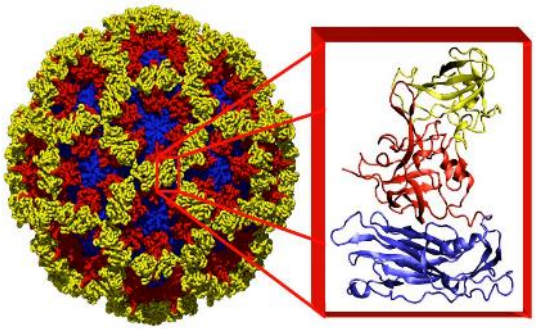
*As of May 2016

WHO, 2016
PATH, 2016

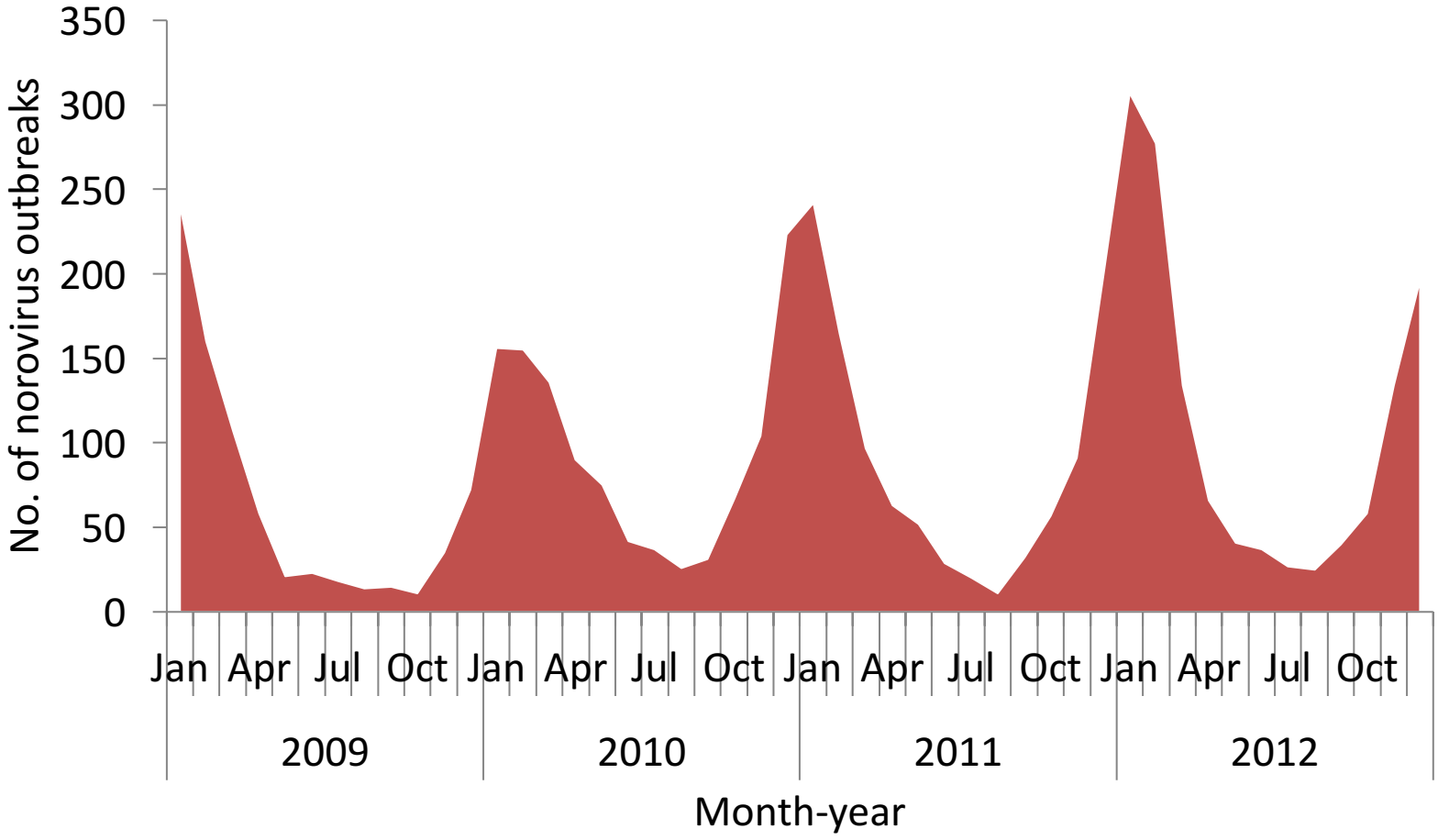
U.S. Norovirus Outbreak Surveillance

- **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**

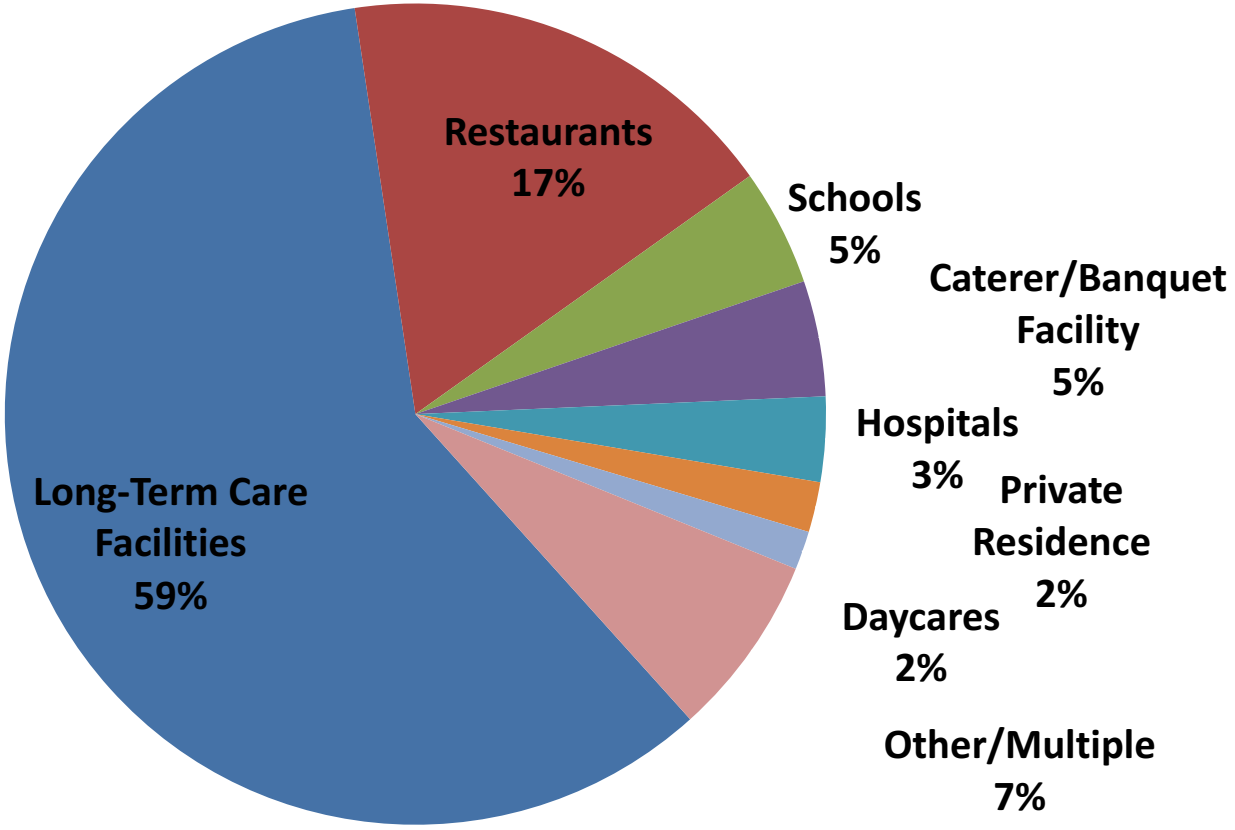


Norovirus Outbreaks by Month, NORS, 2009-2012 (N=4,318)



Hall 2014 MMWR

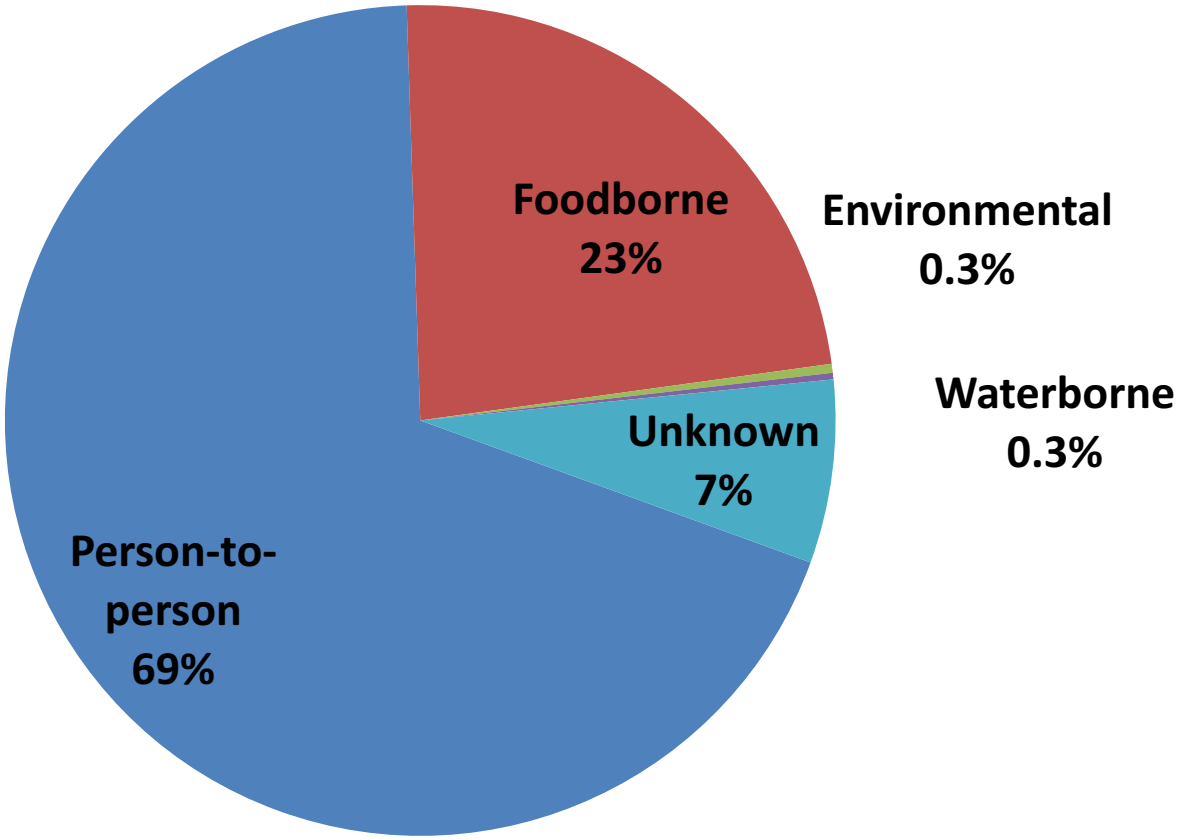
Setting of Norovirus Outbreaks, NORS, 2009-2012 (N=3,243)



Note: Does not include 44 (1%) norovirus outbreaks meeting VSP posting criteria

Hall 2014 MMWR

Transmission Mode of Norovirus Outbreaks, NORS, 2009-2012 (N=4,318)



Hall 2014 MMWR

Outline

- A rough guide to norovirus epidemiology and virology
- US burden of disease
- Global burden and why its so hard to estimate
- Vaccines

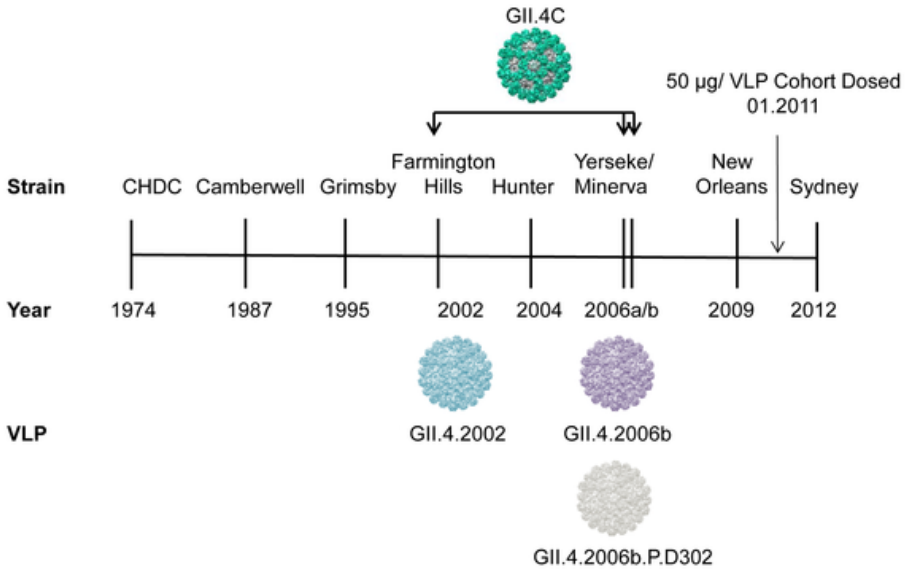
Norovirus vaccines showing promise

- 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

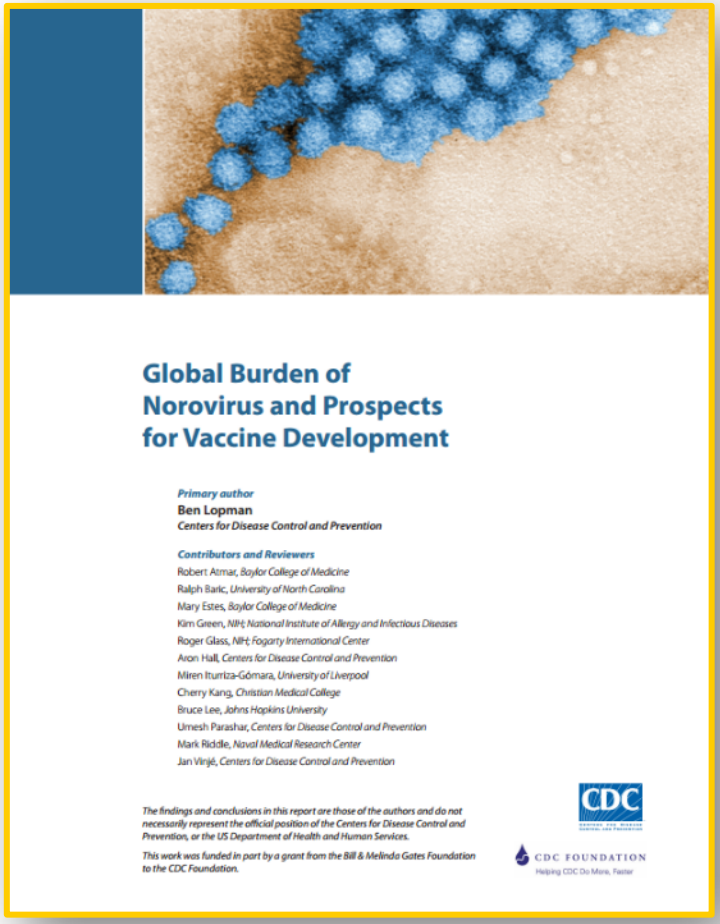
- GI.1
- GII.4 consensus
- Adjuvants
  - Alum
    - Aluminum hydroxide $Al(OH)_3$
  - MPL
    - 3-O-desacyl-4' monophosphoryl lipid A



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?



Global Burden of Norovirus and Prospects for Vaccine Development

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, or the US Department of Health and Human Services.

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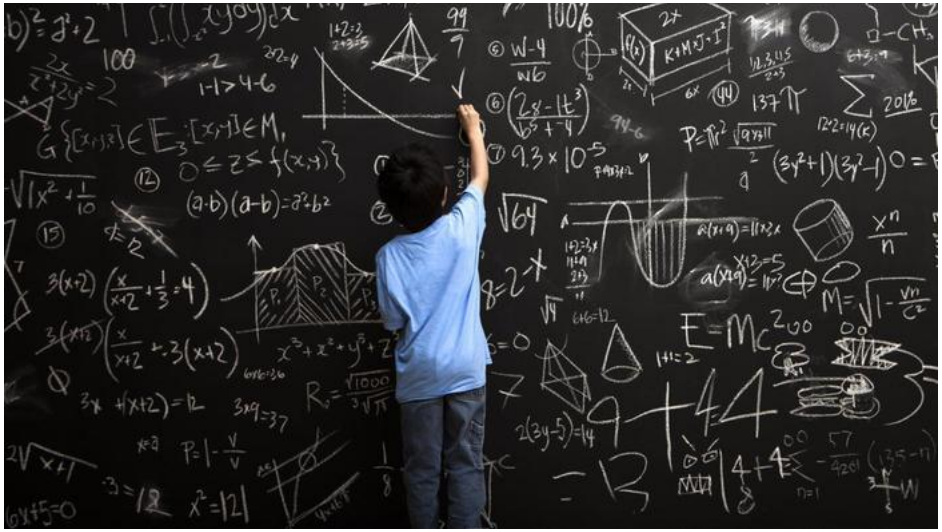
CDC

CDC FOUNDATION
Helping CDC Do More, Faster

http://www.cdc.gov/norovirus/downloads/global-burden-report.pdf

Mathematical models can :

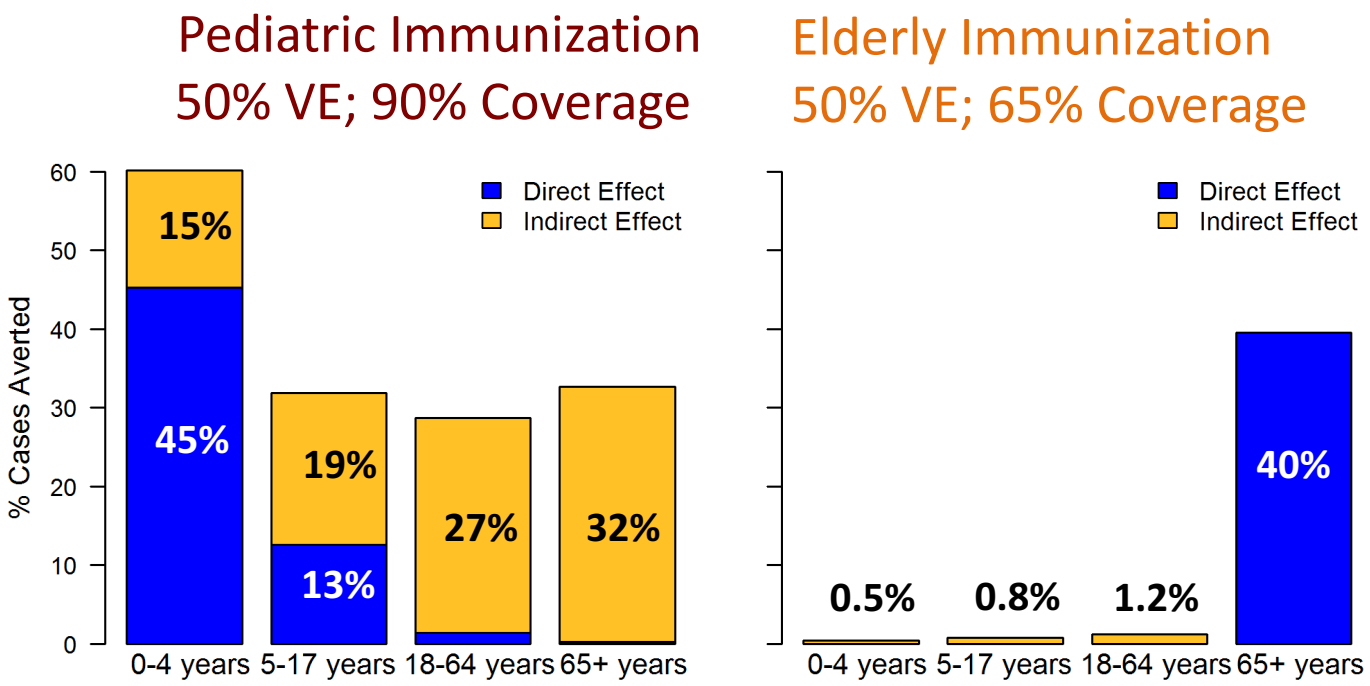
- Quantify the key parameters that will govern vaccine impact
  - Which groups transmit disease
- Address public health-policy questions
  - Which age group(s) should be vaccinated?



Overall goal:
To identify optimal strategies for vaccination

Which age group should be vaccinated to maximize public health impact?

Vaccine Impact



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

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  - John Glasser
  - Aron Hall
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