Norovirus, It's No Picnic

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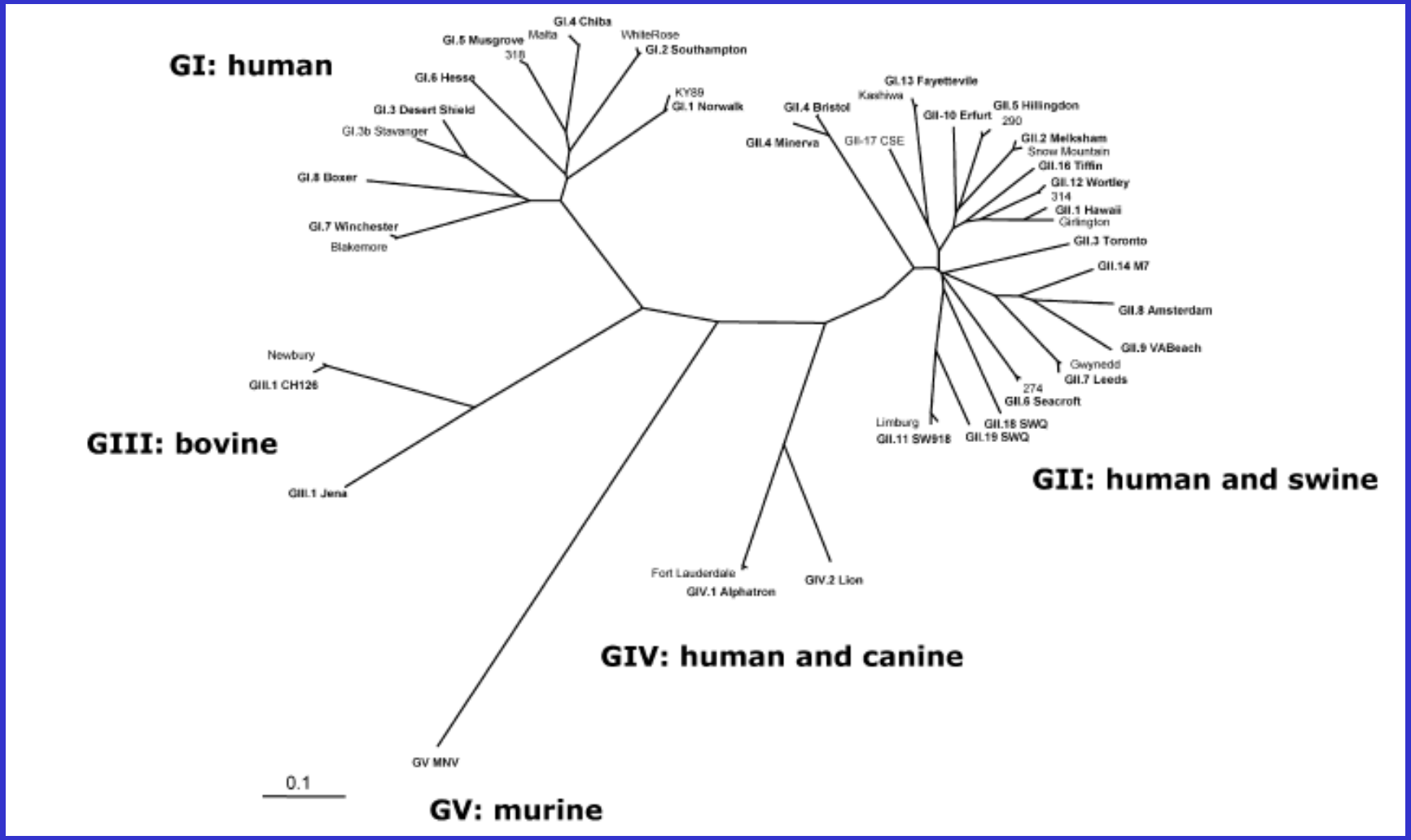
Norovirus

- Outbreak of “winter vomiting disease” described in 1968 in Norwalk, Ohio
  - 50% of students and teachers became ill
  - Nausea, vomiting and abd cramps common
  - 32% of household contacts became ill
- In 1972, Kapikian identified a 27 nm “virus like particle” from stool of a person sick from the outbreak.

Classification of Norovirus

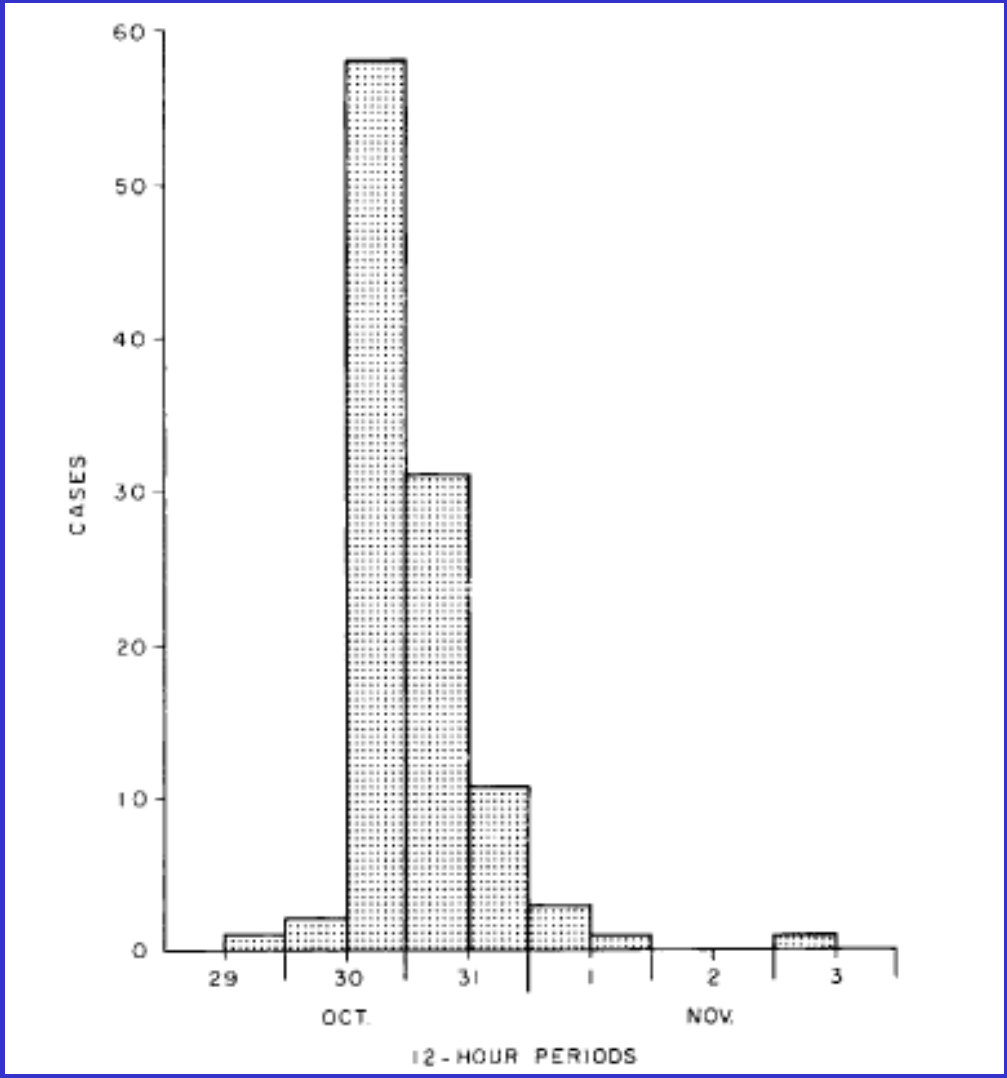


Patel. J Clin Virol. 2009;44:1-8

Clinical Manifestations

- Incubation period of 24-48 hrs. after exposure
- Often starts with nausea and abdominal cramps followed by vomiting and/or diarrhea
- Commonly referred to as “stomach flu”
- Symptoms typically resolve 1-3 days
  - Can be prolonged in young, elderly and immunocompromised

Initial Report of the Norwalk Outbreak, Norwalk, Ohio 1968

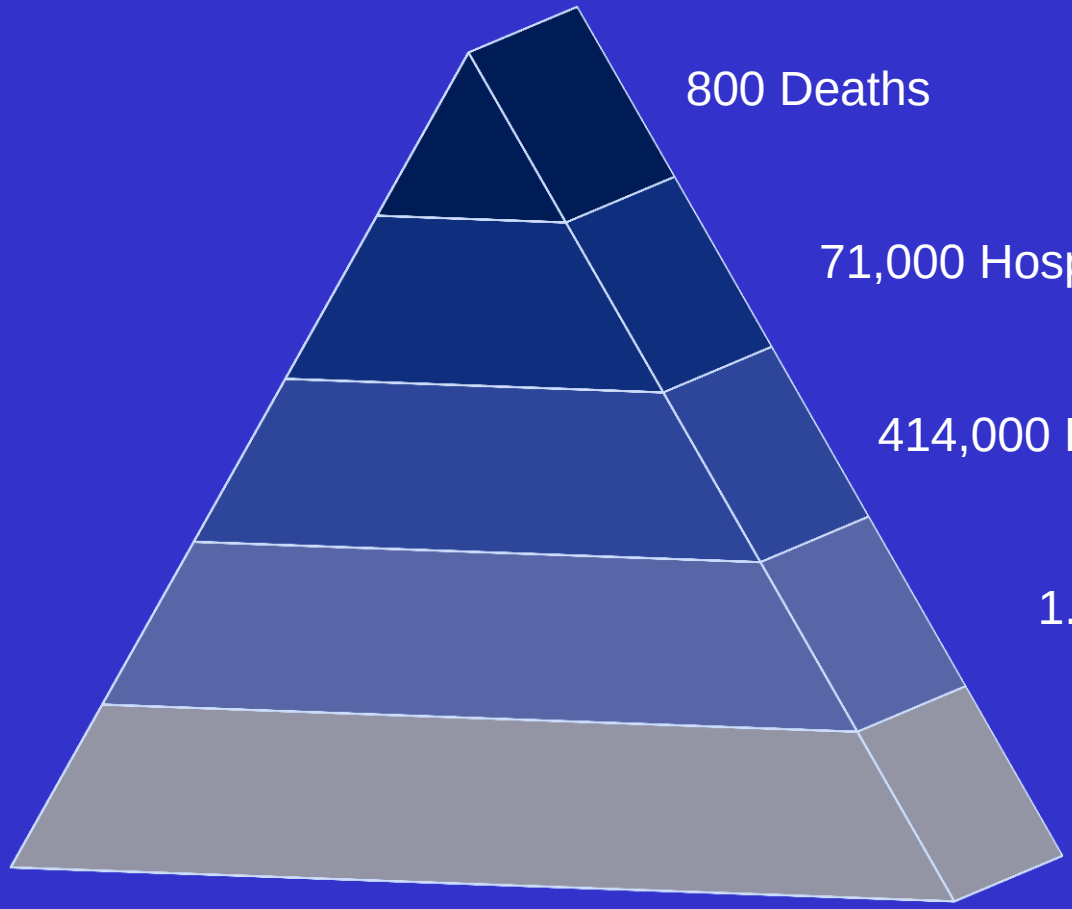


Adler, et al. JID 1968;119:668-73

Disease Caused by Norovirus

- The initial description of NoV was with outbreaks
- First thought to be uncommon etiology
- Improved diagnostics have allowed better understanding of epidemiology of NoV
- Now know 65% of ***all*** foodborne-outbreaks caused by norovirus and >95% of non-bacterial outbreaks
- The improved ability to detect NoV has led to the current estimates of over 21 million cases of NoV occurring yearly in the US

Burden of Norovirus Disease Estimates in the United States



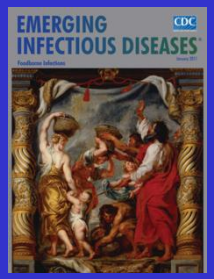
800 Deaths

71,000 Hospitalizations

414,000 Emergency Department Visits

1.7 million Outpatient Visits

21 million Cases



Scallan 2011 EID ; Lopman 2011 CID; Hall 2011 EID; Hall 2012 CID; Gastanaduy 2013 JID

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MMWR

Weekly

June 7, 2002 / 51(22);477-479

Outbreak of Acute Gastroenteritis Associated with Norwalk-Like Viruses Among British Military Personnel --- Afghanistan, May 2002

In the United States, Norwalk-like viruses (NLVs) cause an estimated 23 million episodes of illness, 50,000 hospitalizations, and 300 deaths each year. NLVs can be transmitted by fecally contaminated food and water (*1*) and by direct person-to-person contact or through droplets of infected persons. Outbreaks of NLV-associated gastrointestinal illness are common in military settings. During May 13--19, 2002, a total of 29 British soldiers and staff of a field hospital in Afghanistan became acutely ill after a short incubation period with vomiting, diarrhea, and fever. This report summarizes the investigation of this outbreak and underscores the importance of the diagnostic capacity for NLVs.

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Gastroenteritis in US Marines during Operation Iraqi Freedom

Scott A. Thornton[1], Sterling S. Sherman[2], Tibor Farkas[3], Weiming Zhong[3], Pete Torres[2], and Xi Jiang[3]

Disney ship docks with 195 ill

POSTED BY NOROVIRUS LAWER ON NOVEMBER 23, 2004

Next week's cruise canceled to sanitize vessel
November 30, 2002

PORT CANAVERAL, Florida (CNN) --Sunny skies greeted the Disney cruise ship Magic as it docked here early Saturday, carrying 195 sick passengers and crew members.

Norovirus Hits Sea Princess

POSTED BY NOROVIRUS LAWER ON JULY 01, 2011

For the fourth time since mid-May, the Se Princess's passengers have been sickened by norovirus, a gastrointestinal infection that causes diarrhea, vomiting and stomach pain.

At the end of a 10-day sailing, the ship returned to San Francisco June 29 with 53 of its 2,196 passengers affected by the stomach bug, according to USA Today.

Norovirus Bounces 21 NBA Players Per CDC

POSTED BY BILL MARLER ON APRIL 22, 2011

U.S. health officials say last fall's outbreak of a stomach virus that swept through pro basketball teams sickened 21 players on 13 teams.

They were infected with the norovirus, highly contagious and known for spreading on cruise ships. The federal researchers didn't name the teams. But med included four on the Orlando M

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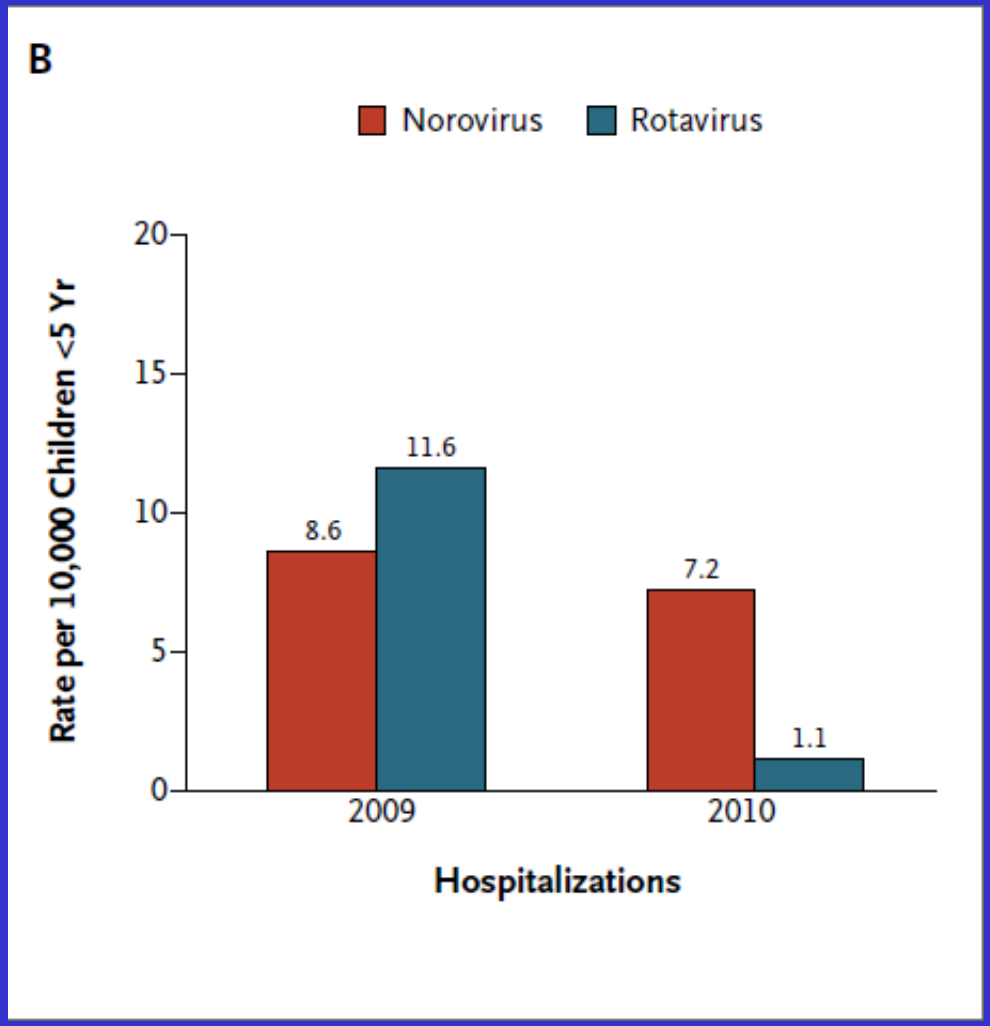
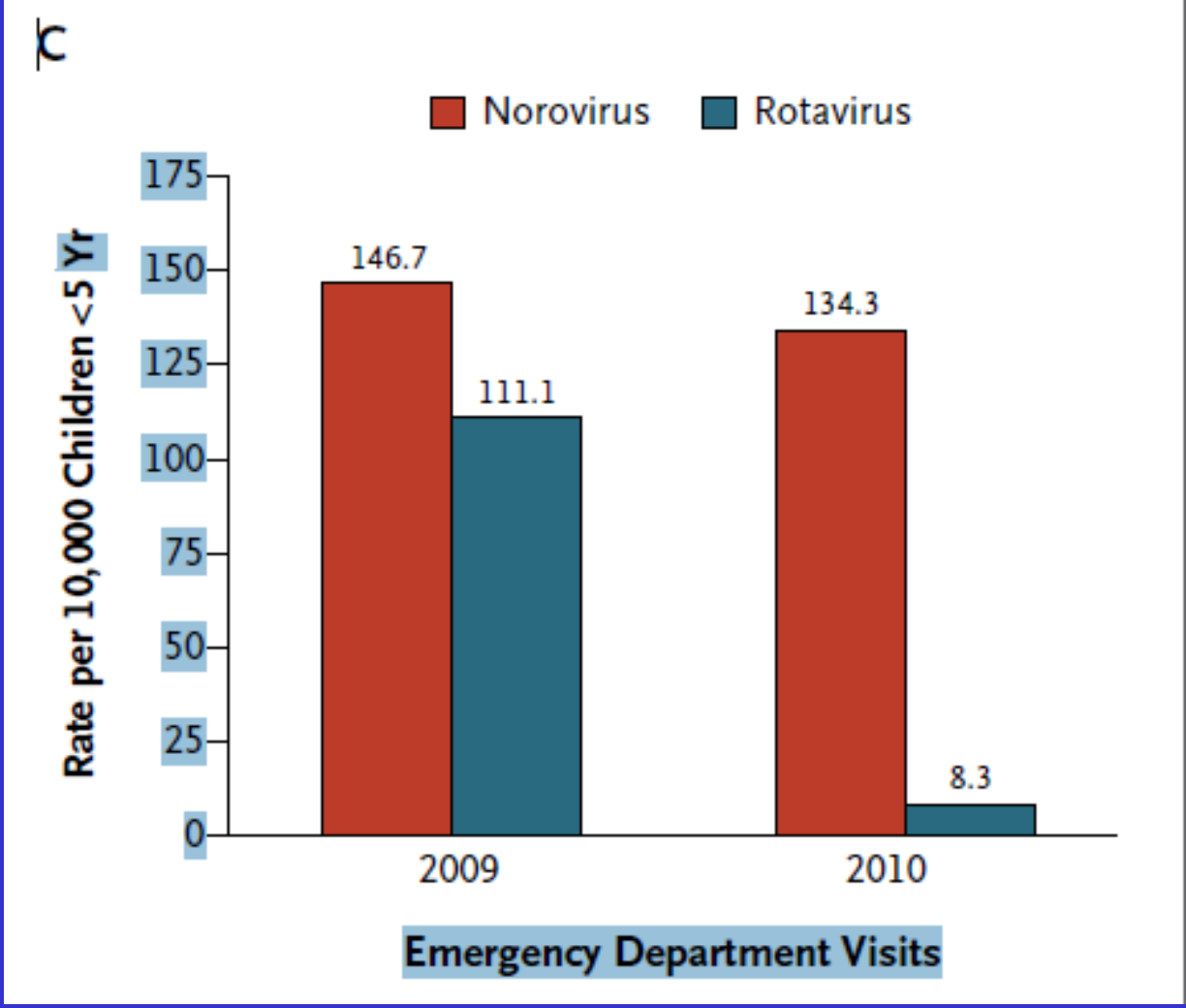
Widespread Outbreak of Norovirus Gastroenteritis among Evacuees of Hurricane Katrina Residing in a Large "Megashelter" in Houston, Texas: Lessons Learned for Prevention

Noro and Rota Hospitalizations Among Children, US 2009-10 (NVSN Data)



Payne et al. NEJM, 2013;368:1121-30

Noro and Rota ED Visits Among Children, US 2009-10 (NVSN Data)



Payne et al. NEJM, 2013;368:1121-30

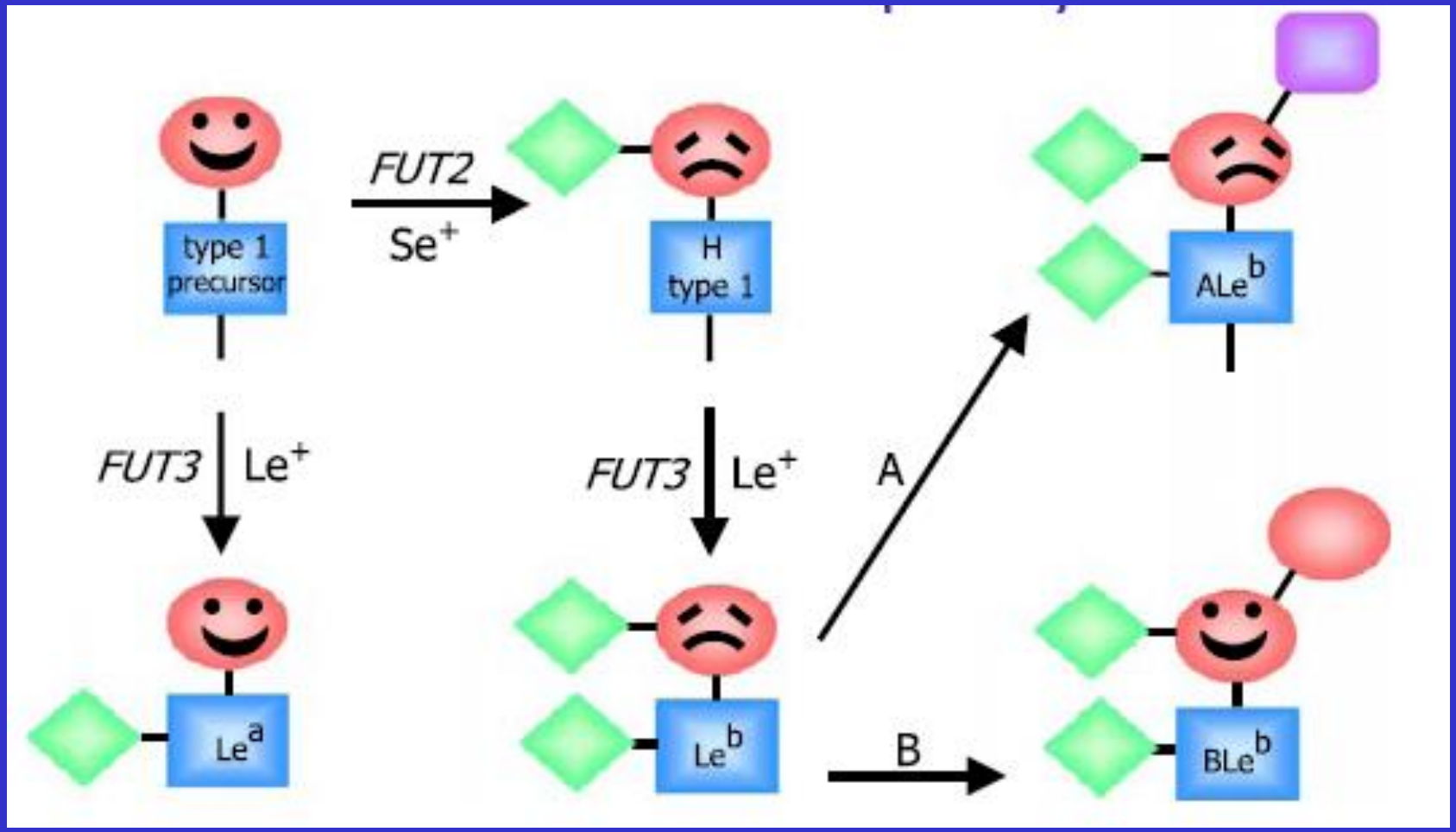
Characteristics of NoV Facilitating Spread

- Low infectious dose
- Prolonged asymptomatic shedding
- Environmental stability
- Lack of lasting immunity

Risk factors for acquiring NoV

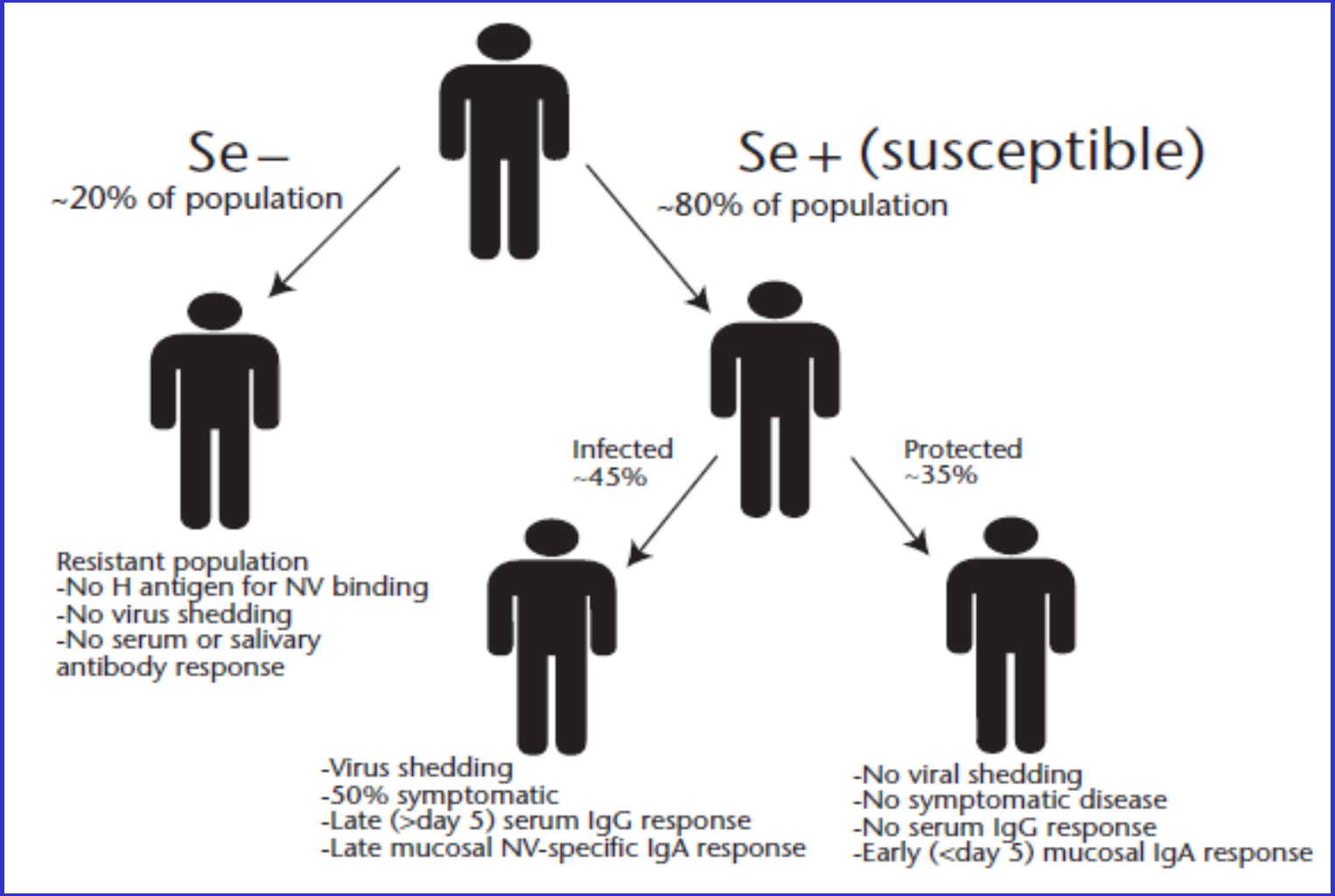
- Crowding
- Poor Sanitation
- Genetic predisposition

Model for Norovirus Susceptibility base on HBGA



Atmar et al. Gastroenterol Clinics NA. 2006;35:275-90

Model of GI.1 NoV Challenge Outcomes



Lindesmith et al, Nat Med. 2003;9:548-53

Studying Norovirus Has Been Difficult

- Unable to culture virus
- No good animal model
- Initial diagnostic modalities were limited
  - Relied on electron microscopy
- Have to gather much of information from
  - Epidemiology studies
  - Human challenge studies

Human Challenge Model Using a Norovirus GII.4 Strain: Susceptility to Infection

Robert Frenck, David Bernstein, Ming Xia, Pengwei Huang, Weiming Zhong, Susan Parker, Monica McNeal, Michelle Dickey, Xi Jiang.
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Study Population/Inclusion Criteria

- Healthy adults 18-49 years old
- Serum IgG antibody titer of $\leq$ 1:1,600 to the challenge strain of norovirus
- Secretor positive or secretor negative

Study Definitions

- **Diarrhea**- ≥3 loose or liquid stools or >480 mL of loose/liquid stool in a 24-hour period
- **Infection**- Stool PCR (+) for norovirus and/or ≥4x rise in antibody titer
- **Disease**- Infection plus vomiting and/or diarrhea

Challenge Strain

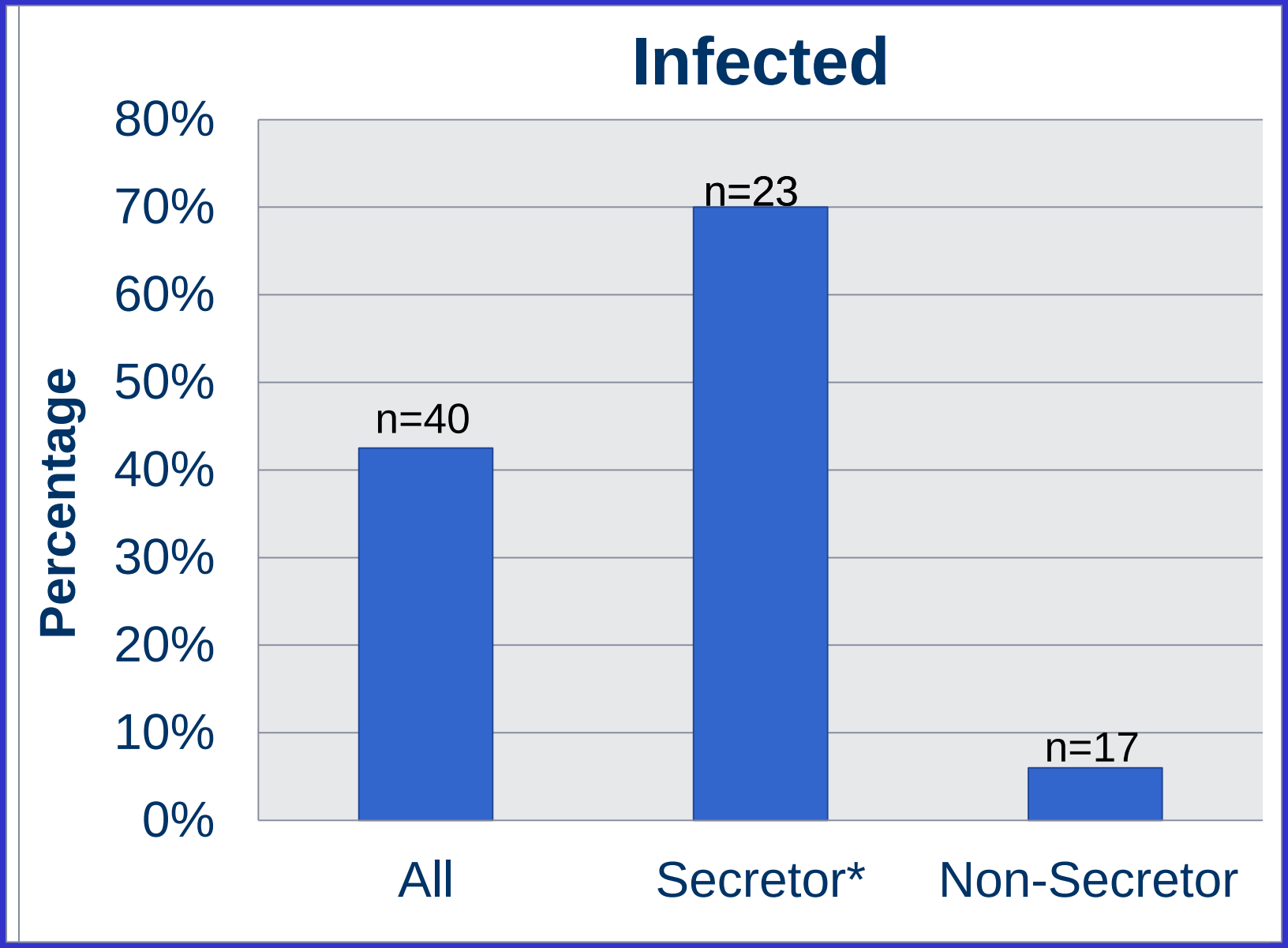
- Isolated from the stool of a male who developed vomiting and diarrhea after attending a picnic.
- Donor had an unremarkable medical history and physical examination, along with negative testing for HIV, Hepatitis A, B, C, syphilis, TB.
- The challenge virus pool was negative for:
  - rotavirus, enteric adenovirus, astrovirus, picornavirus (including hepatitis A),
  - bacteria, mycoplasma, and mycobacteria
  - retrovirus,
  - endotoxin and adventitious viruses.

Methods

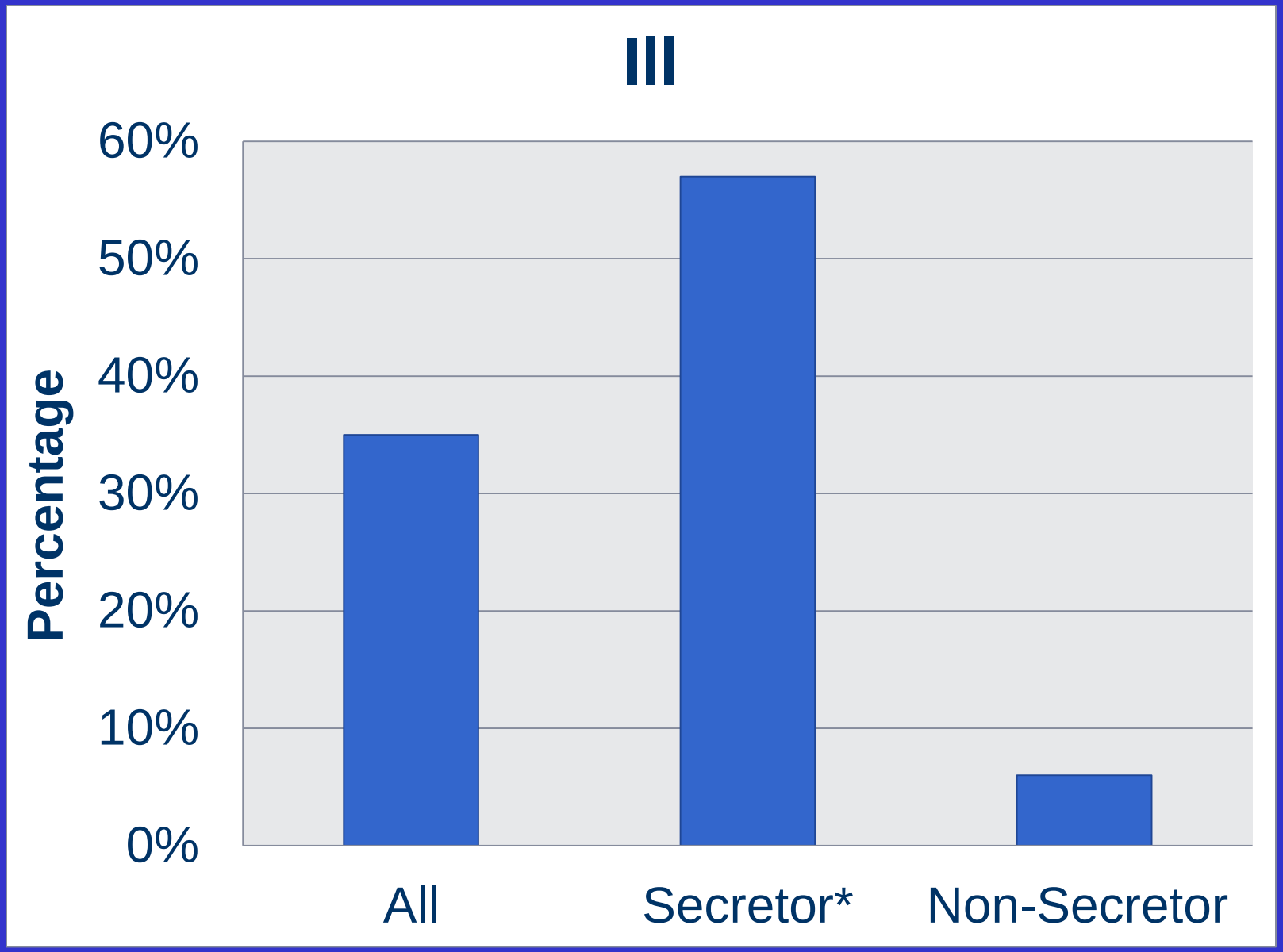
- Subjects challenged orally with $5x10^4$ PCR genome units of GII.4 norovirus.
- Hospitalized to assess for illness.
- Stool collected daily and tested for norovirus.
- Subjects were discharged home on Day 5 or when symptoms resolved, whichever was longer

Results

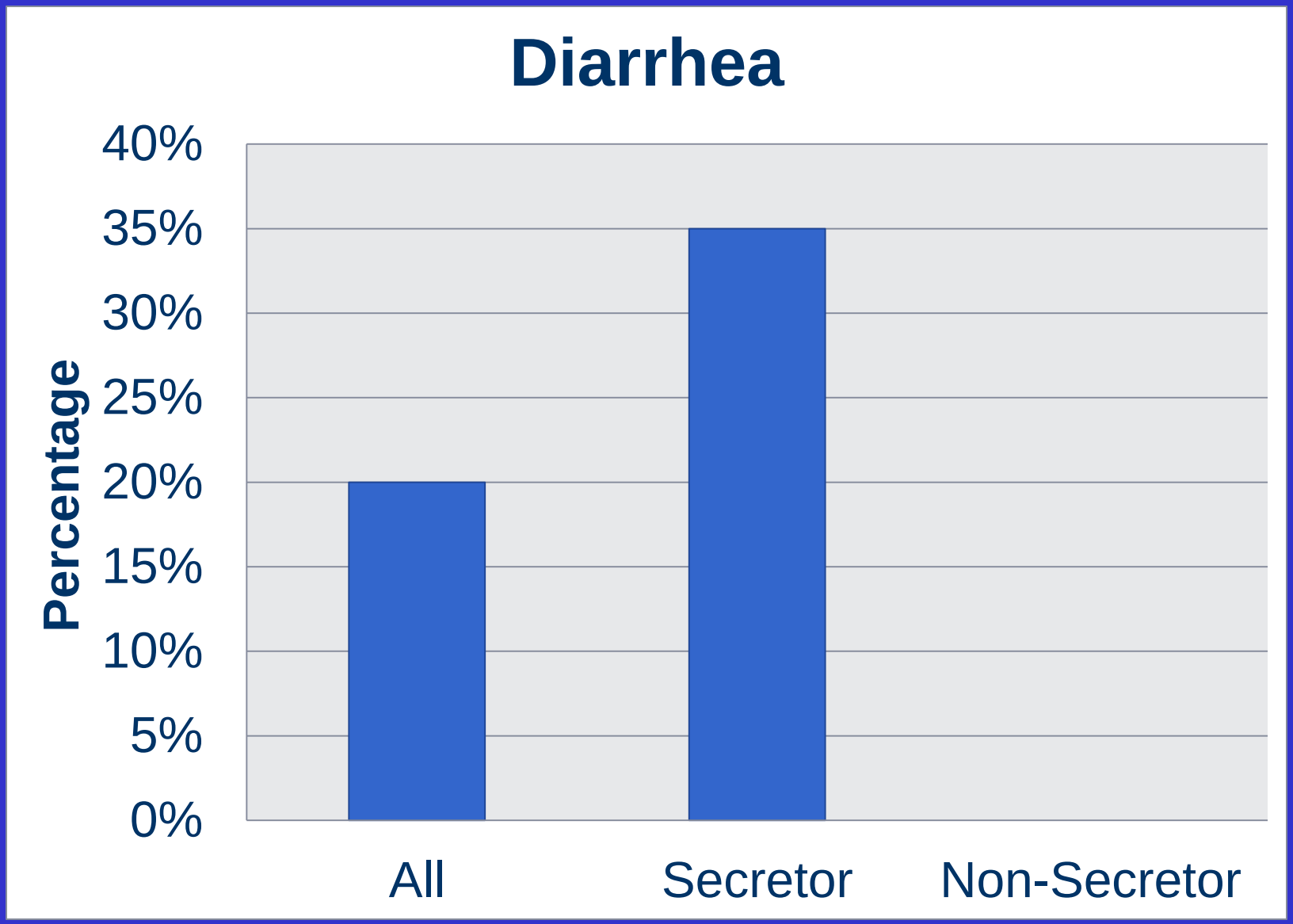
- Forty subjects were enrolled, 23 of whom were secretor positive
- Subjects were administered the challenge strain of norovirus on day 1.
- Infection began 24-48 hours after challenge
- Nausea typically was first symptom.
- Disease was mild to moderate in severity and lasted 1-3 days.

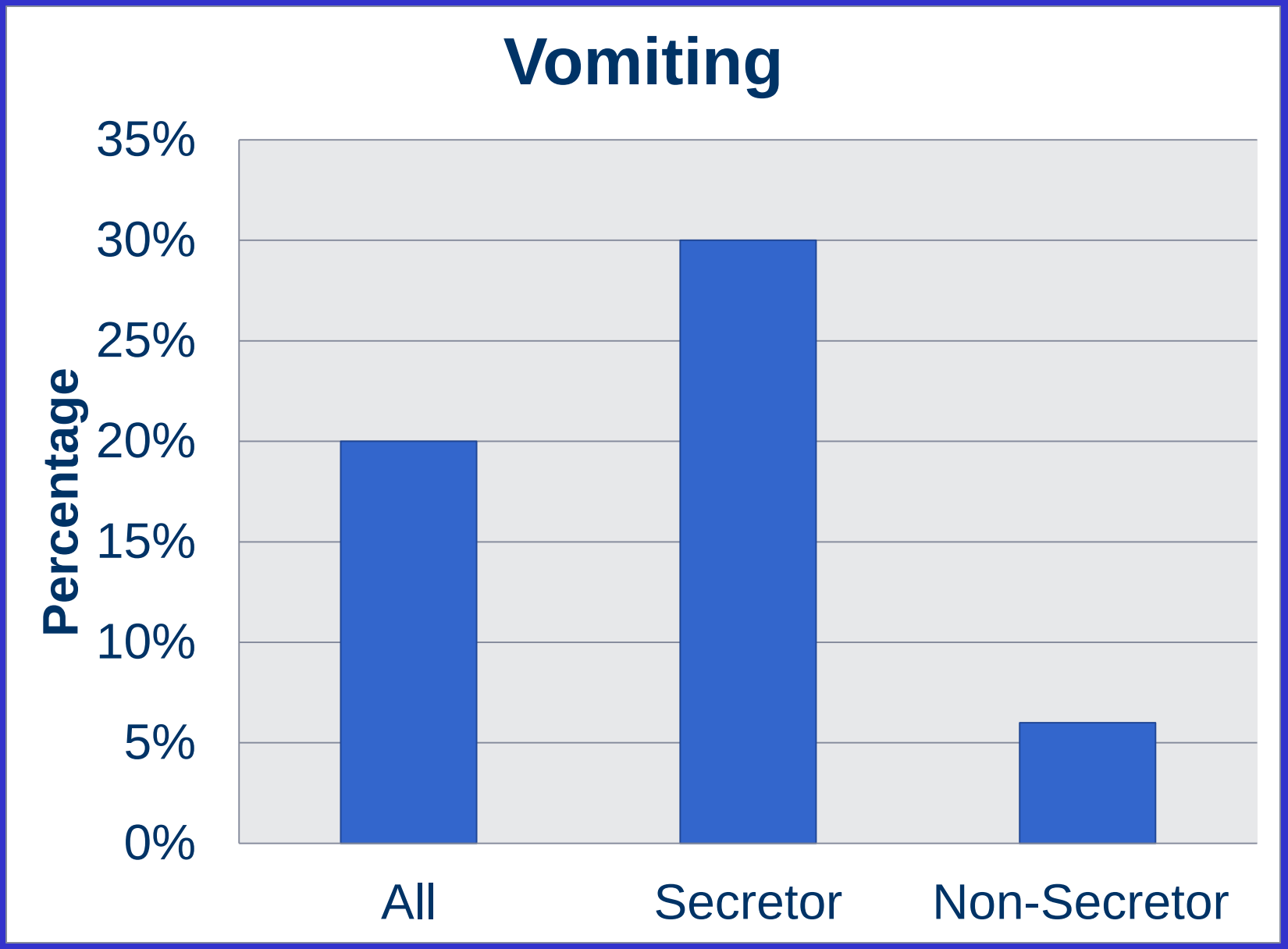

Infected
Percentage
80%
70%
60%
50%
40%
30%
20%
10%
0%
n=40
n=23
n=17
All
Secretor*
Non-Secretor

* = 0.0009



* = 0.0009


Diarrhea
Percentage
40%
35%
30%
25%
20%
15%
10%
5%
0%
All
Secretor
Non-Secretor


Vomiting
Percentage
35%
30%
25%
20%
15%
10%
5%
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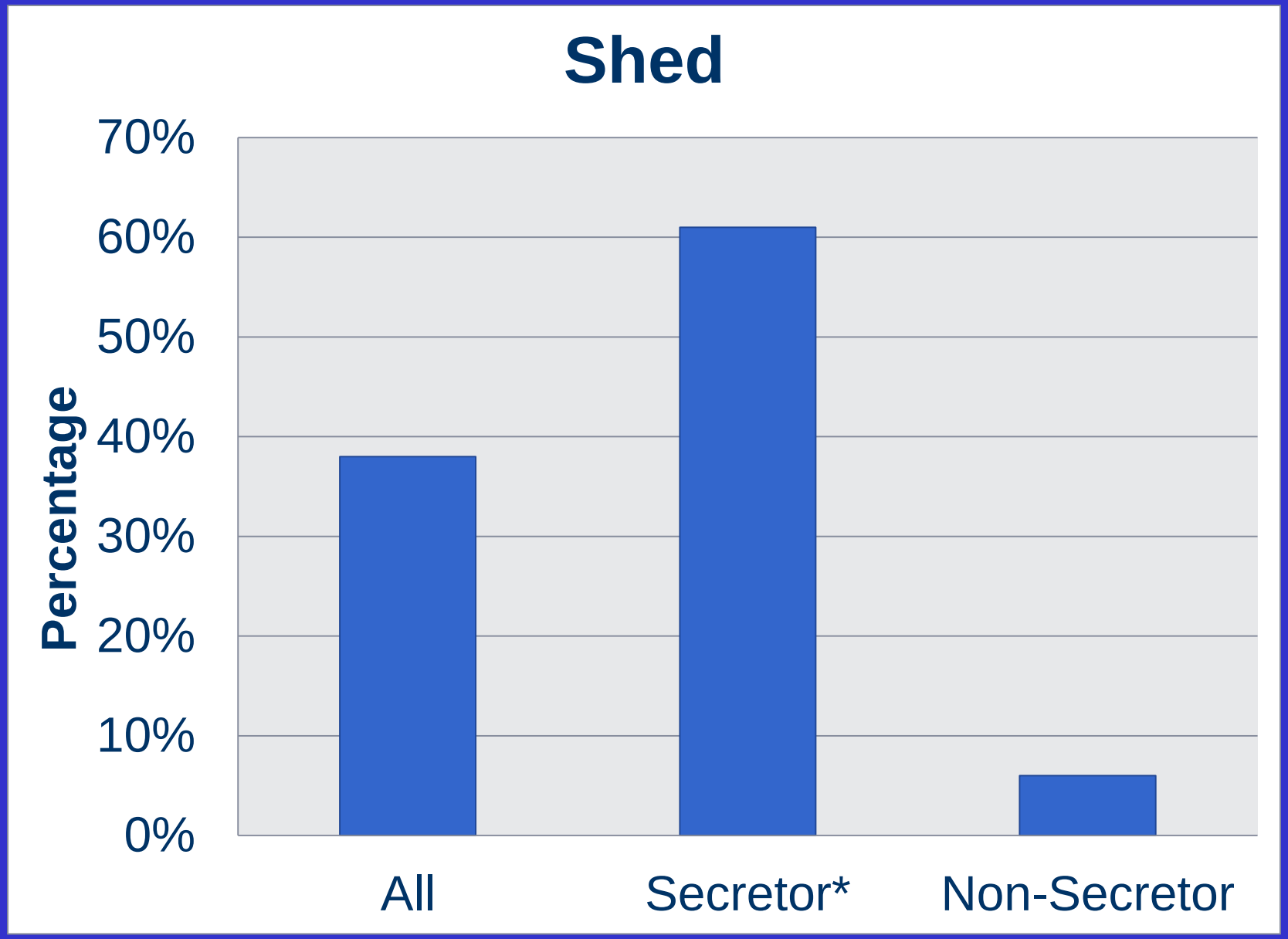
Shed
70%
60%
50%
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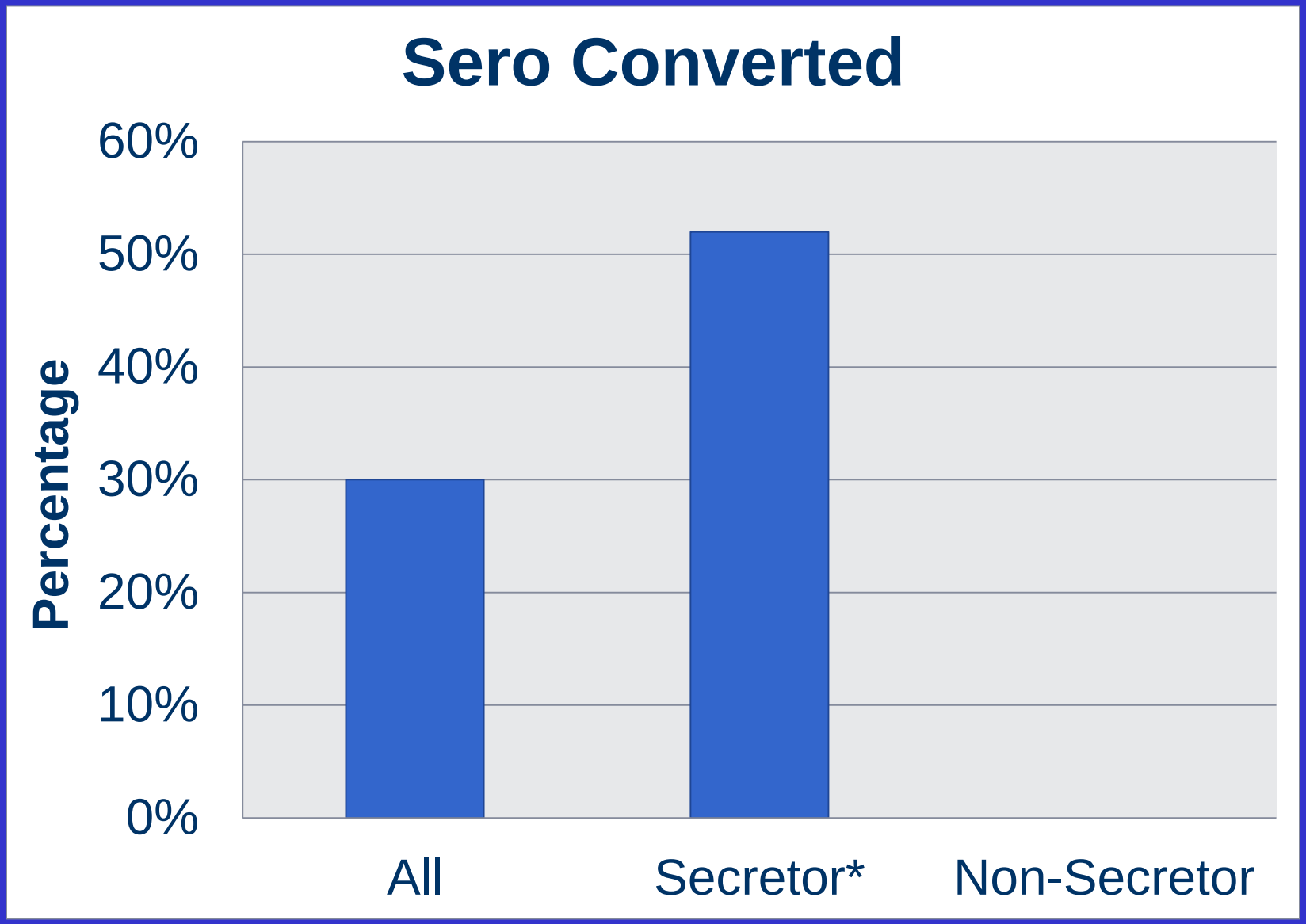
30%
20%
10%
0%
Percentage
All
Secretor*
Non-Secretor

*= 0.0006


Sero Converted
Percentage
60%
50%
40%
30%
20%
10%
0%
All
Secretor*
Non-Secretor

*= 0.0003

Conclusion

- Secretor status determined the susceptibility to a norovirus GII.4 challenge.
- This human challenge model should be useful for evaluating norovirus vaccines and antivirals.

Conclusions

- Norovirus are common causes of outbreak as well as sporadic gastroenteritis
- Norovirus affects all ages
- More work is needed in
  - Optimizing infection control
  - Improved therapeutics
  - Vaccines

Acknowledgements

- David Bernstein
- Jason Jiang
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  - Michelle Dickey
  - Susan Parker