Rotaviruses & noroviruses: virology and clinical features

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Overview

Rotavirus and Norovirus

Significance

Clinical presentation

Viral characteristics

Current research

Rotavirus

Rotavirus
global perspective (pre-vaccine)

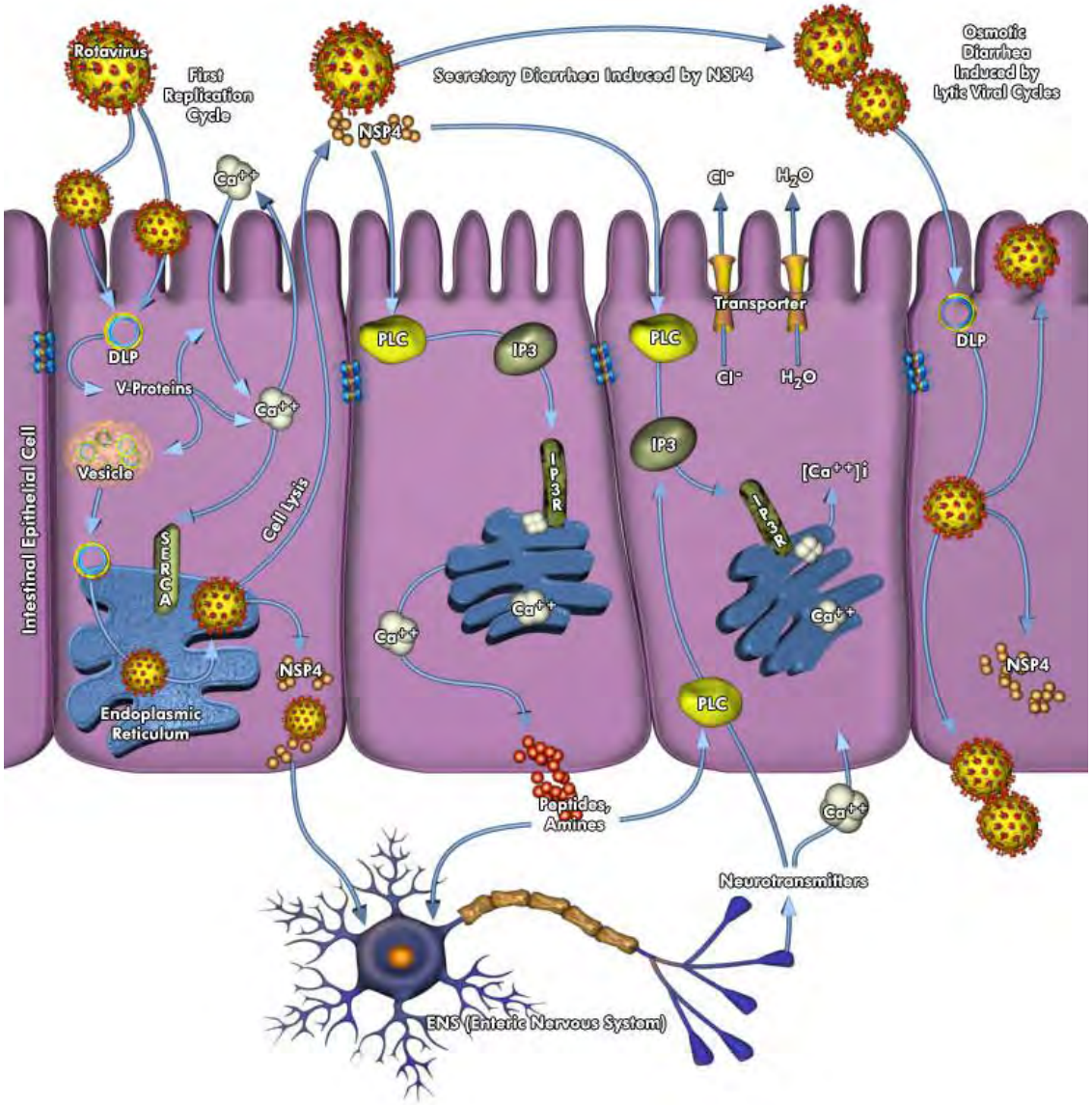
- Nearly all children were infected by age 3, 100% by age 5
- Each year rotaviruses caused:
  - ~111 million episodes of gastro that are treated at home
  - 25 million clinical visits
  - 2 million hospitilisations
  - 352,000 – 705,000 deaths
- Has caused large outbreaks, with several outbreaks overseas involving >20,000 cases

Clinical symptoms of rotavirus

- Incubation period ~2 days
- Symptoms last a median of 2 days, range 2-8 days
- Common clinical manifestations for primary infection include, severe watery diarrhoea, often with vomiting, fever and nausea
- ~30% of infected children have a temperature greater than 39° C
- Can lead to severe dehydration, electrolyte imbalance and metabolic acidosis
- Immunocompromised may experience severe or prolonged rotavirus gastroenteritis and may have evidence of abnormalities in multiple organ systems, particularly the kidney and liver.

Rotavirus pathogenesis

- Viral replication occurs in the villous epithelium of the small intestine



Rotavirus immunology

- Rotavirus immunity poorly understood
  - Cellular and humoral immunity probably both play a role in recovery and protection
- Recovery from 1st infection usually does not lead to permanent immunity
- After a single infection:
  - 38% protected against subsequent infection
  - 77% protected against rotavirus diarrhea
  - 87% protected against severe diarrhea

Rotavirus characteristics

- Infections have some seasonality (winter) in higher income and all year-round in lower income countries

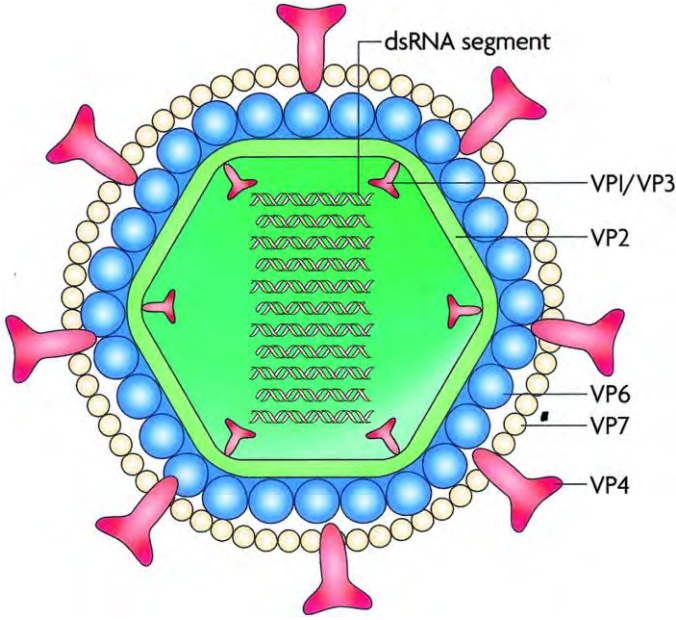
- Tolerant to temperature change

- Highly infectious
  - most infectious during symptomatic phase and first 3 days after

- Shed at high concentrations in faeces (10^12 particles/gram)
  - Environmentally stable (9-19 days)

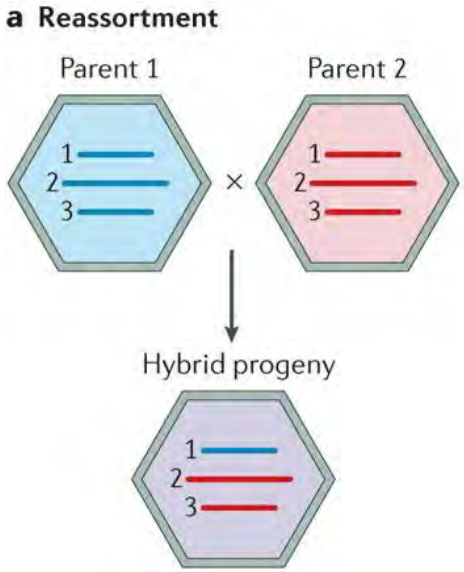
- Low infectious dose (<100 particles)

Rotavirus virology



- Capsid virus, with 3 protein coats
- Segmented, double stranded (ds) RNA virus
- 11 dsRNA segments

- Reassortment of segments common

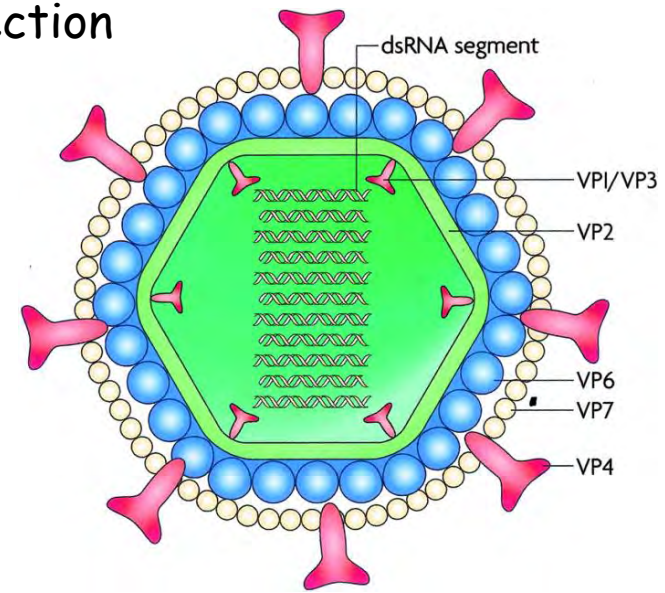


- Many animal rotavirus strains too
  - birds, pigs, cows etc.
  - animal strains thought to be less virulent in human host, but reassortment with human strains has occurred and new variants have emerged.

Rotavirus virology

- Classified into 5 groups called A-E
  - A causes 90% of human rotavirus infections
  - Further classified into serotypes based on surface proteins VP4 (P serotype) and VP7 (G serotype)

- VP4 and VP7 are neutralising antibody targets
  - Neutralisation of either one will provide protection



Rotavirus virology

- 27 G serotypes, of which 18 infect humans
  - -G1, G2, G3, G4 and G9 are the most common in humans

- 14 P serotypes and 25 P genotypes eg. P1A[8]

- Before introduction of vaccine 80-90% of rotavirus infections caused by 5 combinations:
  - - G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]
  - -Different geographical distributions

- RotaTeq = pentavalent (G1, G2, G3, G4, P[8])
- Rotarix = monovalent (G1P[8])

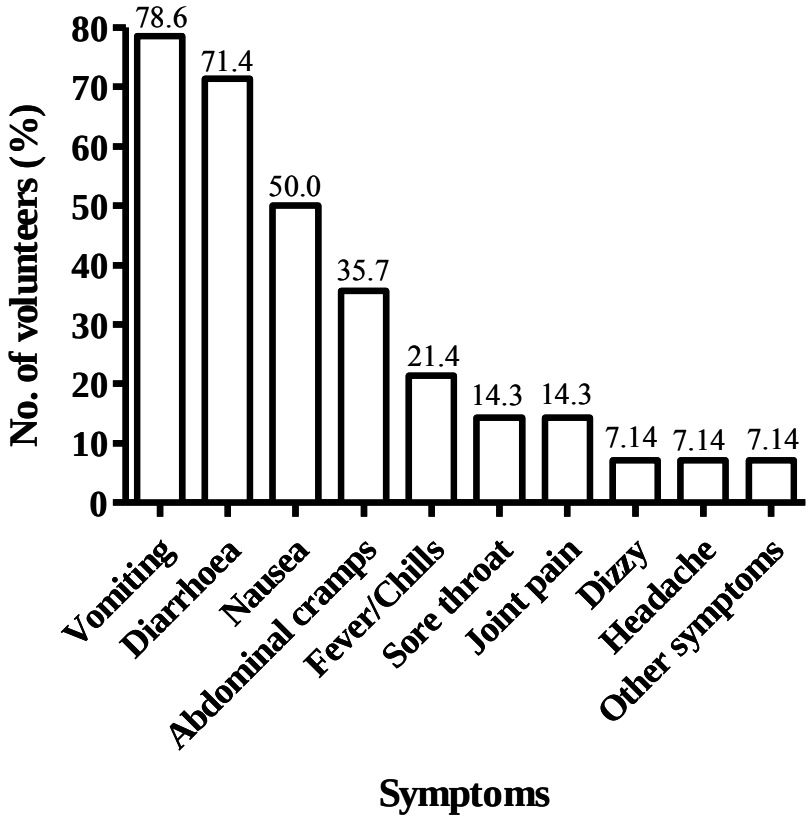
Rotavirus epidemiology (post vaccine)

- Rotarix effectiveness: 57-84% from high to low child mortality countries
- RotaTeq effectiveness: 45-90% effective in high to low child mortality countries
- In the USA rotavirus positive tests have declined by ~75%
- Some concern that vaccine might selectively lead to increase in non-vaccine strains but this doesn't seem to be the case so far

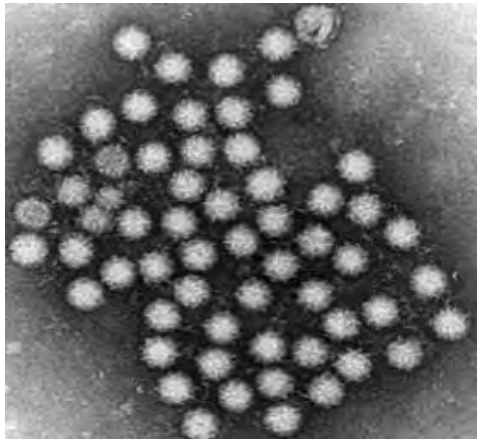
Norovirus

Clinical symptoms of norovirus

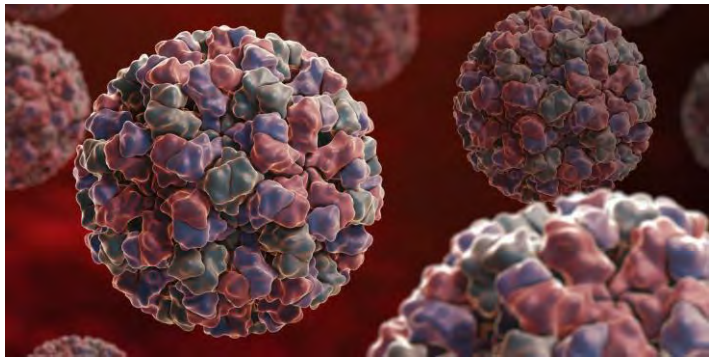
- Incubation period 12-24 hours
- Symptoms last a median of 2 days, range 0-3 days
- Common clinical manifestations: vomiting, diarrhoea and nausea
- Generally less severe than rotavirus

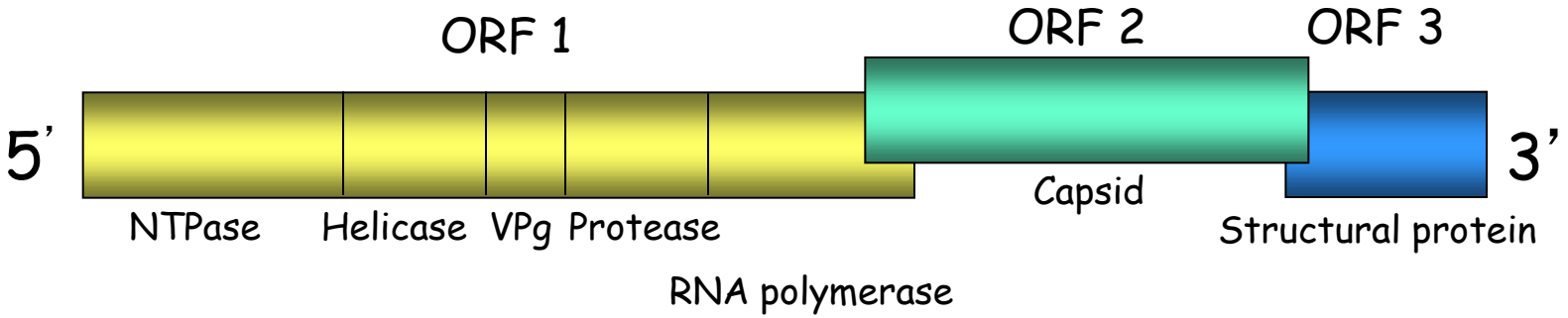


Norovirus (NoV) Genome



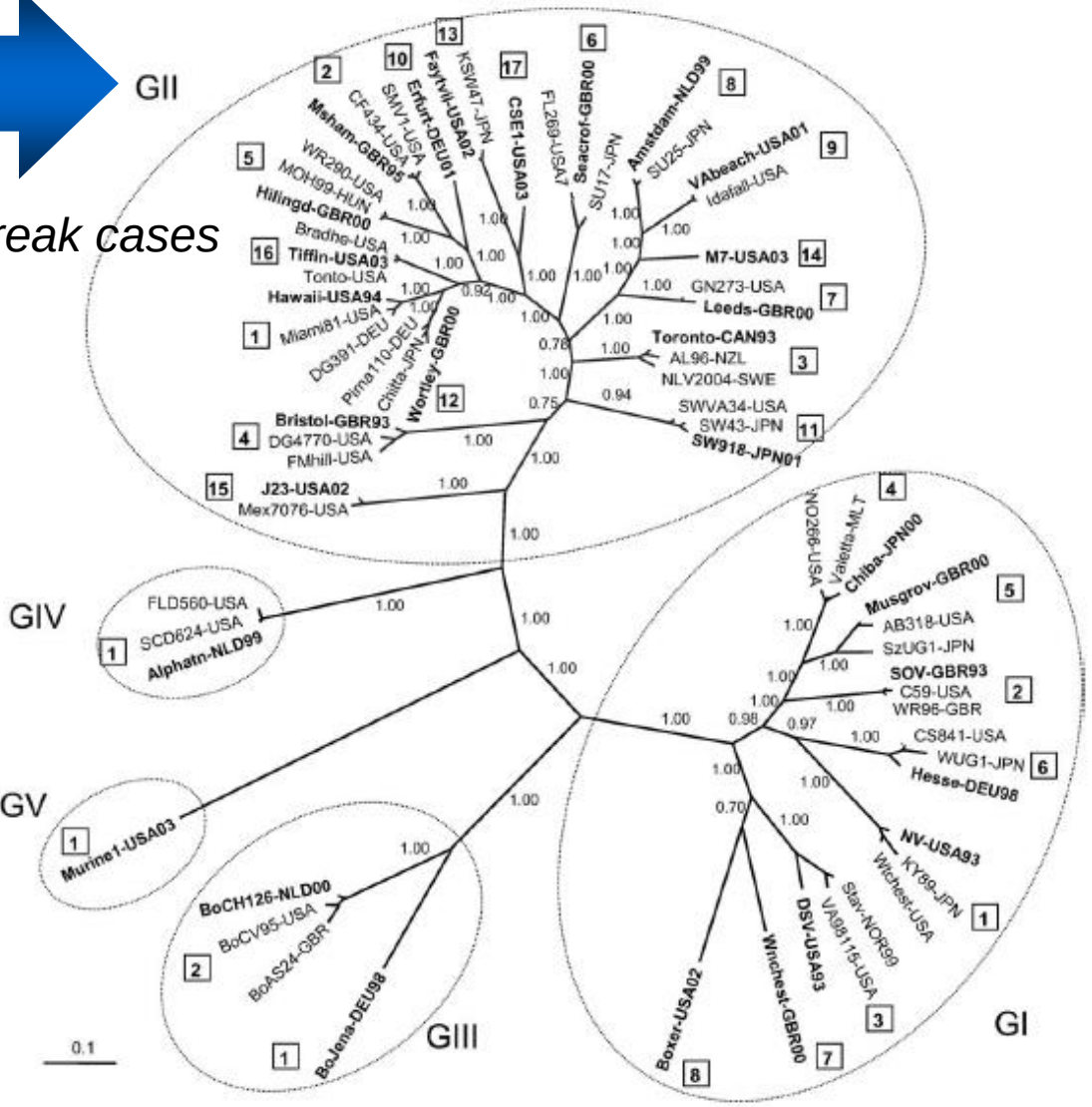
- 27 – 32 nm
- Non-enveloped
- single stranded RNA virus
- 7,400 – 7,700 nucleotides





Norovirus Classification

Most common in outbreak cases



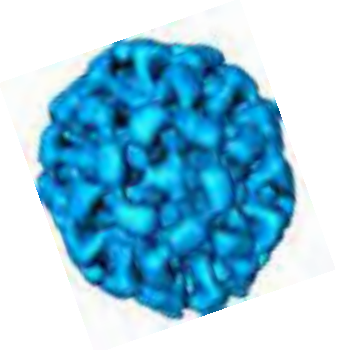
Zheng etal. 2006. Virology 346, 312-323

Norovirus characteristics

- Tolerant to temperature change
  - can survive temperatures as high as 60° C and quick steaming processes that are often used for cooking shellfish

- Survives high levels of chlorine
  - decontaminate with chlorine bleach solution at a conc. of 1000–5000 ppm

- Highly infectious
  - Low infectious dose (20-1300)
  - Virus continues to be shed for at least 2 weeks



Norovirus, the perfect pathogen?

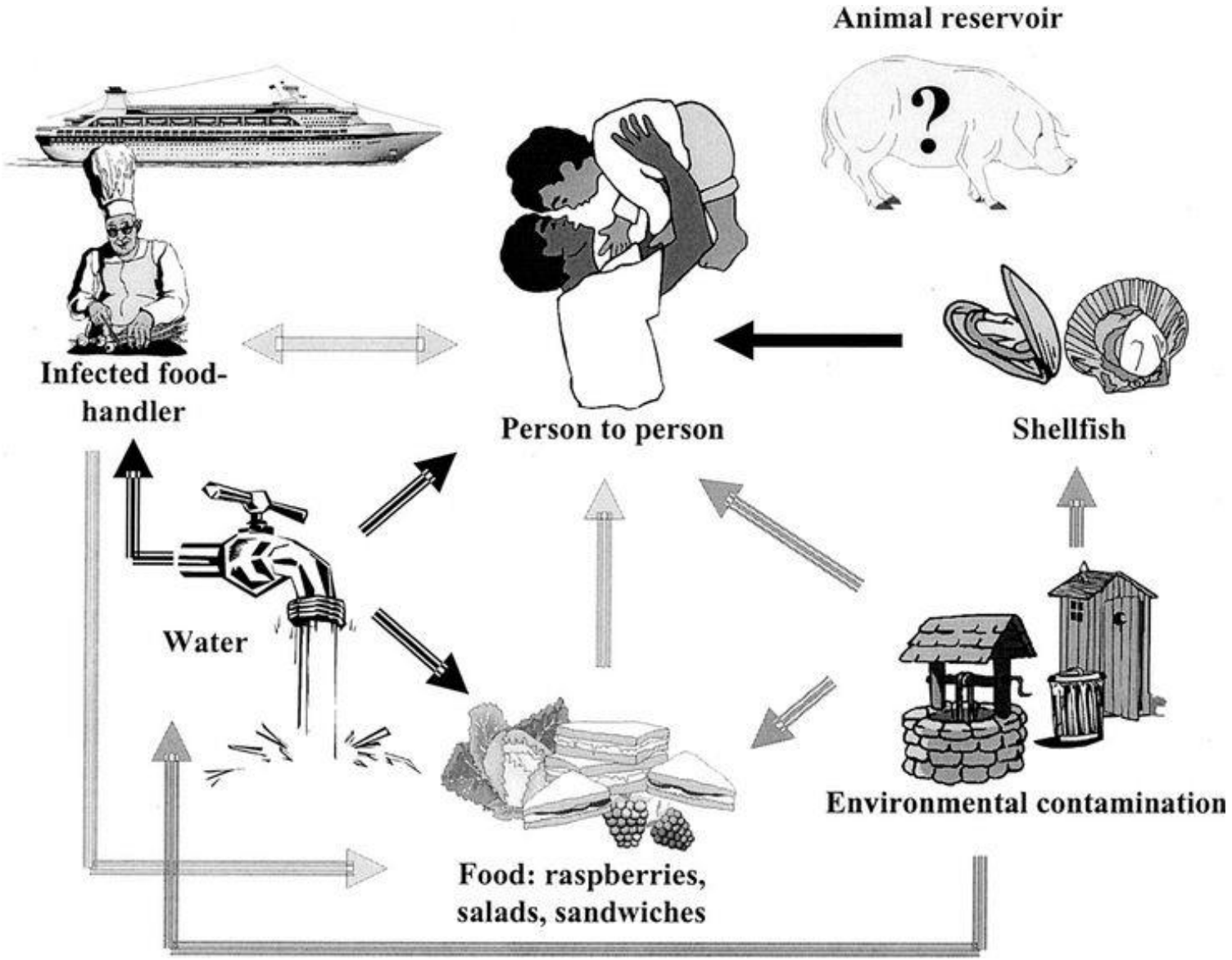
- rapidly and prolifically shed

- constantly evolving, limited immunity, only moderately virulent, allowing most of those infected to fully recover, thereby maintaining a large susceptible pool of hosts

- these characteristics have enabled noroviruses to become the leading cause of:
  - endemic diarrheal disease across all age groups,
  - foodborne disease, and
  - cause of half of all gastroenteritis outbreaks worldwide

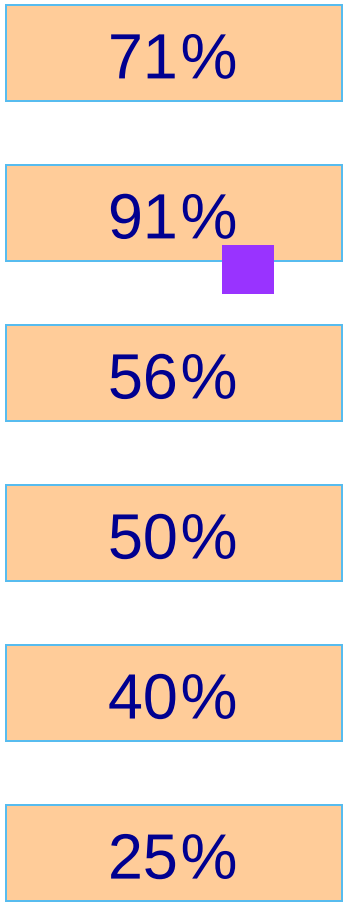
- Worldwide cause ~267 million infections and >200,000 deaths (mainly young and elderly)

Norovirus Transmission



Maunula et al. 2005. Emerg Infect Dis 11.1716-1721

Airborne transmission of NoV in a restaurant



- **Hotel restaurant with 126 patrons**
- **Patron (■) vomited at table**
- **52 of 83 survey responders ill**
  - **63% overall attack rate**
- **Attack rates higher at closer tables**
- **Consistent with airborne transmission of NoV**

Marks et al. Epidemiol. Infect. 2000.

Norovirus contamination in a pediatric unit

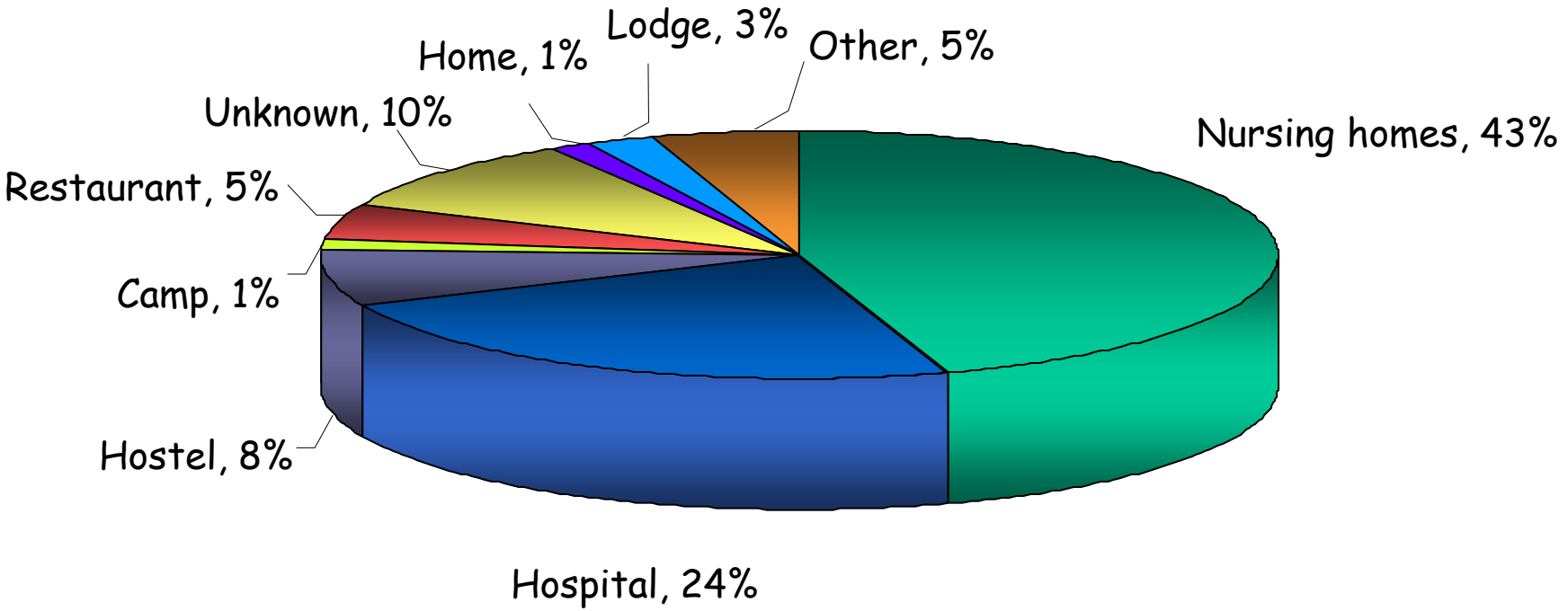
TABLE 1. Patient and environmental swab sample data[a]

Date[b]	Sample	Genotype	S type (patient no.)	P2 type	GenBank accession no.
8 October	Patient 1, sample 1	GII-3	1	Patient 1-01	GU252731
30 October	Patient 2, sample 1	GII-3	2	Patient 2-01	GU252734
5 November	Patient 2, sample 2	GII-3	2	Patient 2-02	GU252735
12 November	Patient 1, sample 2	GII-3	1	Patient 1-02	GU252732
14 November	Patient 2, sample 3	GII-3	2	Patient 2-02	NA
	Biscuit tin	GII-3	2	Env. swab 1	GU252737
	Sluice surface	GII-3	2	Env. swab 2	GU252738
16 November	Patient 2, sample 4	GII-3	2	Patient 2-02	NA
19 November	Patient 1, sample 3	GII-3	1	Patient 1-02	NA
22 November	Patient 1, sample 4	GII-3	1	Patient 1-02	NA
	Keyboard	GII-3	2	Env. swab 3	GU252739
	Trolley	GII-3	1	Patient 1-01	GU252740
	Sluice surface	GII-3	2	Env. swab 4	GU252741
	Toilet handle	GII-3	2	Env. swab 5	GU252742
	Draining board, staff	GII-4	NA	ND	NA
	Cubicle door handle	GII-4	NA	ND	NA
	Bathroom taps, parents	GII-4	NA	ND	NA
10 December	Patient 1, sample 5	GII-3	1	Patient 1-03	GU252733
12 December	Clinical waste bin	GII-3	2	Patient 2-02	GU252743
	Telephone keypad	GII-3	2	Env. swab 6	GU252744
	Cubicle waste bin	GII-3	1	Env. swab 7	GU252745
	Mattress top, parents	GII-3	1	Env. swab 8	GU252746
	Taps in bathroom	GII-3	1	Env. swab 9	GU252747
	Bathroom door, parents	GII-4	NA	ND	NA
	Floor outside corridor	GII-4	NA	ND	NA
15 December	Clinical waste bin	GII-3	1	Env. swab 10	GU252748
	Chair arms	GII-3	1	Env. swab 11	GU252749
	Under bed frame	GII-3	1	Env. swab 12	GU252750
	Trolley	GII-3	1	Patient 1-02	GU252751
17 December	Patient 1, sample 6	GII-3	1	Patient 1-03	NA
	Patient 2, sample 5	GII-3	2	Patient 2-03	GU252736
22 December	Cubicle sink tap	GII-3	1	Env. swab 13	GU252752
	Chair arms	GII-3	2	Env. swab 14	GU252753
	Bed side, parents	GII-3	1	Env. swab 15	GU252754

[a] Abbreviations: S, shell domain; P2, protruding 2 domain; NA, not applicable; ND, not determined; Env., environmental.
[b] Date of sample collection (patient samples were from feces, and other samples were environmental swabs).

Xerry et al. 2010 JCM

Outbreak settings in NSW



n = 80 norovirus outbreaks

Tu et al. CID 2008

Norovirus epidemics and pandemics

Experts warn of virulent gastro strain

ABC News

Posted Mon Aug 27, 2007 7:00am AEST
Updated Mon Aug 27, 2007 7:49am AEST

Researchers from the University of New South Wales and the Prince of Wales H warning of a virulent strain of gastroenteritis that has arrived in Australia.

Parents have been warned that the disease could childcare centres.

Experts predict hundreds of thousands of Australia of the virus mutated to a more contagious form th

MEDIA, NEWS & EVENTS

Mutant virus causing Australian
28 August 2007

Tens of thousands of people across Australia gastroenteritis, UNSW and Prince of Wales H

Gastro epidemic sweeping nation: expert

August 01, 2007 06:05pm

A GASTROENTERITIS outbreak at a Newcastle hospital is the latest case in an epidemic sweeping Australia and the world, a NSW health expert says.

So far this month, New South Wales, Victoria, Queensland and Tasmania have experienced gastro outbreaks in hospitals, nursing homes and retirement villages.

Yesterday, authorities banned family and friends from Newcastle's Calvary Mater Hospital, where 80 staff and patients have experienced complications associated with the airborne virus.

ospital were closed to visitors as a
emain closed until Friday.

asting for about three days. No
the new spate of gastroenteritis

An artist's impression of a norovirus

Gastro bug set to hit hard

Article from: The Courier Mail

Font size: Email article: Print article: Submit comment:

Janelle Miles
August 27, 2007 11:00pm

HUNDREDS of thousands of Australians are expected to be infected with this year's highly contagious strain of the norovirus gastro bug.

A team led by University of NSW virologist Peter White has identified the norovirus responsible as the 2006b strain, first described in Europe in February last year.

Dr White said the virus was expected to hit hardest in crowded environments such as childcare centres, nursing homes and hospitals.

The infection causes vomiting and diarrhoea, usually lasting for about three days.

"We'll be expecting another month or two of outbreaks right across the country, spreading to New Zealand," Dr White said.

He said global norovirus epidemics had been reported in 1996, 2002, 2004 and 2006, and scientists were unsure why they appeared to be becoming more frequent.

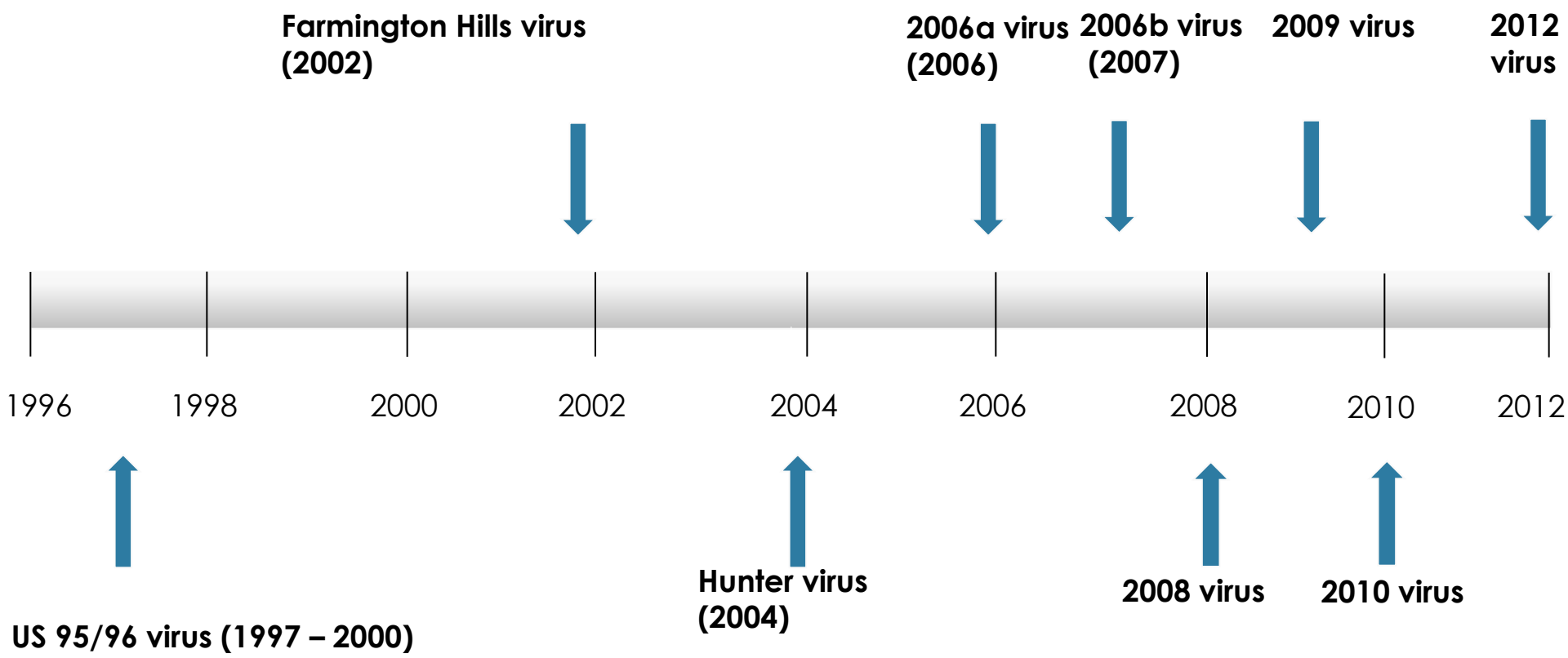
"The distance between them is getting shorter and shorter. That's a serious health problem," Dr White said. "What would normally only be happening every five to 10 years is now happening every year."

Spread by air, water and personal contact, noroviruses are highly contagious and can survive in food, water and the environment for long periods.

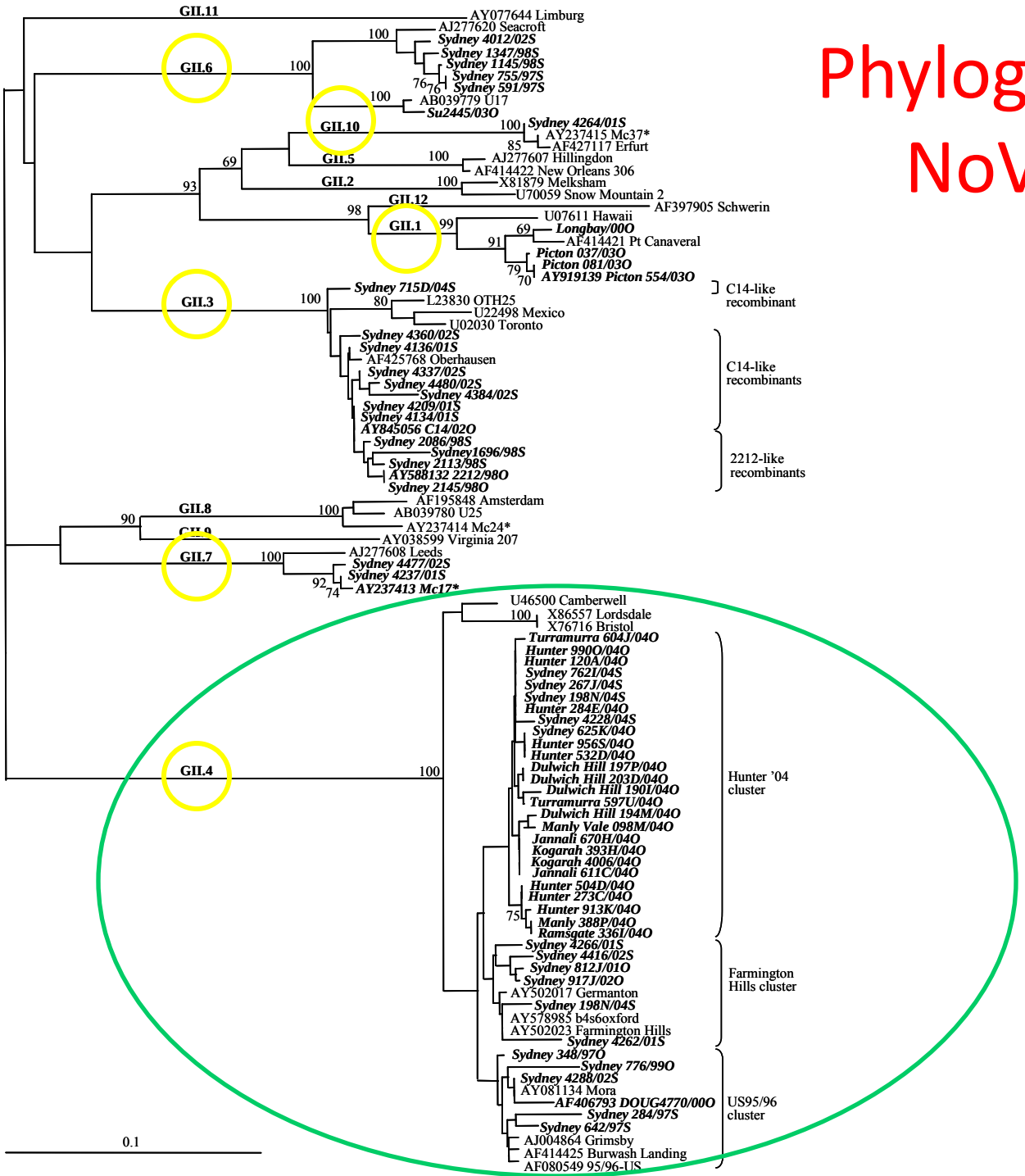
LATEST strain is highly contagious . . . Dr Bill Rawlinson.

Early gastro warning

Norovirus epidemics in Sydney



Phylogenetic tree of NoV GII capsid



Investigate Mechanisms of GII.4 Dominance

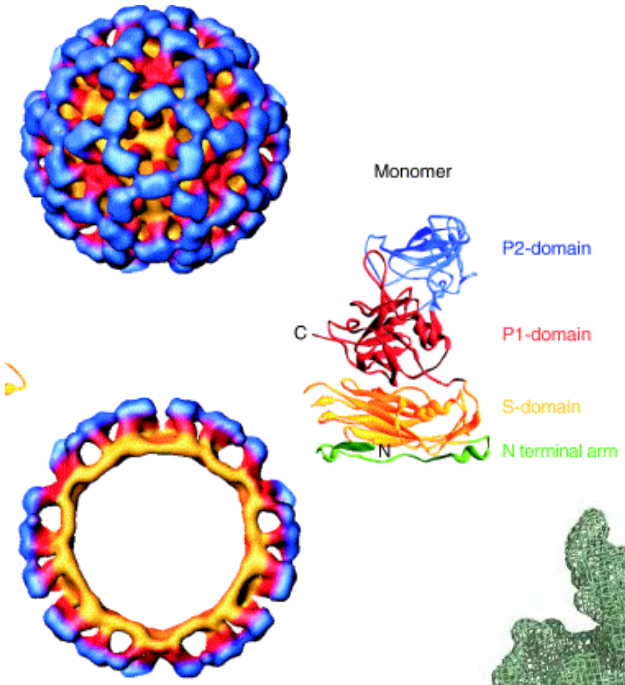
- **Two mechanisms used to evolve:**

1. Nucleotide substitution **Antigenic Drift**

2. Recombination **Antigenic Shift**

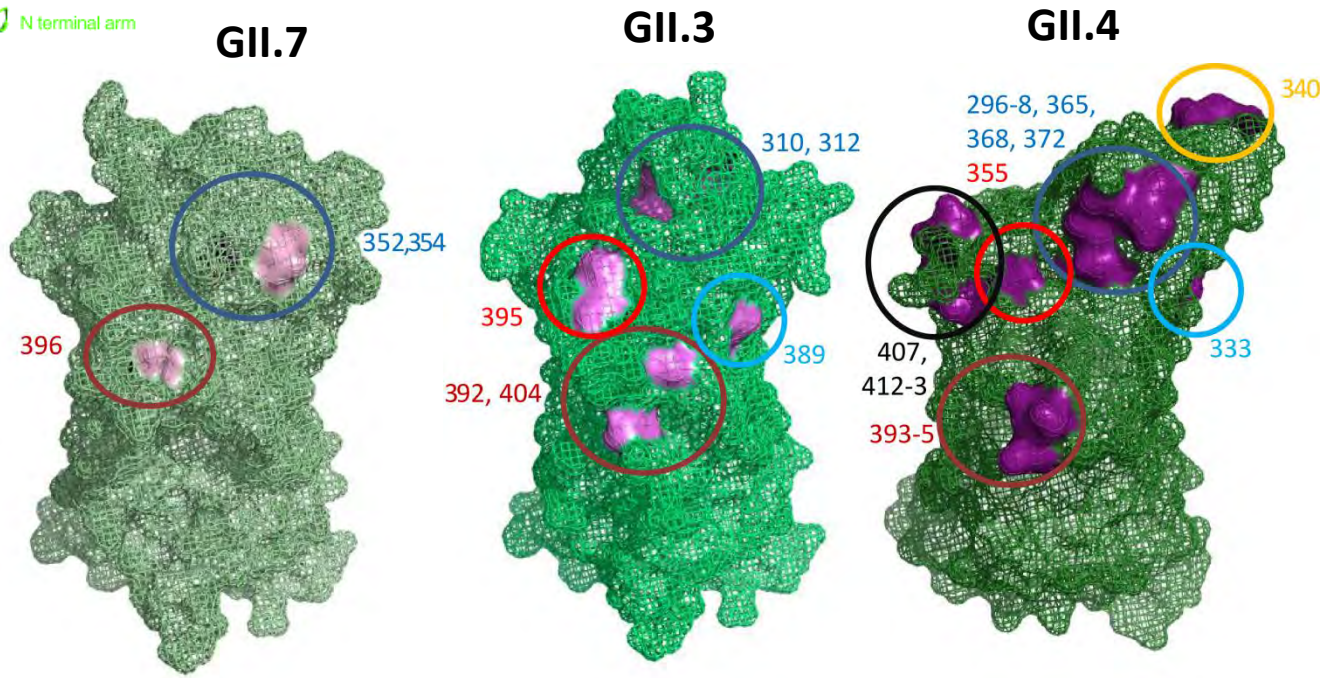
- different regions of genome originate from different viruses

Evolution Hotspots in the Capsid



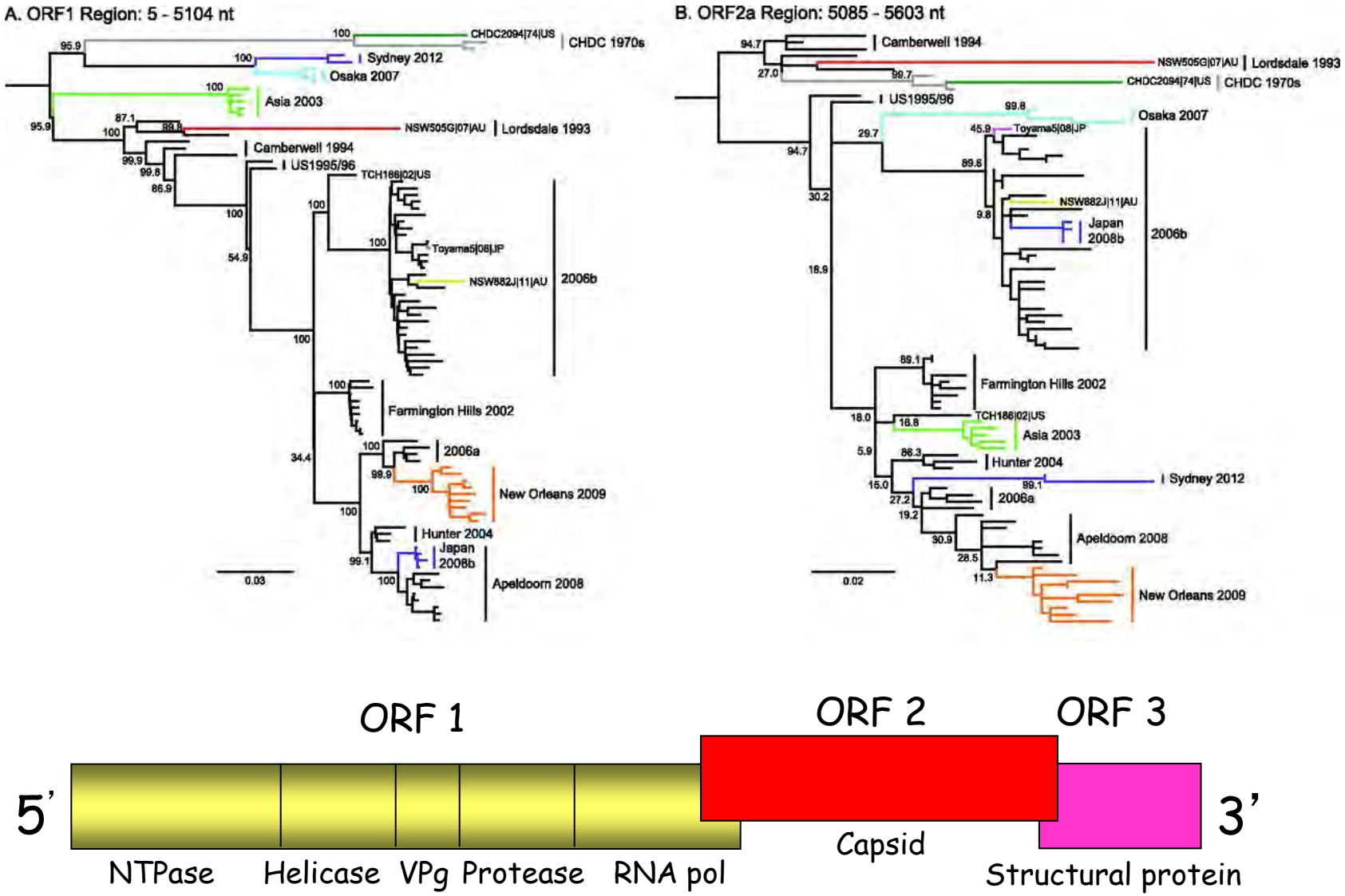
Hutson, et al. 2004. Trends Microbiol

- Variation hotspots in the P2 domain
- Greater immune escape in GII.4



Bull, et al. 2010. PLOS path.

Recombination contributes to genome diversity and emergence of new epidemic variants



John-Sebastian Eden et al. J. Virol. 2013;87:6270-6282

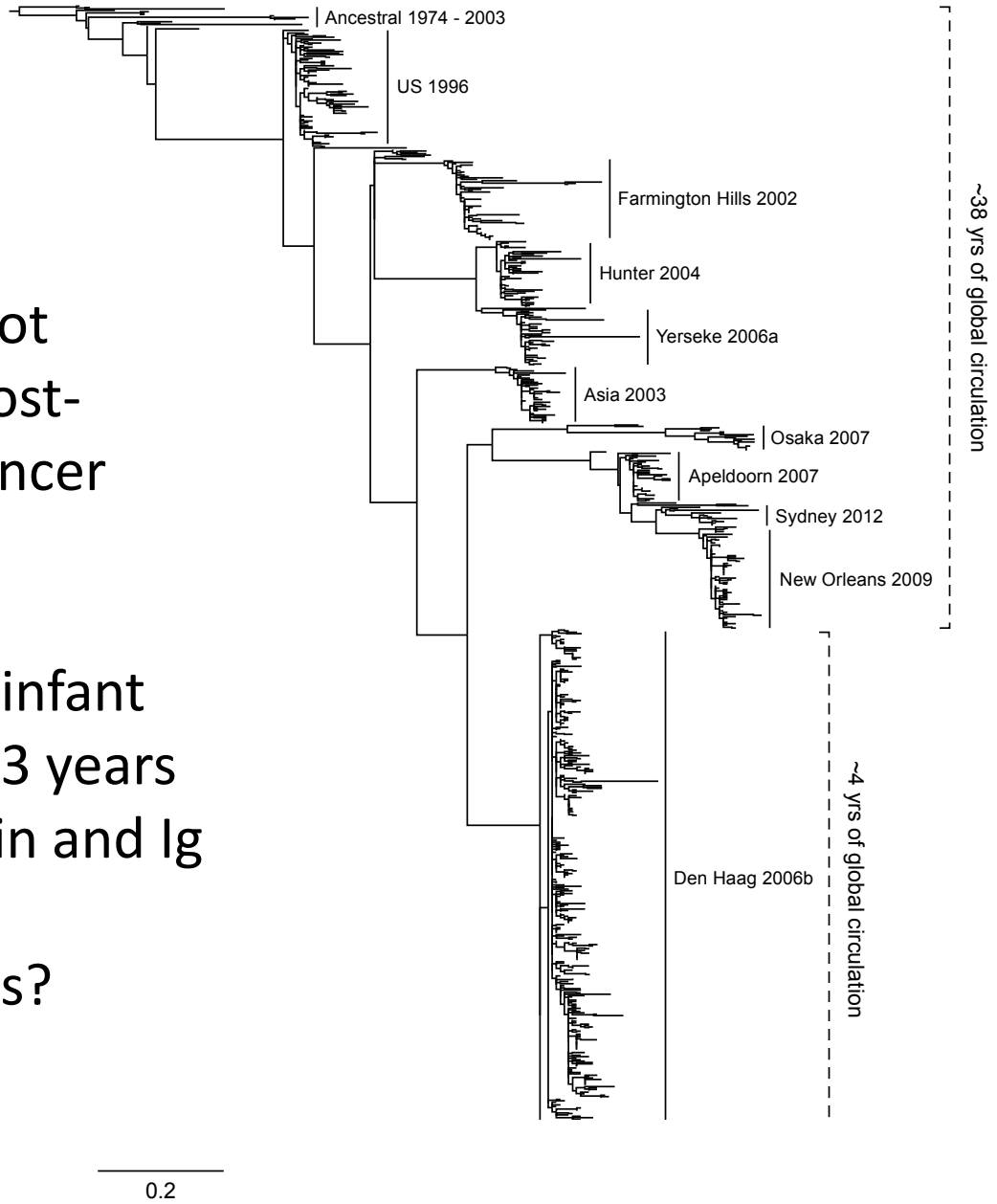
Journal of Virology

Chronic NoV

- Chronic infection in immunocompromised not uncommon including, post-transplant recipients, cancer patients etc.

- Immunocompromised infant infected from birth for >3 years
  - -treated with ribavirin and Ig

  Source of new strains?



Acknowledgments

UNSW
- John-Sebastian Eden
- Peter White
- Fabio Luciani

Prince of Wales Hospital
- Dr Elise Tu
- Dr Chris McIver
- Prof Bill Rawlinson