

Noroviruses

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The Erasmus MC logo features the text "Erasmus MC" in a bold, dark blue font, with "Universitair Medisch Centrum Rotterdam" in a smaller, lighter blue font below it. A large, stylized, light blue signature-like graphic of the word "Erasmus" is positioned behind the text.

Key messages

- The burden of disease due to noroviruses is increasing (globally)
- Clinical impact in health care outbreaks much greater than currently appreciated
- Norovirus outbreaks (probably) can not be prevented, but rapid control reduces impact and size



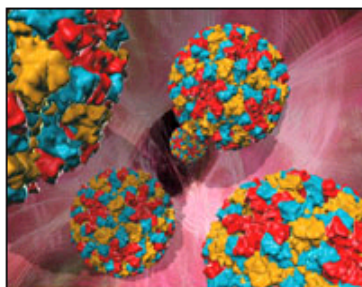
Last Updated: Thursday, 3 January 2008, 22:44 GMT

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Stomach bug sweeping the country

People struck down by a stomach bug sweeping the UK have been urged not to go back to work.

Doctors estimate more than 100,000 people a week are catching norovirus, which causes diarrhoea and vomiting.



Norovirus causes sudden vomiting and diarrhoea

Workers need to remain at home for 48 hours after the symptoms have gone and stay away from surgeries and hospitals, the Royal College of GPs warned.

At least 56 hospital wards across England and Wales have been closed to new patients, the BBC has learned.

The Worcestershire Acute Hospitals Trust says it is cancelling all non-urgent operations until 9 January because of what it calls the "unrelenting pressure" caused by the virus.

The Royal Oldham Hospital has 11 wards closed which is more than a quarter of its total and Birmingham Heartlands Hospital says six areas of the hospital are affected.

Some hospitals, including two in Bristol and one in Bedford, have told people not to visit if they have been sick or if their visit is not essential.

The Health Protection Agency confirmed the number of cases this year is the highest since 2002.

VIDEO AND AUDIO NEWS

Advice on how to combat the virus and its symptoms

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JOURNAL OF VIROLOGY, Nov. 1972, p. 1075-1081
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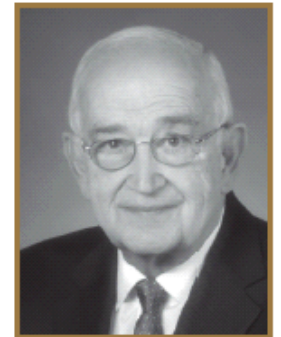
Visualization by Immune Electron Microscopy of a 27-nm Particle Associated with Acute Infectious Nonbacterial Gastroenteritis

ALBERT Z. KAPIKIAN, RICHARD G. WYATT, RAPHAEL DOLIN, THOMAS S. THORNHILL,
ANTHONY R. KALICA, AND ROBERT M. CHANOCK

*Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, Maryland 20014*

Received for publication 3 August 1972

A 27-nm particle was observed by immune electron microscopy in an infectious stool filtrate derived from an outbreak in Norwalk, Ohio, of acute infectious nonbacterial gastroenteritis. Both experimentally and naturally infected individuals developed serological evidence of infection; this along with other evidence suggested that the particle was the etiological agent of Norwalk gastroenteritis.



Challenges to control of noroviruses

Low infectious dose (10)
high level of shedding (10^7)
prolonged shedding (weeks)
Chronic shedding
environmental persistence

**Extensive outbreaks,
difficult to control**

poor immune response
Great diversity

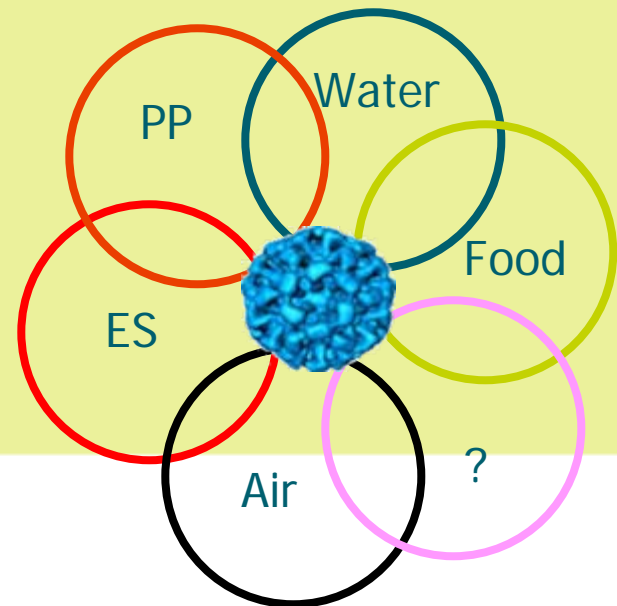
All age groups

No cell culture system
Shift and drift

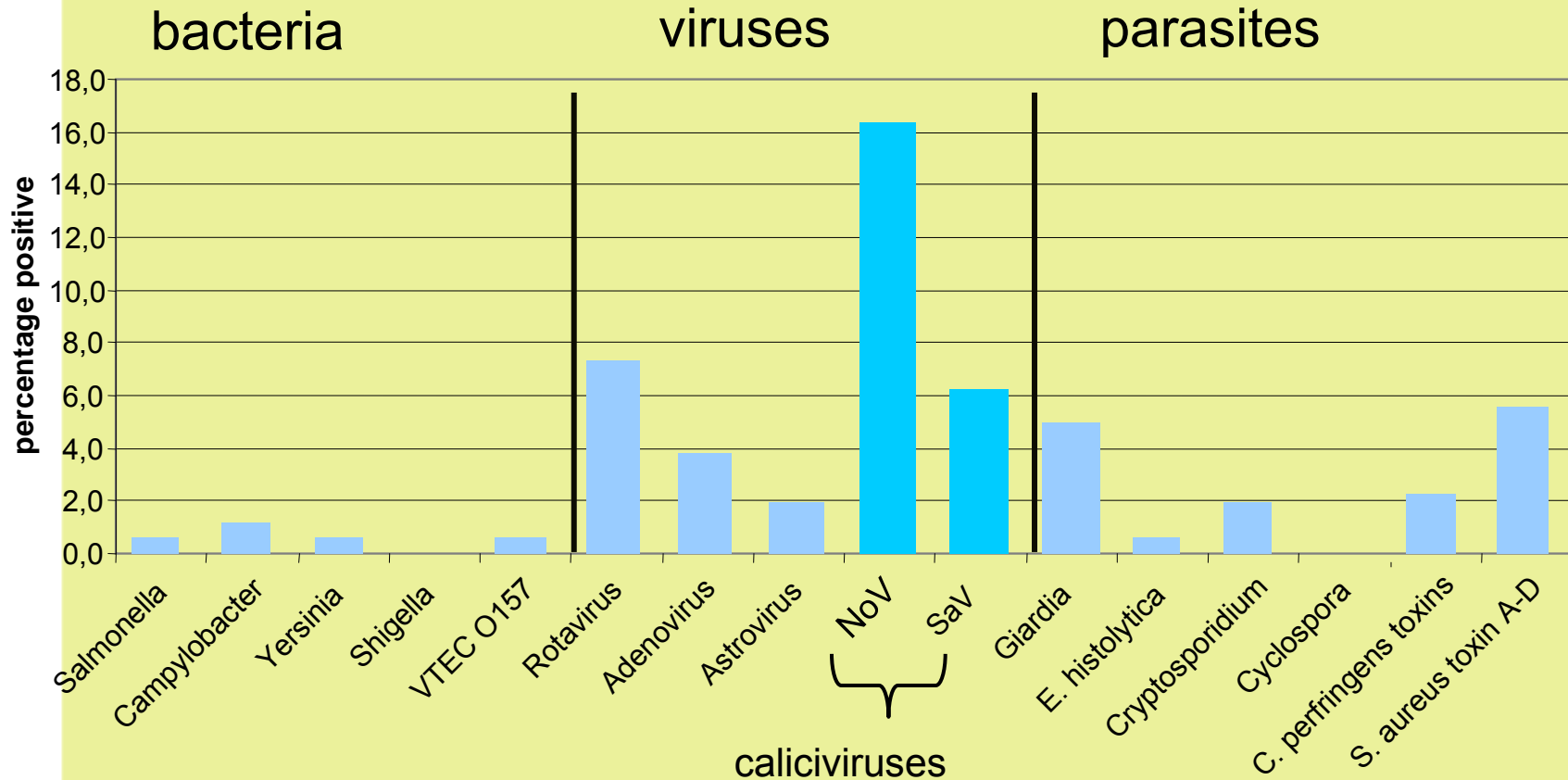
Diagnostic problem

NOROVIRUS TRANSMISSION

- “fecal-oral” route, Person-person contact
- Air-borne: aerosolization with vomitus
- Food-borne: Shellfish (oysters, clams, mussels), fresh produce, prepared foods (food-handler)
- Water-borne
- Environmental surfaces
- Unknown?

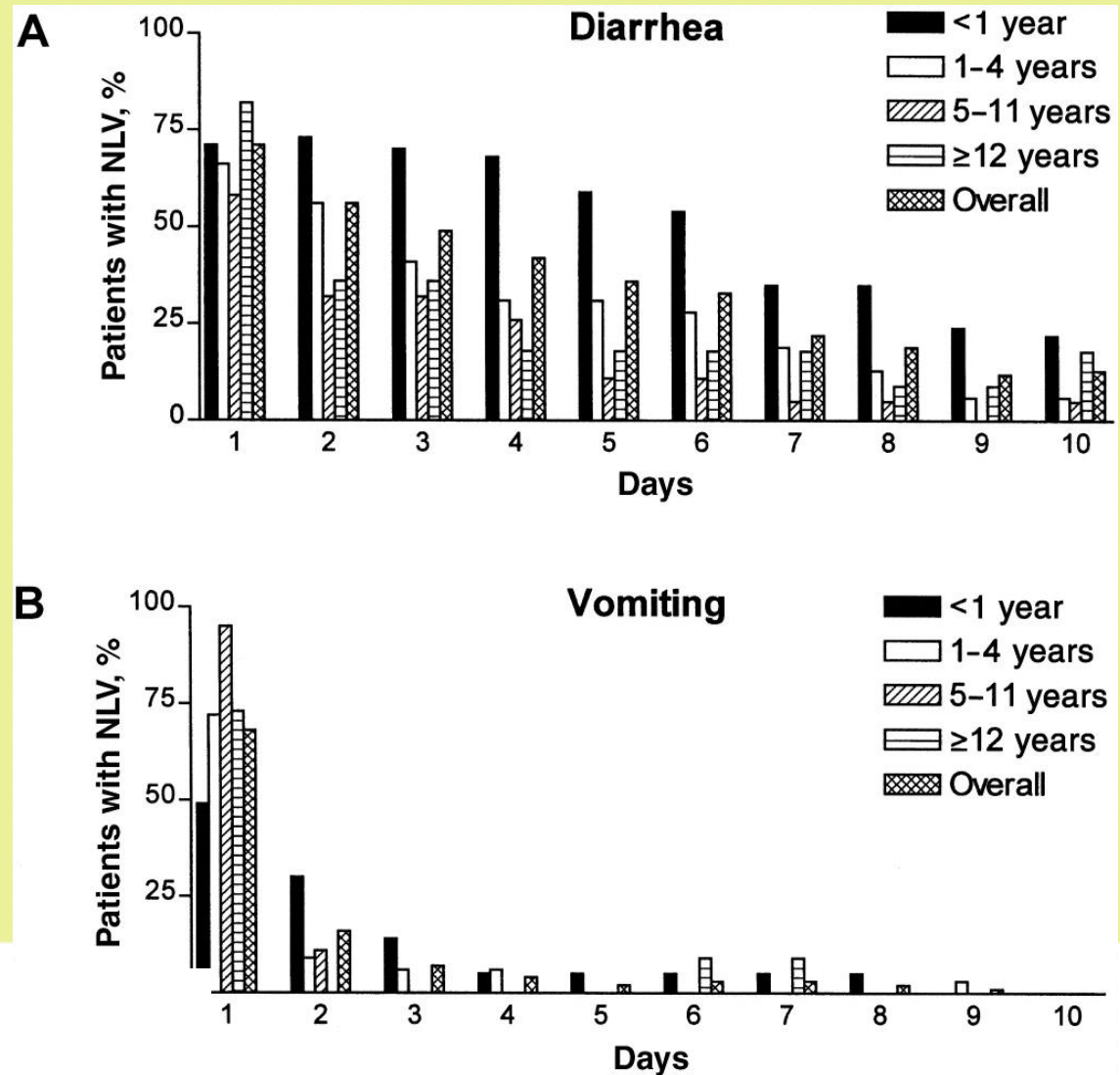


Viruses are the most common cause of community-acquired gastro-enteritis, in people of all age groups



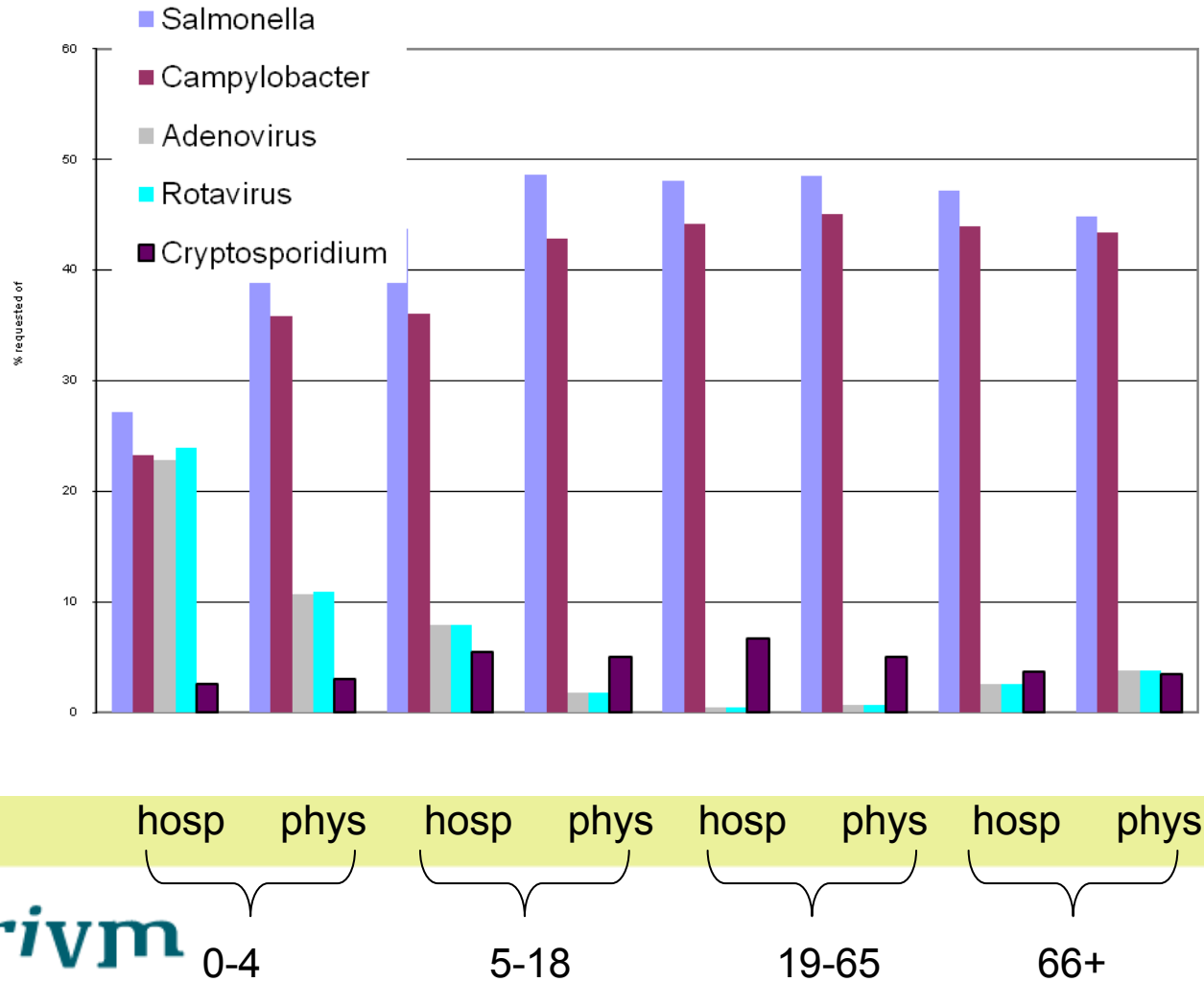
De Wit et al, *Am J Epidemiol* 2001; *EID* 2003
Vinje et al, 1996, 1997; *JID*
Sethi et al., 1999

Average duration of symptoms, community



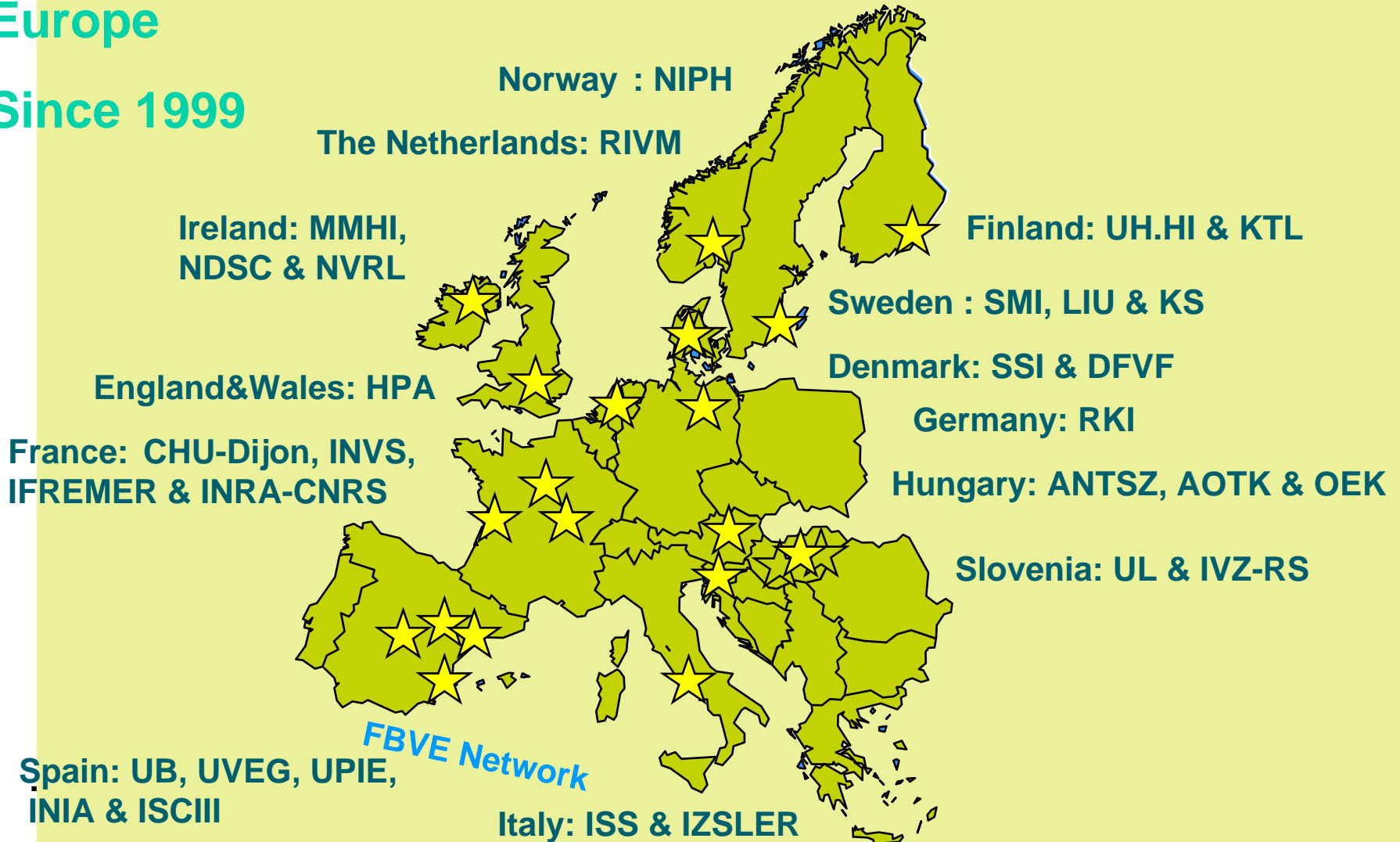
Rockx et al., 2002

The typical diagnostic work-up of a stool specimen in patients with gastro-enteritis: strong bias for bacterial pathogens



Molecular epidemiology network enteric viruses in Europe

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Epidemiological data



Virological data



The screenshot displays two web pages side-by-side. The left page is titled 'Viral Gastroenteritis Outbreak UPDATE Form' and contains several input fields: 'Reporting Institute' (NL-National Institute for Public Health and the Environment), 'Outbreak Number' (EP2002040), 'Reporter's Name' (Yvonne van Duynhoven), and 'Today's date' (14/03/2002). Below these is a 'Transmission' section with a dropdown menu set to 'PERSON TO PERSON' and a text box for 'if "other", specify'. The right page is titled 'Divine and Event FBVE Network' and features a section 'Available sequences databases' with a list of links: 'Norovirus sequences (participants only)', 'Hepatitis A sequences (participants only)', and 'Quick typing of NoV sequences (public)'. A blue double-headed arrow at the bottom of the browser window indicates a connection between the two pages.



Trend Analysis
Signaling unexplained outbreaks



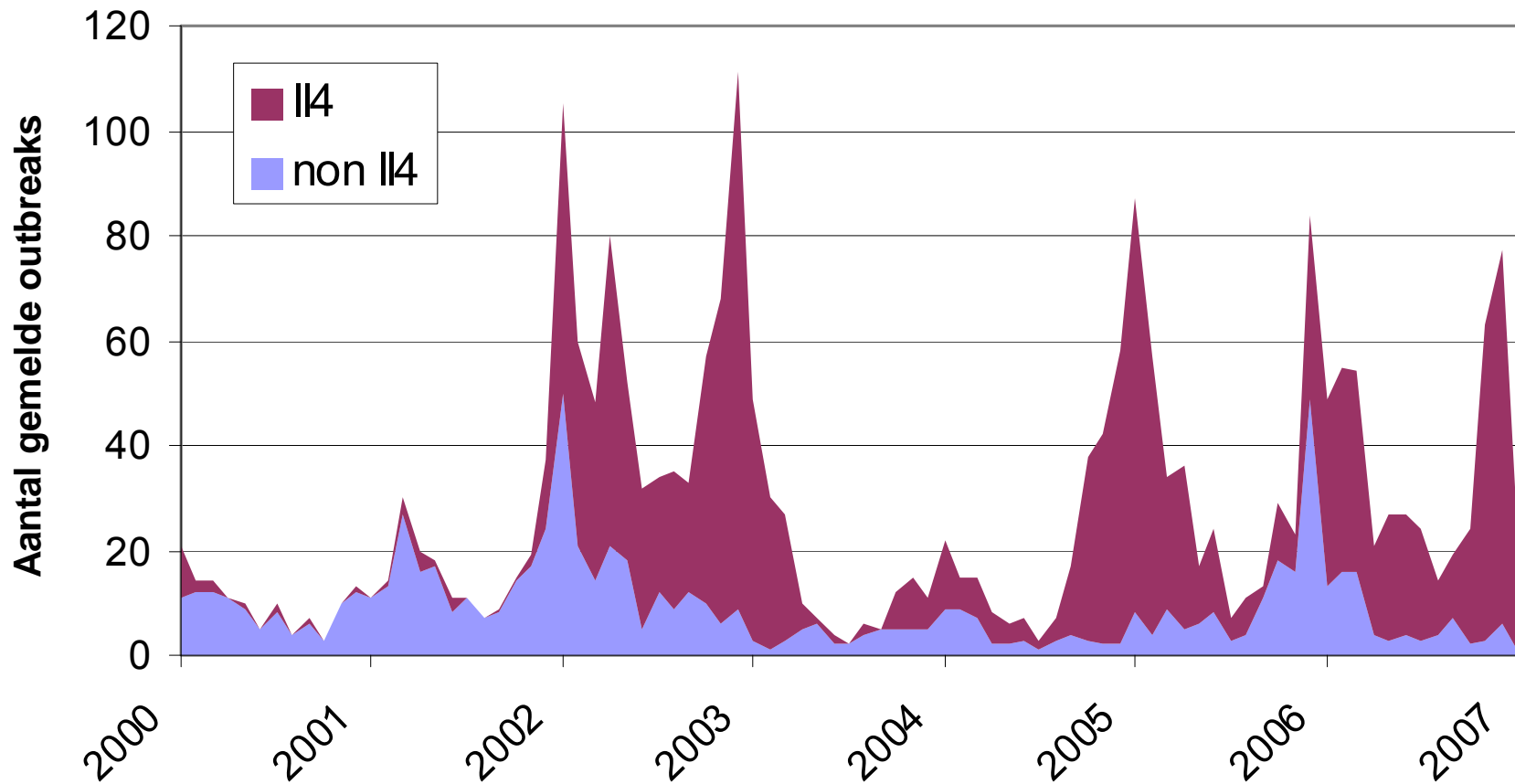
Molecular epidemiology,
evolution, phylodynamics



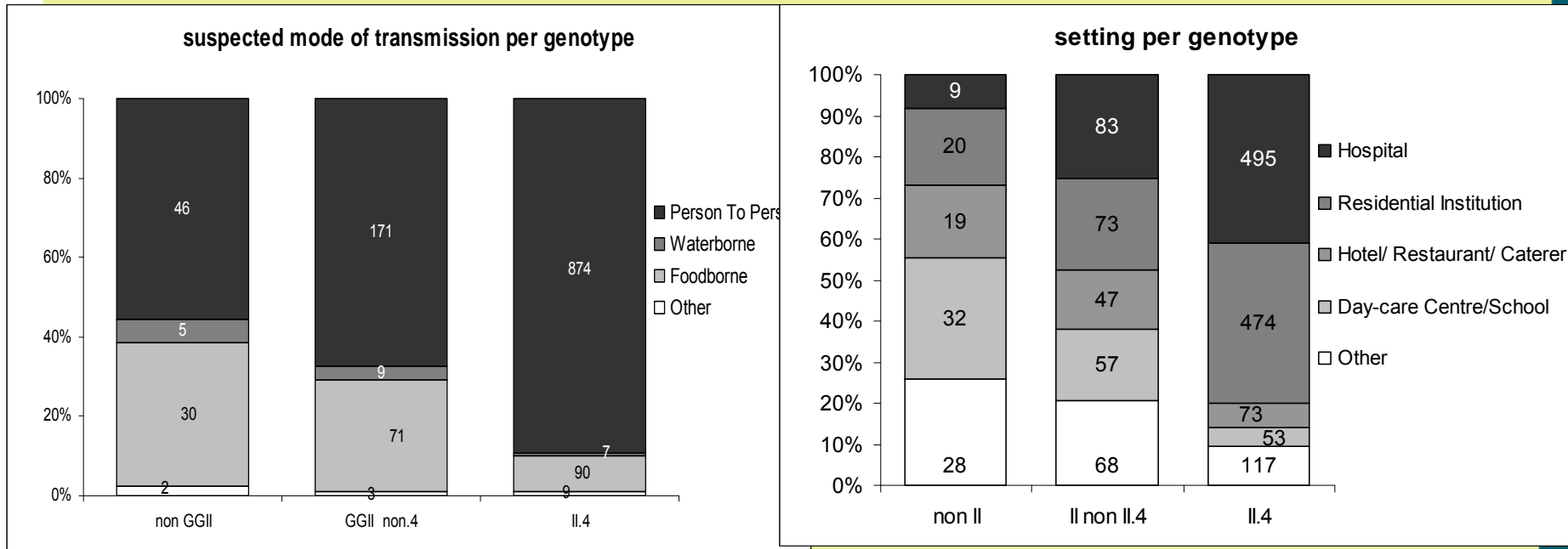
Strain matching
Genotyping

Dominance of GII4 genotype strains since 2002

GII4 greatest fluctuations



Differences in epidemiology of GII4 versus other noroviruses



Multivariate logistic regression, $p < 0.001$

Kroneman et al., 2008

Family *Caliciviridae*

vesivirus

sapovirus

genus

norovirus

genogroup

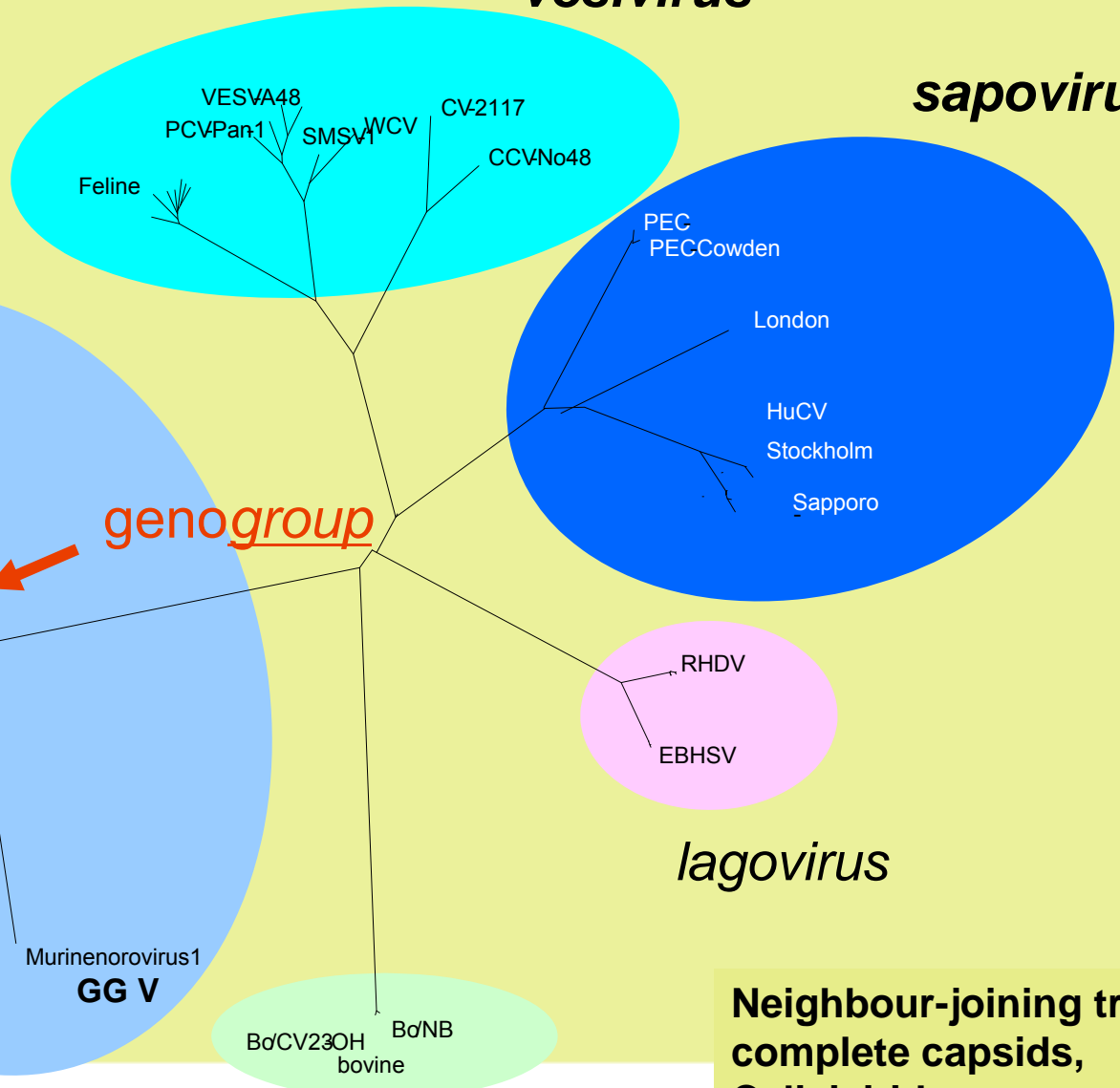
lagovirus

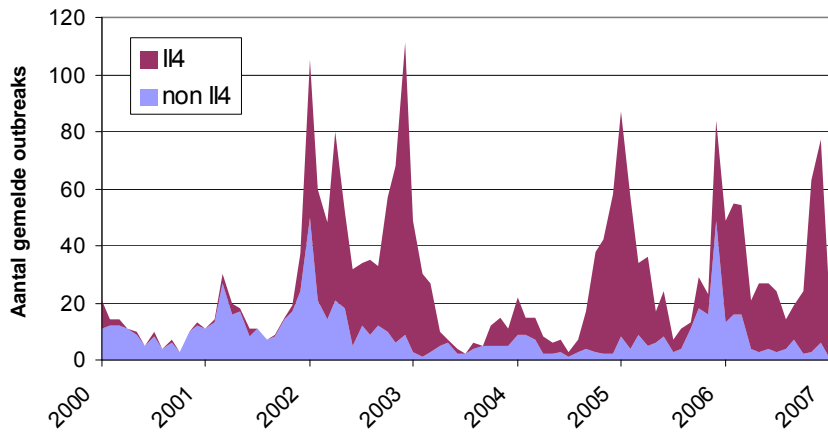
Nebovirus

Neighbour-joining tree,
complete capsids,
Caliciviridea

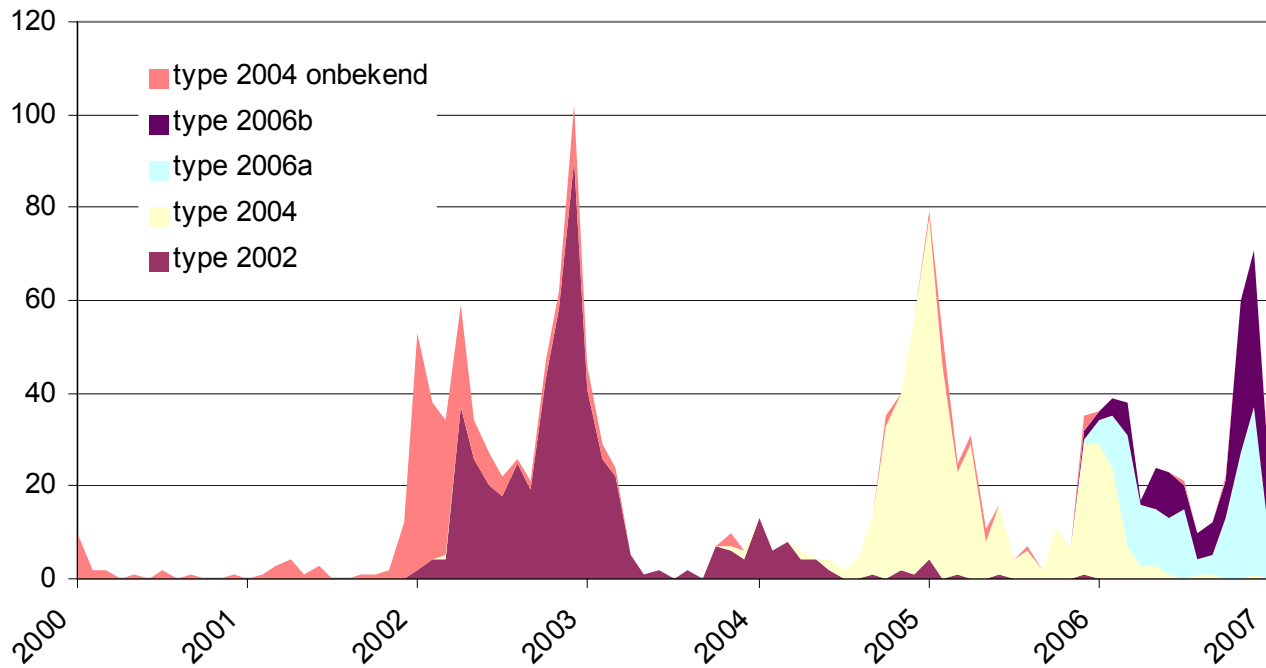
_0.1

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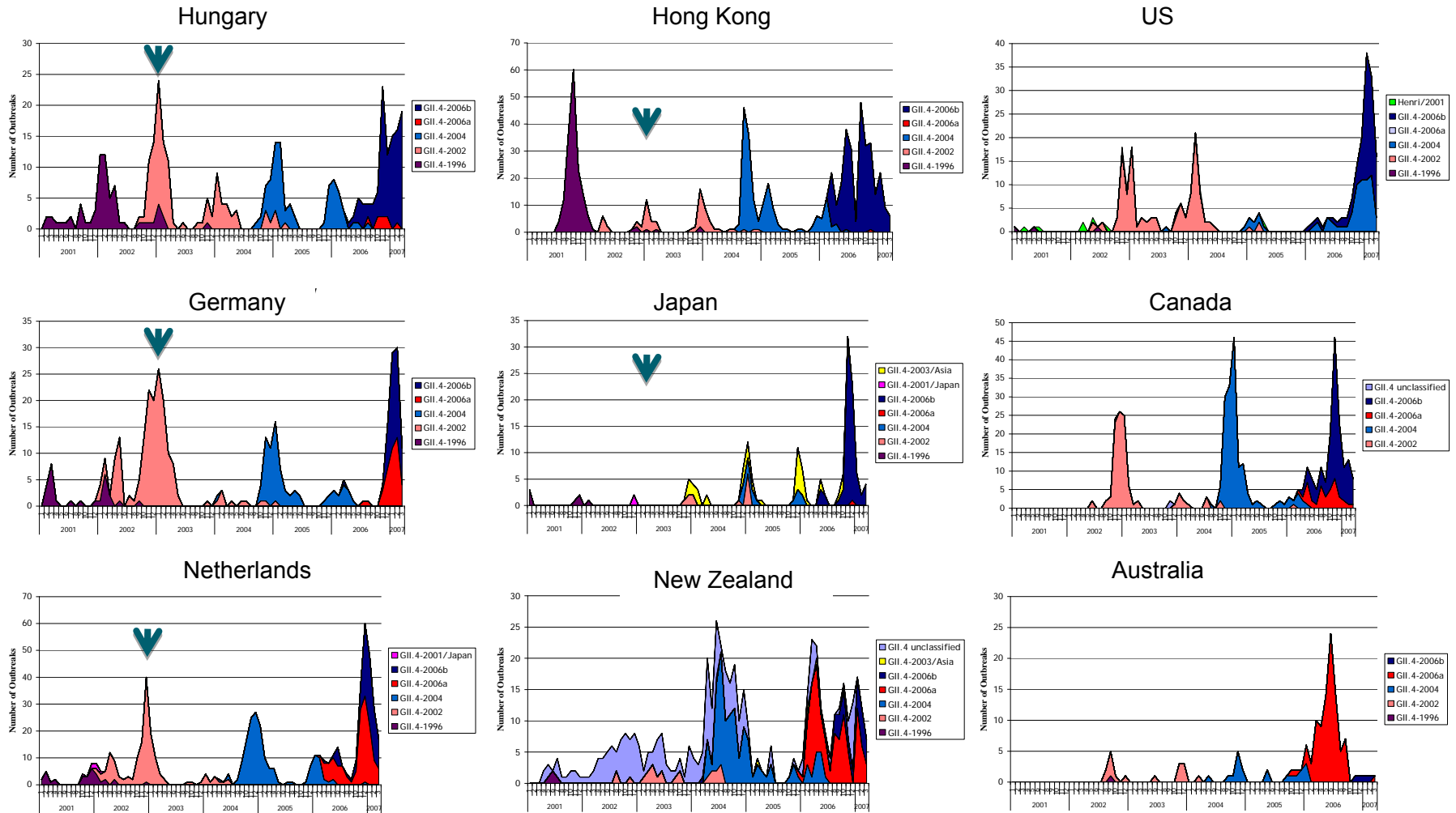




Epidemiology of NoV is shaped by rapid evolution of GI4 strains (similar to influenza A)

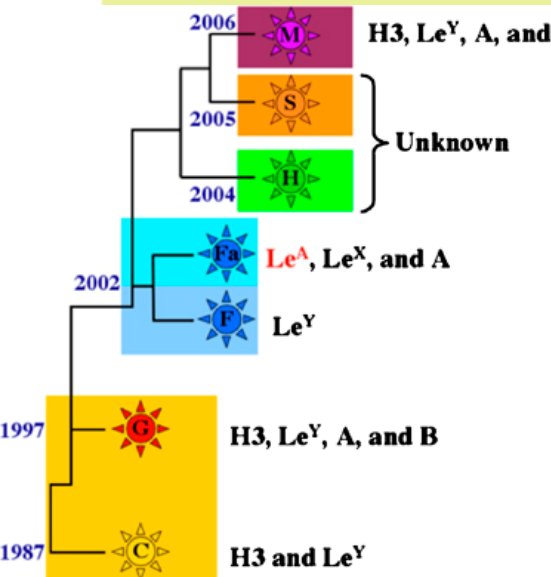
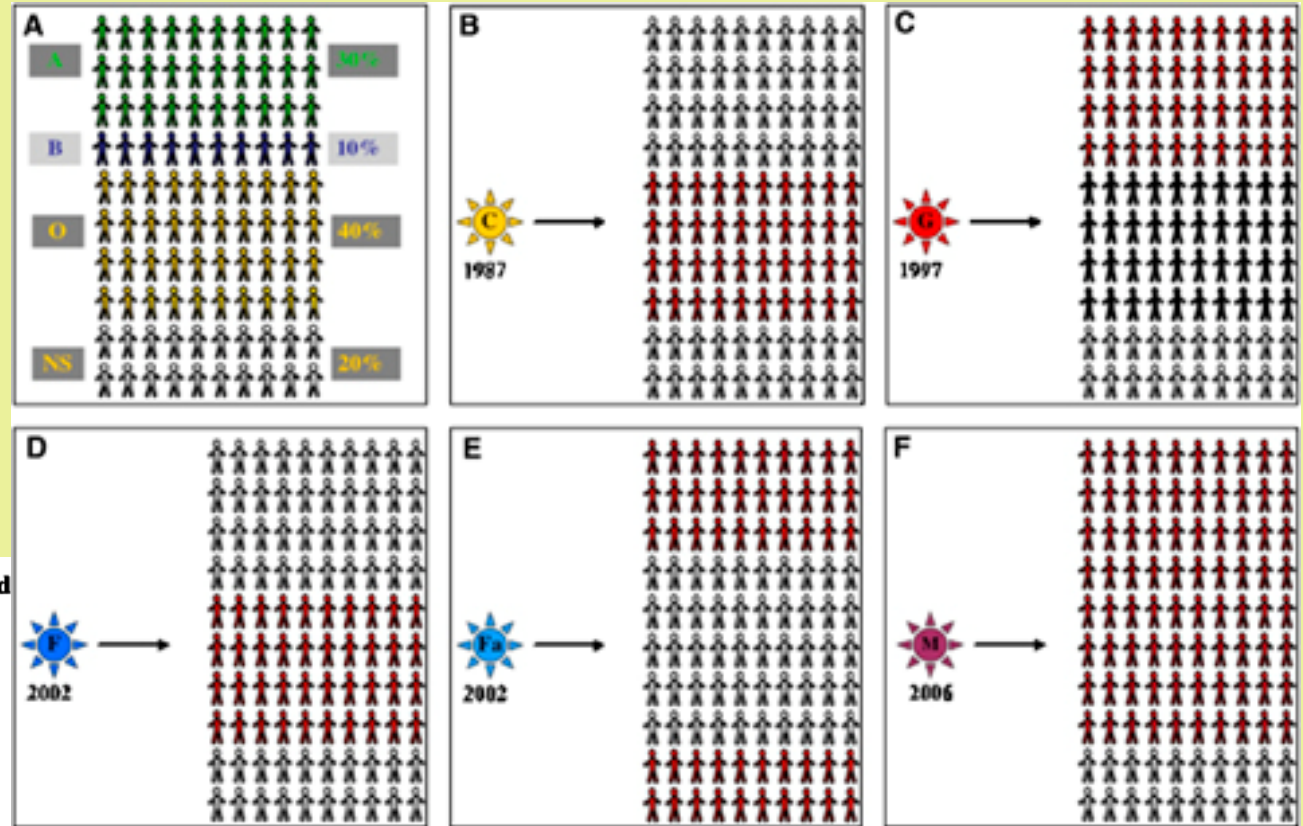


Global picture similar, but some remarkable differences > host susceptibility?



Siebenga et al. submitted
The global norovirus network. Noronet@rivm.nl

Hypothesis: GII4 variants differ in host binding properties and therefore population segment targeted and level of immunity in that group



Severity of illness in risk groups (comorbidities, elderly)

Mattner et al, 2005

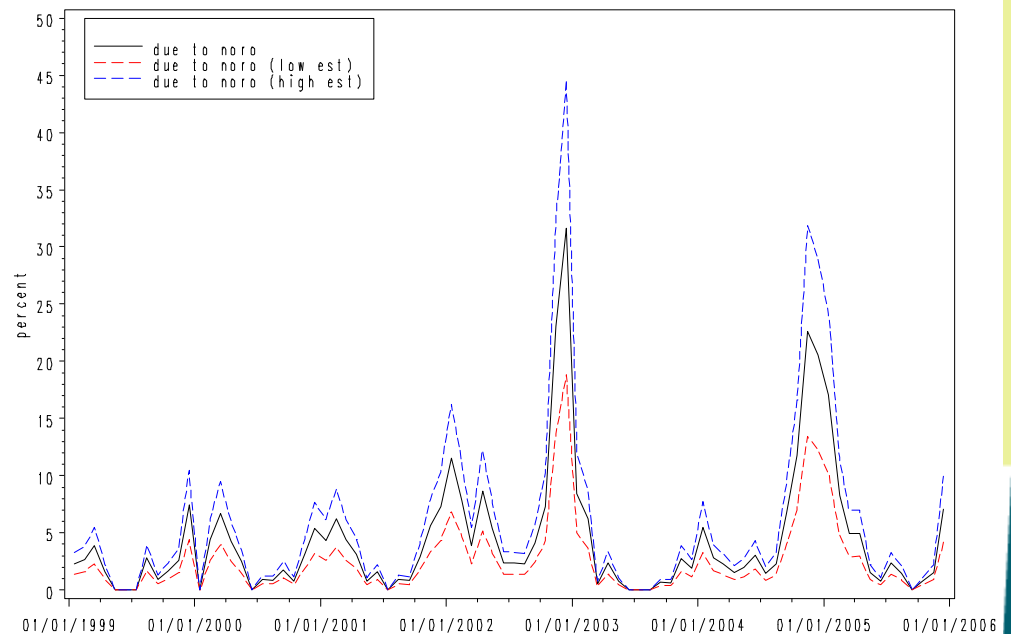
Janssen et al., 2008

Mortality associated with new variants

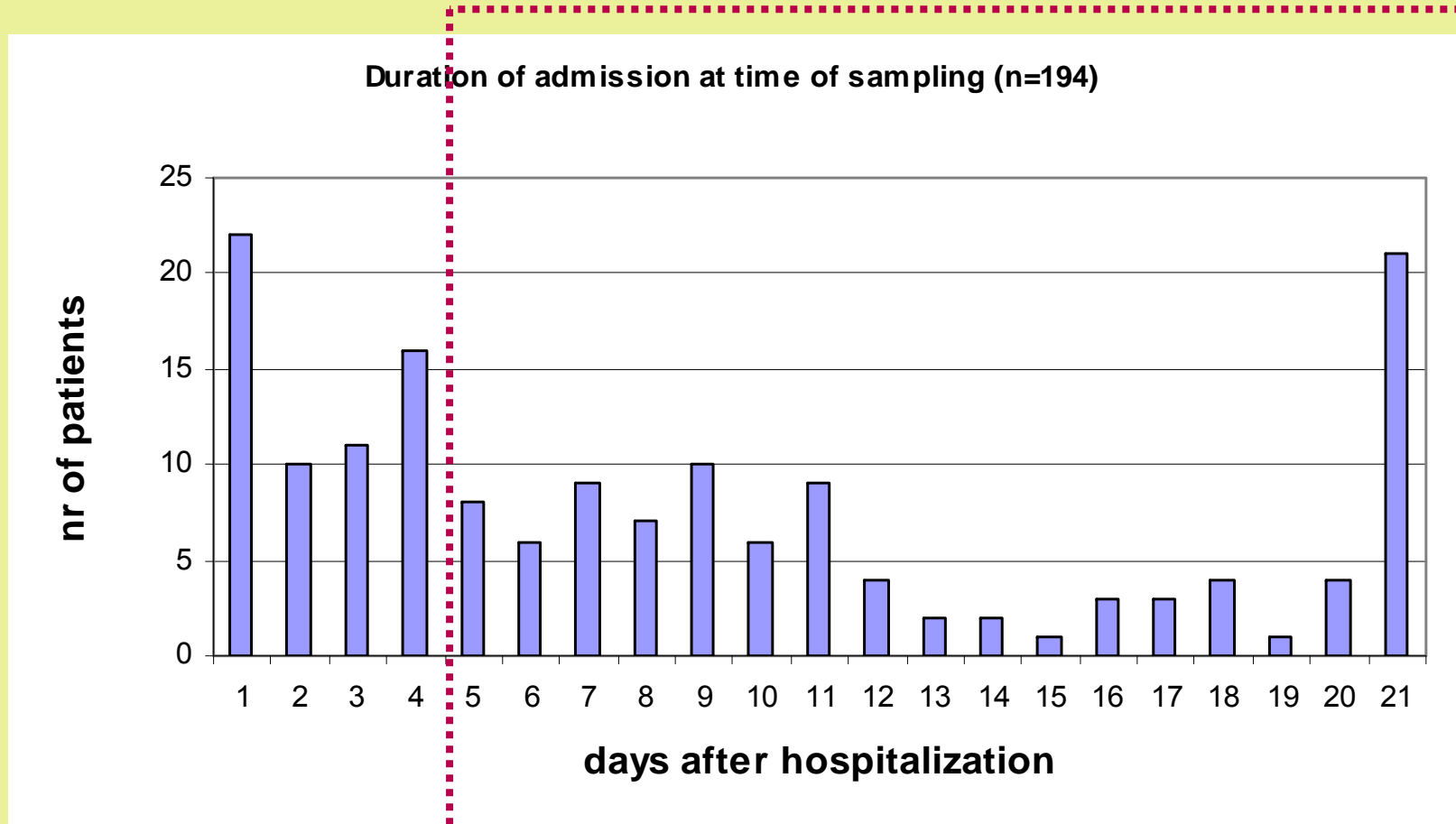
Harris et al., 2008

Van Asten et al., submitted

Estimation of GE deaths attributable to norovirus



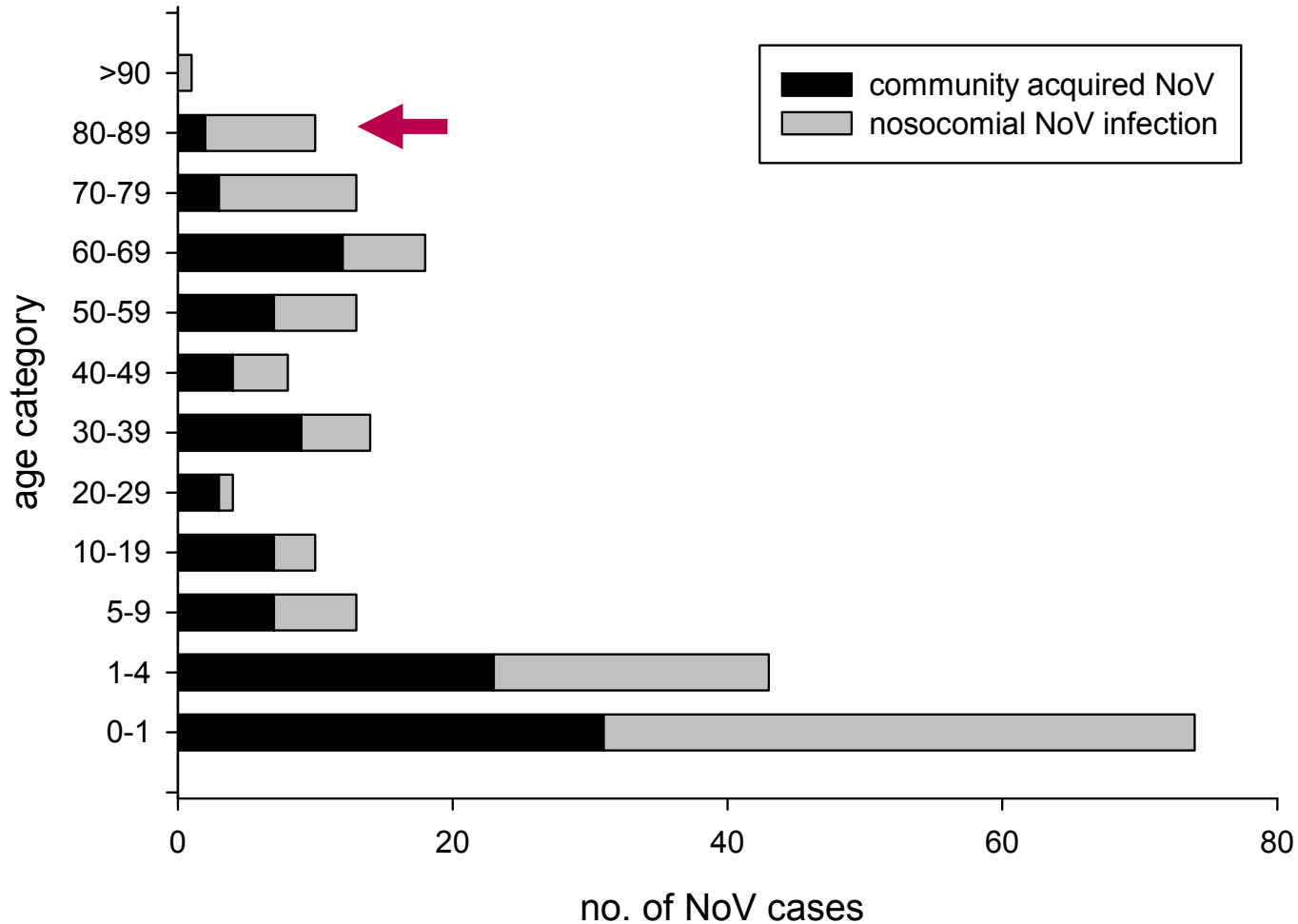
Review of all norovirus positive cases from 2002-7 in an academic hospital



Beersma et al, in press.

**Nosocomial
Transmission, > 60%**

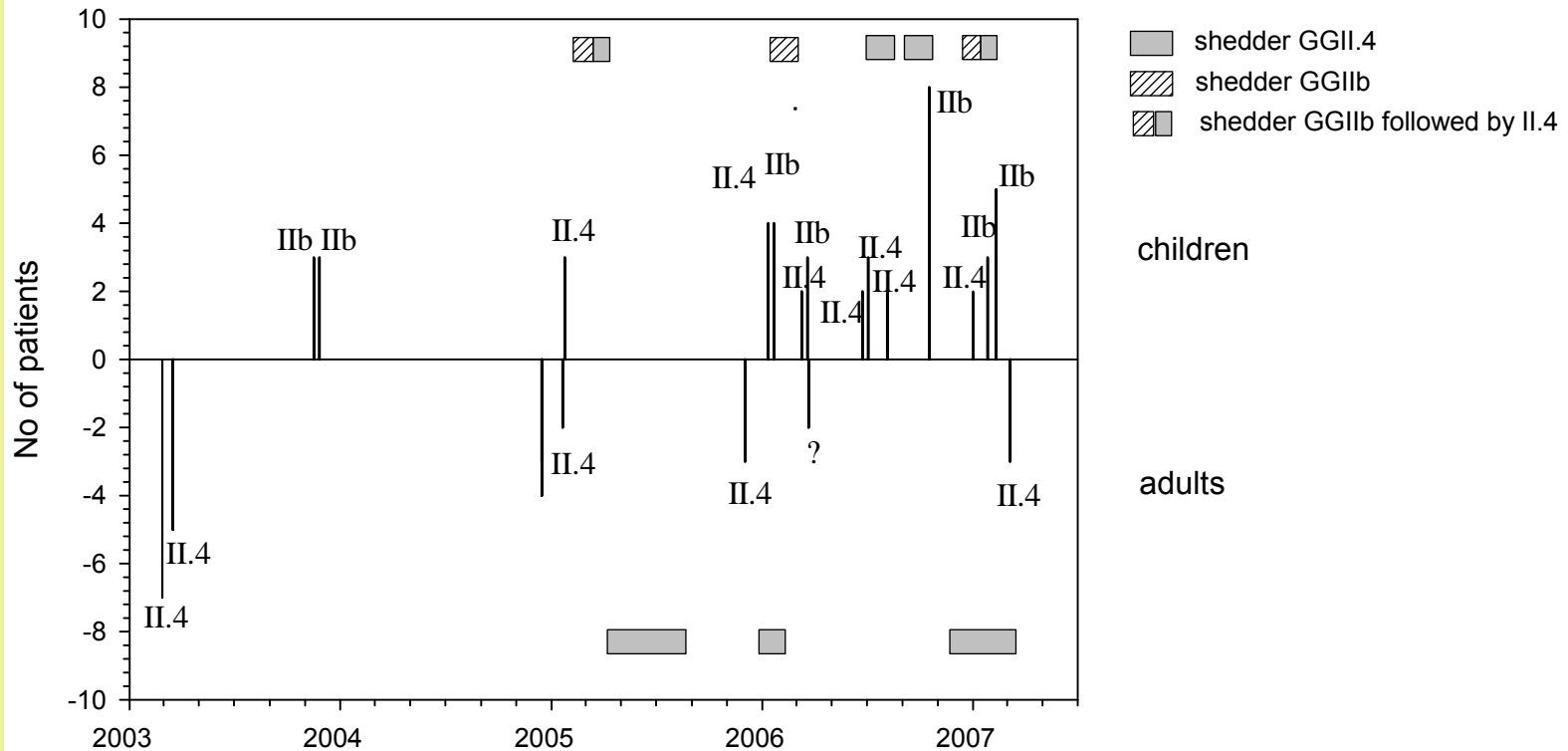
Nosocomial norovirus infections (60% of norovirus diagnoses)



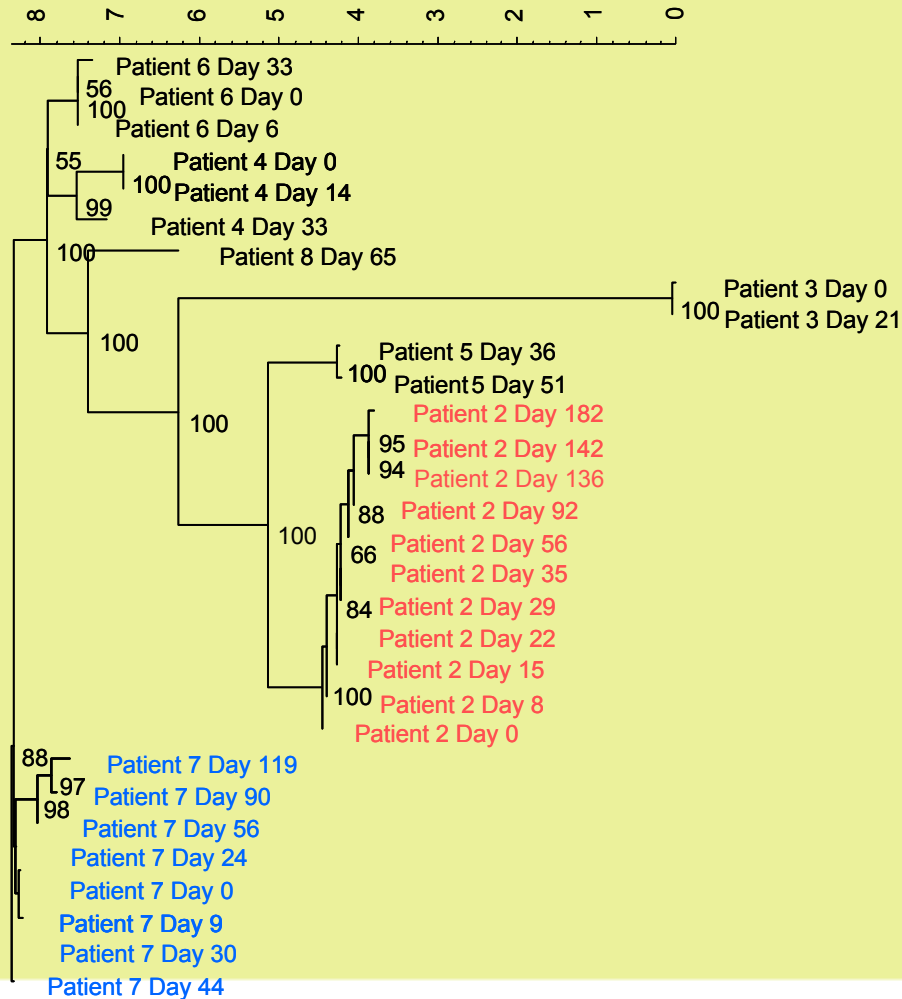
Beersma et al, 2008

Clusters of norovirus identified through record linking And chronic shedders (6% of all tested, 22% of patients with follow-up)

Figure 6



Use of molecular typing for studying hospital epidemiology



- Accumulation of mutations:

- patient 2 in 182 days: 6 aa
- patient 7 in 119 days: 13 aa

- Very high non-syn / syn mutation ratio's

Full capsids, aa sequences, NJ, bootstraps 1000 iterations

Systematic evaluation of control protocols

- 75 wards, 31 outbreaks

Table: average and range at ward level

	Total	Start protocol ≤ 3 days	Start protocol > 3 dagen
Duration outbreak (days)	16 3-53	16 3-53	19 6-50
Attack rate patients	35% 0-87	36% 0-77	39% 13-87
Attack rate staff	22% 0-95	20% 0-95	33% 15-67

- Fast introduction of control may reduce spread

Control measures with effect (nursing home)

Variables:		mean duration in days (25, 75 percentiles)
Cohorting of symptomatic residents		
	no	17.2 (7.0, 29.0)
	yes	10.0 (8.0, 13.0)
Suspending of group activities		
	no	10.5 (7.0, 11.0)
	yes	18.4 (7.0, 32.0)
Disinfection with chlorine		
	no	8.9 (5.5, 11.5)
	250 ppm	9.3 (7.0, 13.0)
	1000 ppm	21.0 (8.0, 33.0)
Size of ward		
	? 20 residents	18.3 (8.0, 31.0)
	21-30 residents	20.5 (7.5, 36.0)
	? 31 residents	11.3 (5.0, 13.0)

No clear effect hand washing residents, room quarantine, masks, enhanced toilet cleaning, no visits

Conclusions

Medical community needs to be educated about risks of norovirus

Need for better understanding of sources of infection

Evidence based infection control

Vaccination?