

ROTAVIRUS: LA MALATTIA CLINICA E L'EPIDEMIOLOGIA



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Lavoro e Formazione

gratifica

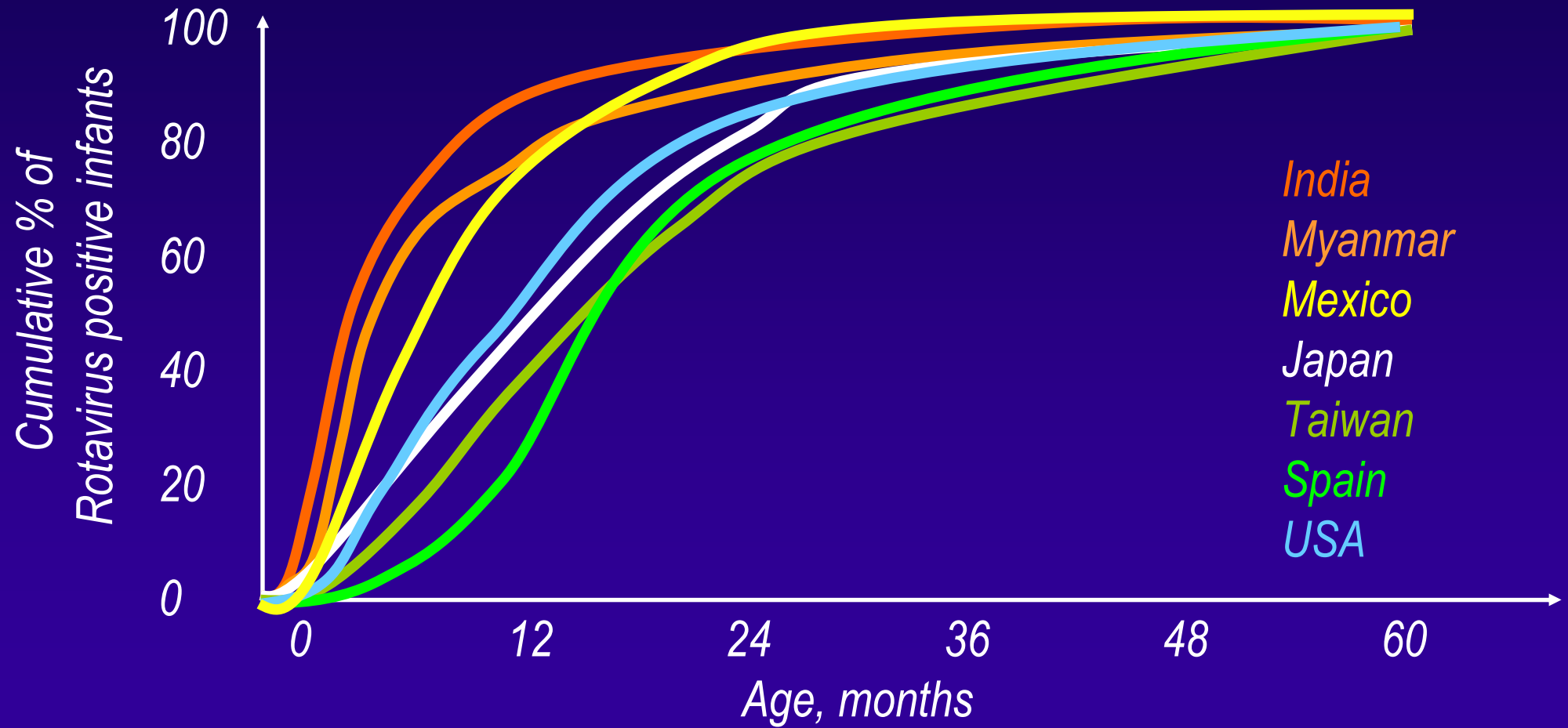
RETE VACCINI
Genova

THE FACE OF ROTAVIRUS

- *Diarrhea*
- *Vomiting*
- *Dehydration*
- *Shock*
- *Death*



A "DEMOCRATIC" VIRUS



A MORE AND MORE DEMOCRATIC VIRUS

...slower rate of decrease in hospitalizations for RV compared with other causes of severe childhood diarrhea. (Parashar et al., *Emerg Infect Dis* 2006)

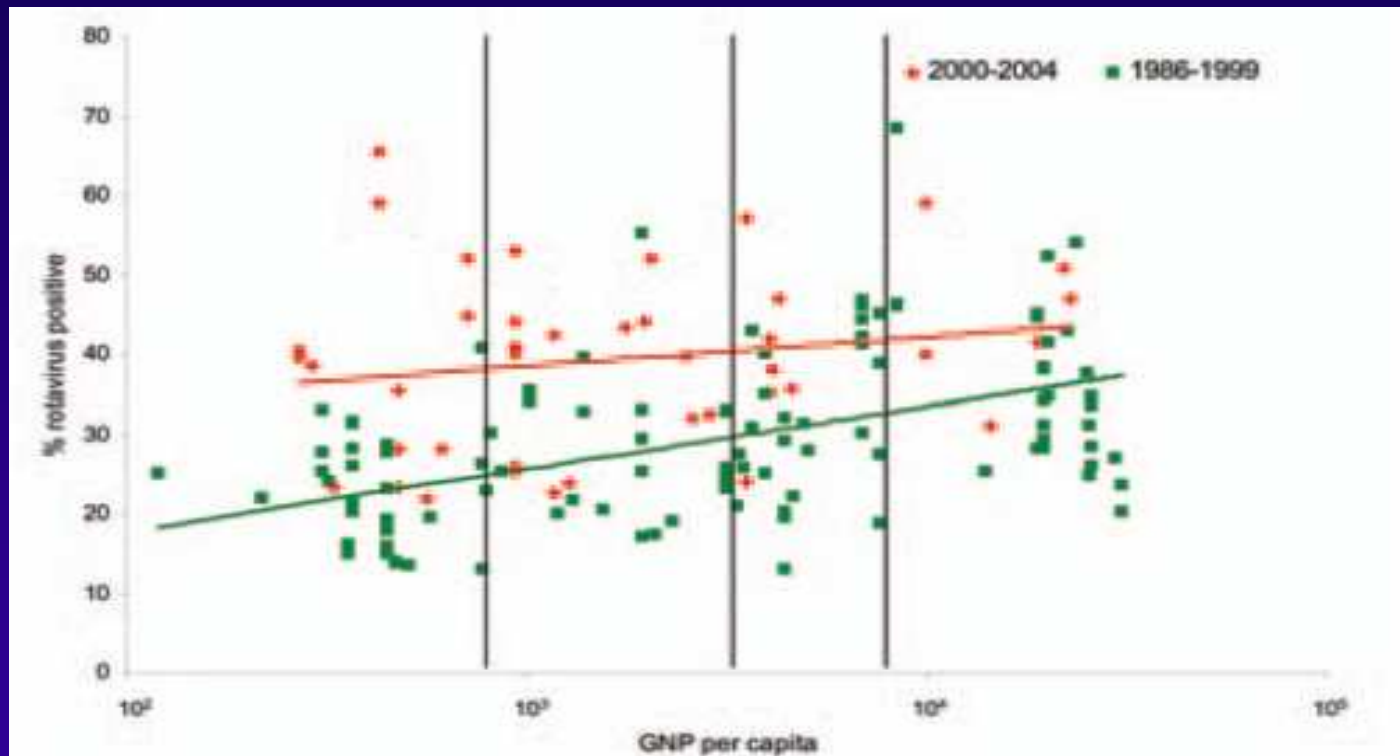


Figure 1. Percentage of severe diarrhea cases attributable to rotavirus for countries in different World Bank income groups, by per capita gross national product (GNP), for studies published in 1986–1999 and 2000–2004. GNP is in US dollars. Upper line, trend for 2000–2004; lower line, trend for 1986–1999.

WHY SO DEMOCRATIC VIRUS

■ *Rotavirus (RV) is highly infectious*

- *Infectious dose low: 10 PFU/ml*
- *Shedding $\geq 10^{10}$ particles/g feces (PFU/ml)*
- *Duration of shedding ~8-10 days, sometimes extended in severe primary RV infection*

■ *Highly resistant, it can survive for weeks*

in contaminated water, on human hands, in hard surfaces

■ *Main route of Transmission : fecal-oral route, but other modes of transmission:*

- *through respiratory secretions*
- *person-to-person contact, especially hands*
- *contaminated environmental surfaces*

Kapikian AZ et al. In: Virology in Fields, 2001

Kapikian AZ et al. Dev Biol Stand 1983

Ward RL et al. J Infect Dis 1986

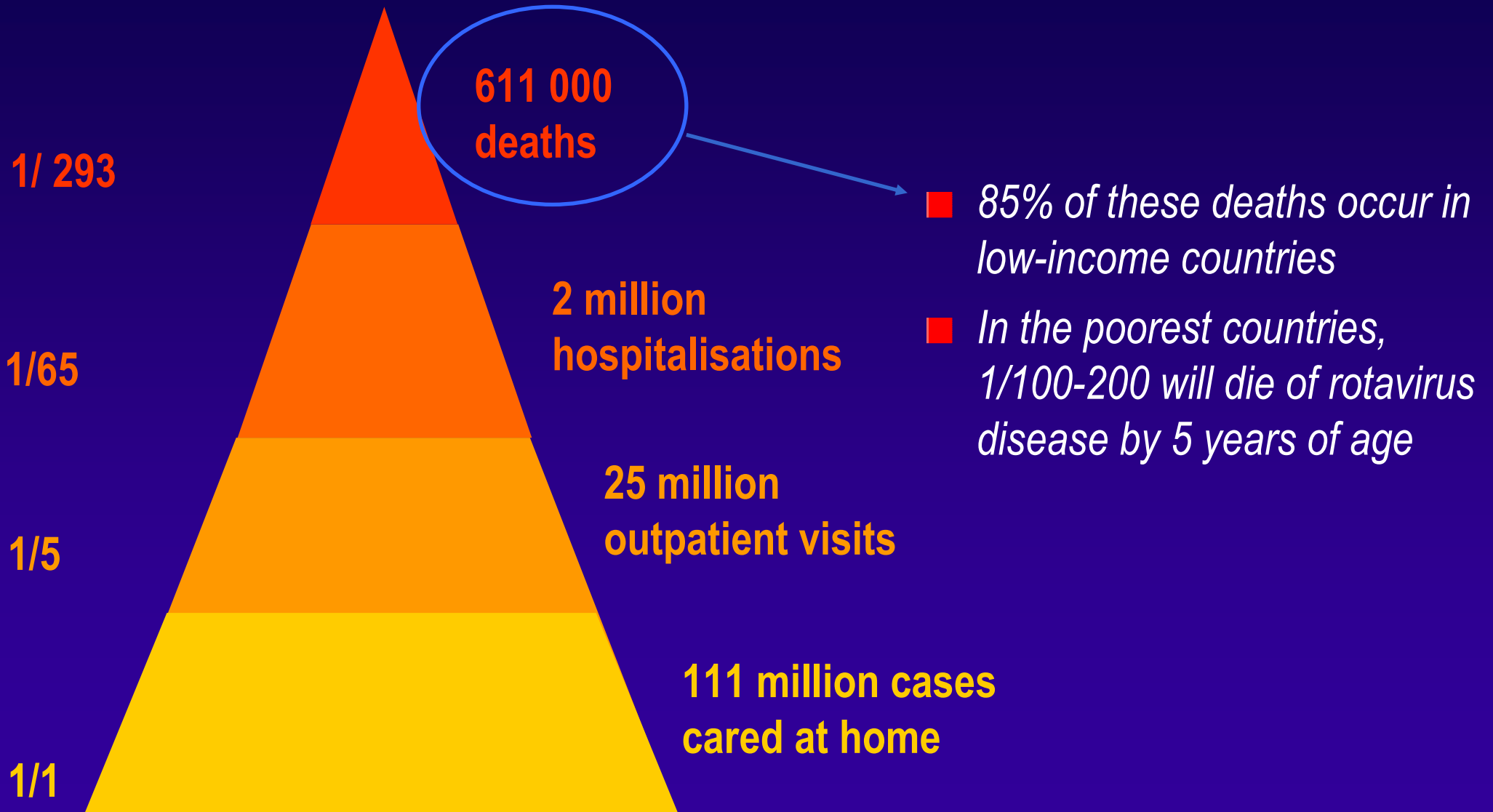
Bishop RF. Arch Virol 1996

Richardson S et al. Lancet 1998

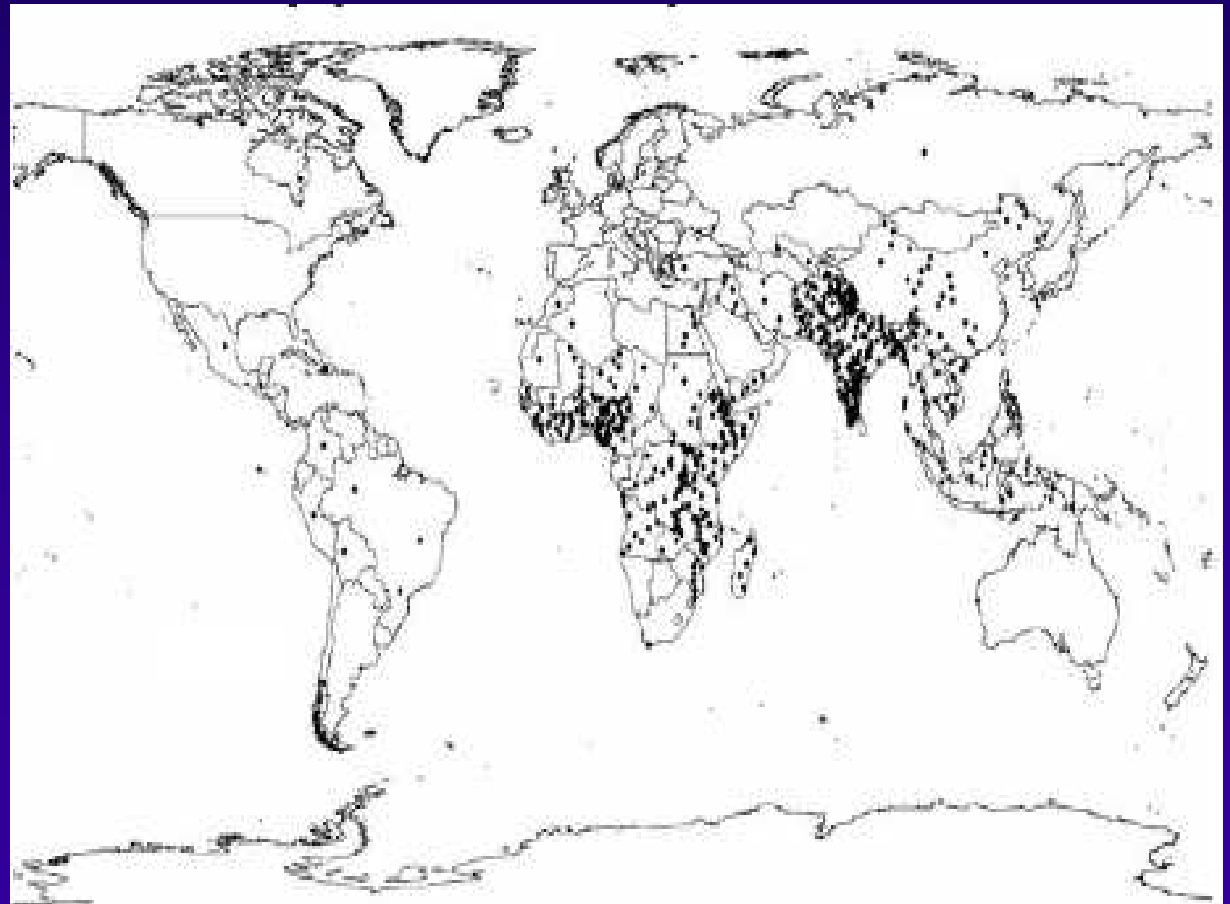
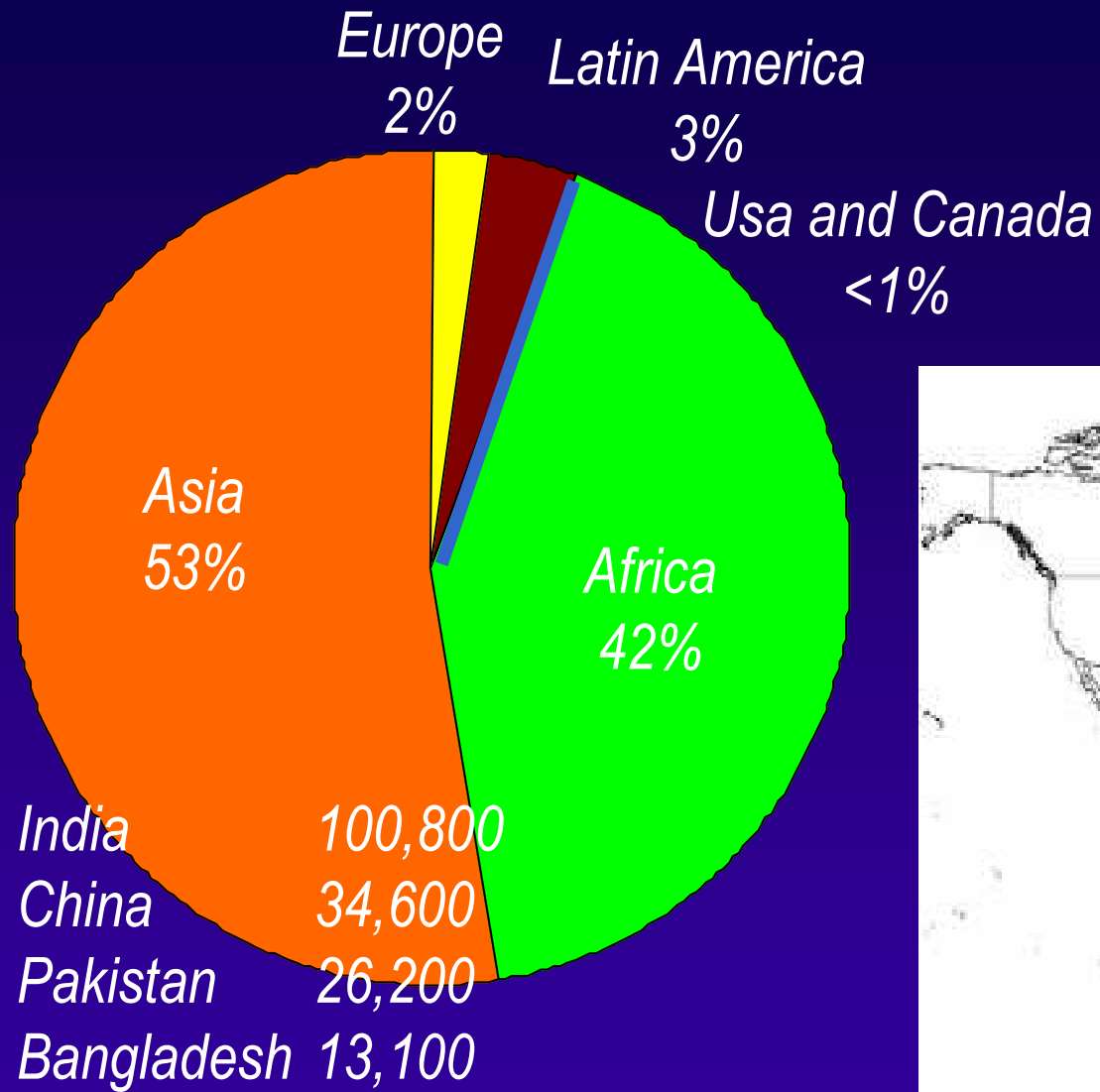
Ansari SA. Review of Infectious Diseases 1991

WORLDWIDE IMPACT OF ROTAVIRUS DISEASE IN CHILDREN <5 YRS

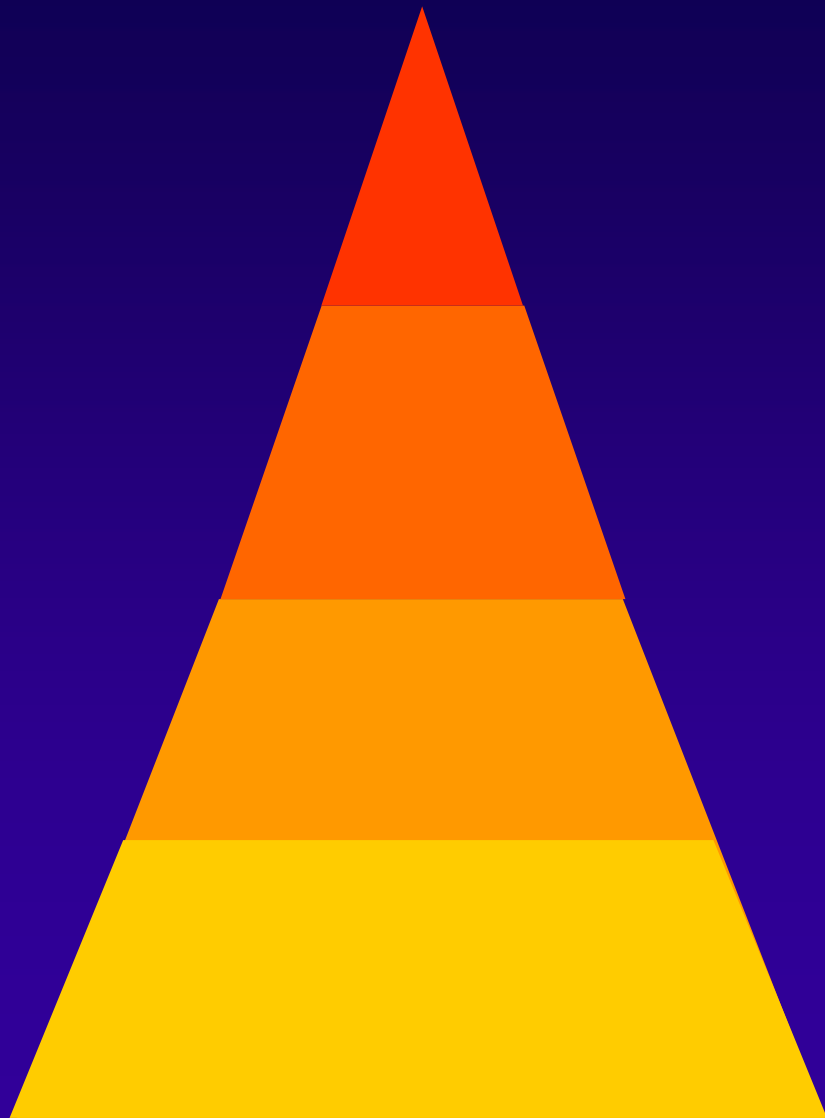
Parashar UD et al. *Emerg Infect Dis* 2003 and 2006
Breese JS et al., *Paed Infect Dis* 2005



DISTRIBUTION OF ROTAVIRUS ASSOCIATED DEATHS BY REGION, 2005



IMPACT OF ROTAVIRUS DISEASE IN CHILDREN <5 YRS, INDUSTRIALIZED COUNTRIES



	<u>Risk</u>		<u>Absolute Burden</u>
	<u>Industrialized</u>	<u>Developing</u>	<u>Industrialized</u>
	1/1,200-48,000	1/293-542	About 10,000 deaths
	1/23-74	1/500	223,000 hospitalisations
	1/4	1/35	1.8 million outpatient visits
	1/1	1/1	7 million cases

IMPACT OF ROTAVIRUS DISEASE IN CHILDREN <5 YRS, INDUSTRIALIZED COUNTRIES

IMPACT OF ROTAVIRUS DISEASE IN CHILDREN <5 YRS, EUROPE

<i>Country</i>	<i>Episodes cared at home</i>	<i>Outpatient visits</i>	<i>Hospitalization</i>	<i>Deaths</i>
<i>Austria</i>	<i>44,890</i>	<i>11,220</i>	<i>1400</i>	<i>1</i>
<i>France</i>	<i>455,900</i>	<i>113,980</i>	<i>14,250</i>	<i>14</i>
<i>Germany</i>	<i>434,340</i>	<i>108,580</i>	<i>13,570</i>	<i>13</i>
<i>Italy</i>	<i>321,700</i>	<i>80,430</i>	<i>10,050</i>	<i>11</i>
<i>U.K.</i>	<i>409,170</i>	<i>102,290</i>	<i>12,790</i>	<i>14</i>
<i>25 European Countries</i>	<i>2,794,000</i>	<i>698,500</i>	<i>87,310</i>	<i>231</i>

THE BURDEN OF NOSOCOMIAL ROTAVIRUS INFECTIONS IN EUROPE

(Berner R et al., 1999; Frühwirth M et al., 2001; Maille L et al., 2000; Piednoir E et al., 2003; Thuret A et al., 2004; Chandran et al., 2006)

... is one of the most important causes of nosocomial infections in childhood

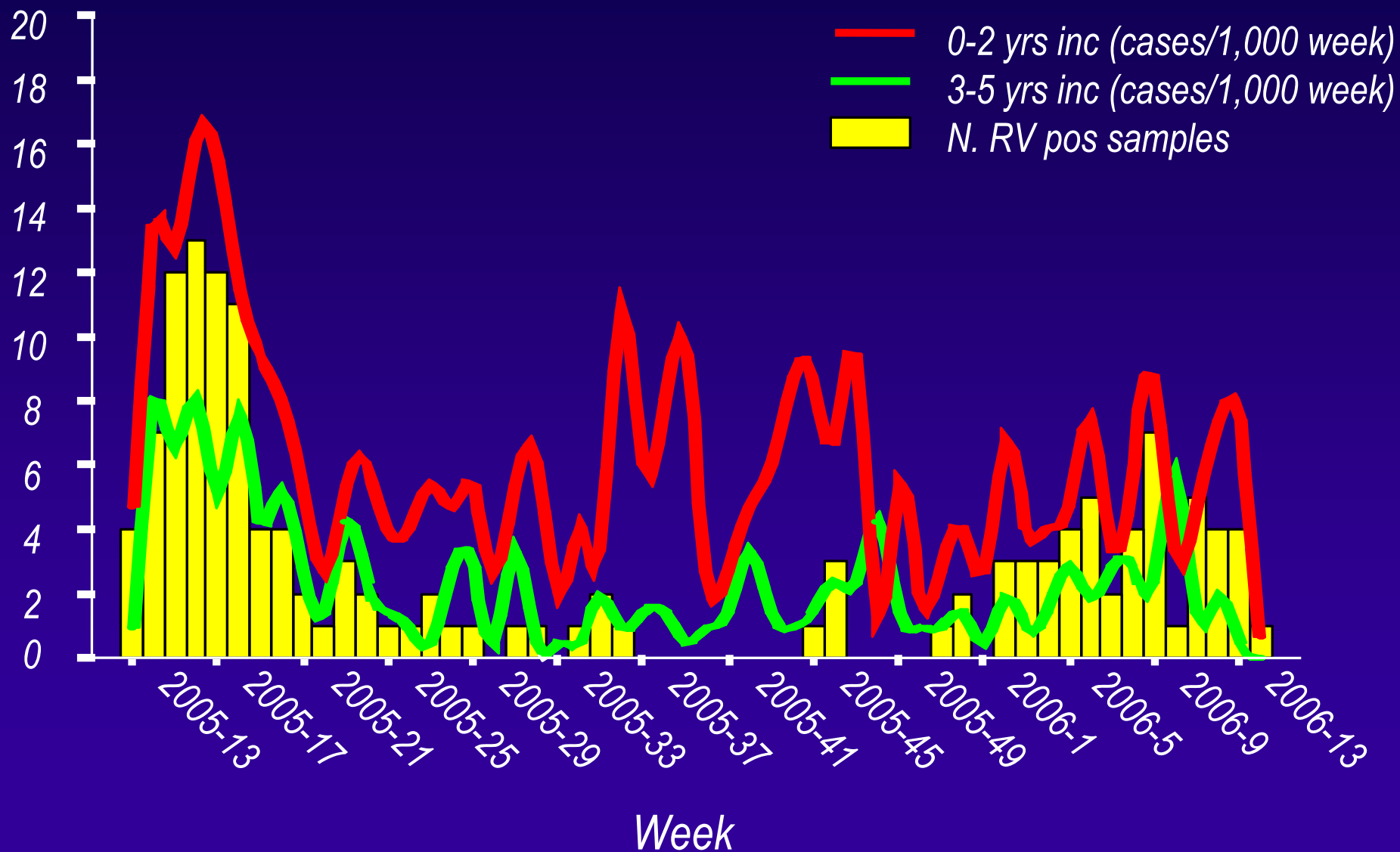
- *High incidence (NRV infections/admission)*
 - *In Pediatrics ward 5.8-27.7% (Italy, Germany, Poland, Brazil)*
 - *25-50% of children in hospital with rotavirus acquired it as a nosocomial infection*
 - *Re-admission is required in 27% of cases*

- *High impact and costs*
 - *Rotavirus nosocomial infection increases length of hospital stay to around 10 days*
 - *Average cost per case: 1930 € in France*
2442 € in Austria
 - *Estimated cost per year: 6.2 M€ in Austria*

SENTINEL-BASED NETWORK FOR CLINICAL-EPIDEMIOLOGICAL AND VIROLOGICAL SURVEILLANCE OF RV

- *10 paediatricians who surveyed 8675 children living in Leghorn, Italy (0-2 yrs:1488;3-5yrs:2123;6-10yrs:2979; 11-14yrs:2085) this sample corresponds to 24% of the entire 0-5 year district population.*
- *They reported on a weekly basis the number of new cases of gastroenteritis, defined as the occurrence of three or more watery stools in a period of 24 hours (Velazquet et al., 1996)*
- *Stool samples were collected from every child aged 0-5 yrs(n.=3611) with gastroenteritis and were tested for rotavirus using a real-time PCR*
- *Positive samples were P- and G-genotyped using a primer-specific semi-nested multiplex PCR; molecular characterization of G9 strains was performed by sequence analysis of VP7 and VP4 genes (Ituriza et al., 2004)*

GE INCIDENCE AMONG 0-5 CHILDREN FROM LENGHORN



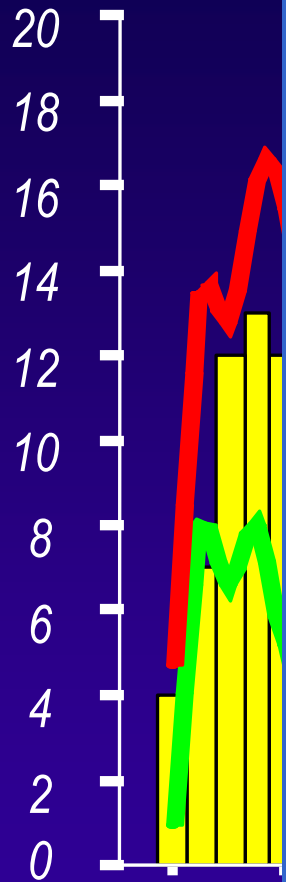
GE INCIDENCE AMONG 0-5 CHILDREN FROM LENGHORN

0-2 yrs cumulative incidence: 32.9%

3-5 yrs cumulative incidence: 12.6%

es/1,000 week)

es/1,000 week)

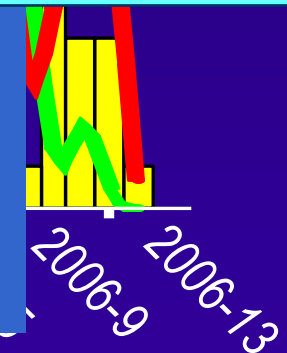


	0-4 yrs ILI cumulative inc.
2003/04	13.6%
2004/05	19.5%
2005/06	10.4%

757 GE episodes

595 (79%) analyzed samples

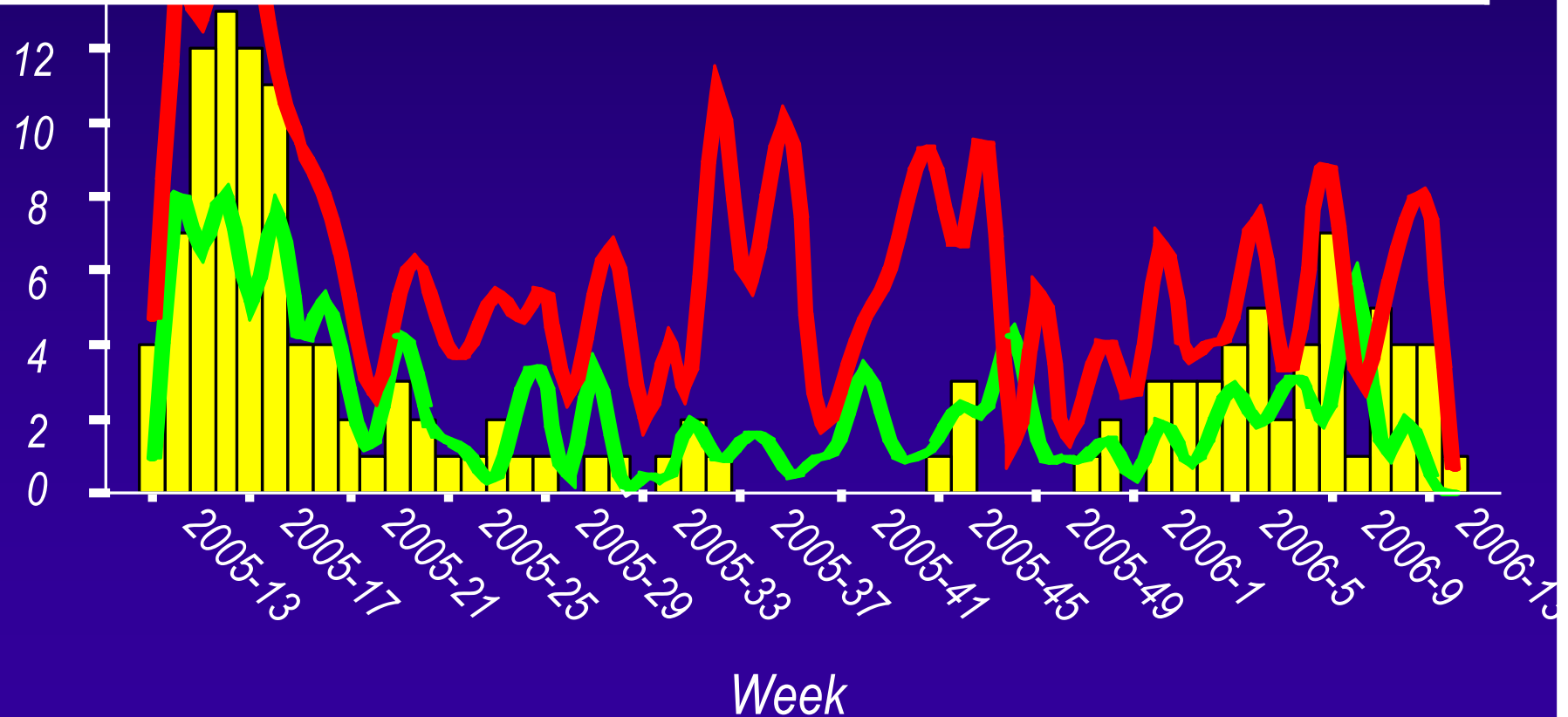
234 out of 595 (34.1%) real-time pos for RV



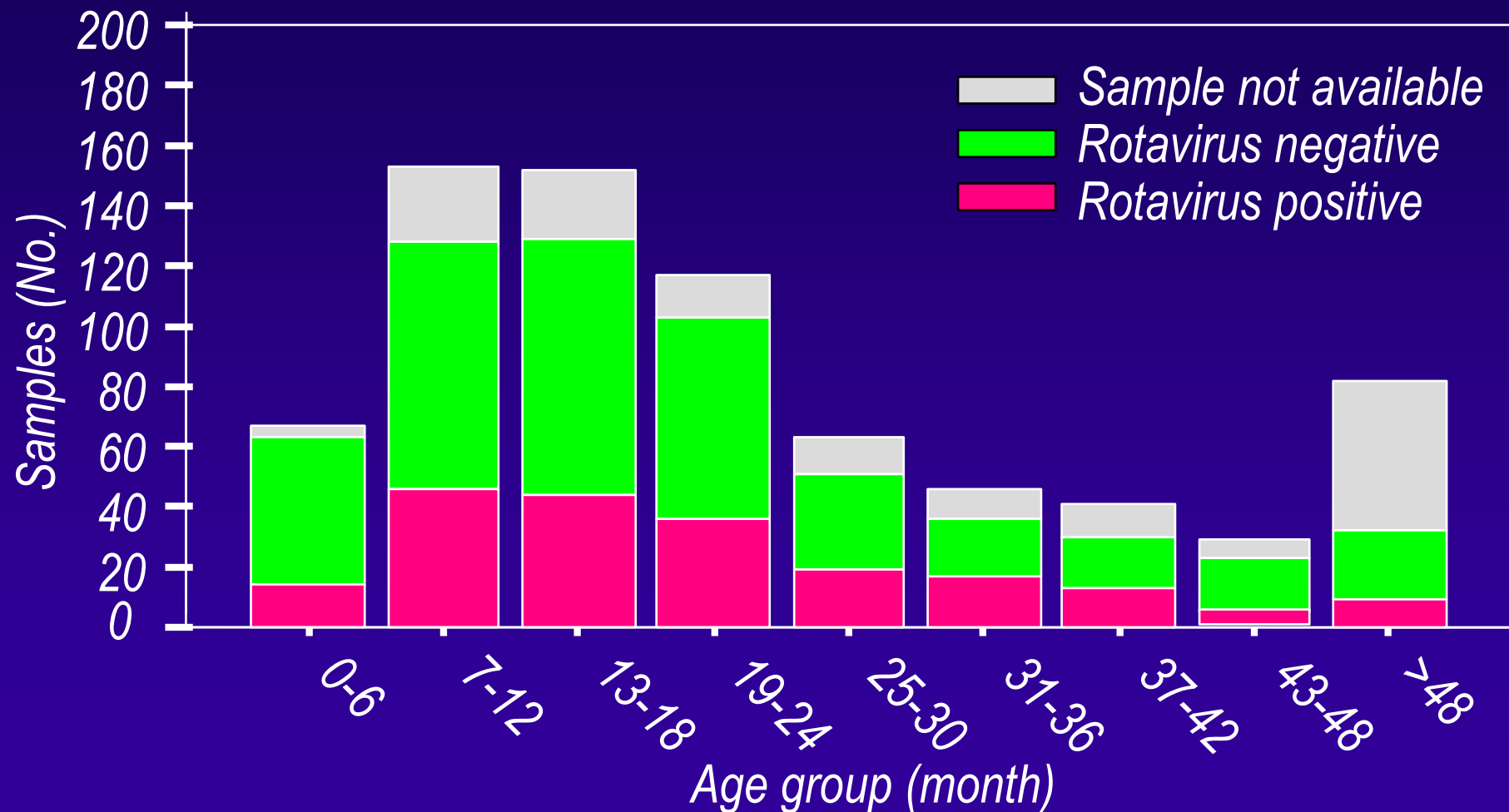
Week

GE INCIDENCE AMONG 0-5 CHILDREN FROM LENGHORN

Incidence	High	Intermediate	Intermediate
RV circulation	High	Low	Intermediate
Pos sample/week	12.2	0.81	4.8
0-2 yrs RV pos	50.7%	10.1%	51.1%
3-5 yrs RV pos	60.3%	14.3%	42.9%



AGE DISTRIBUTION FOR SUBJECTS WITH ROTAVIRUS AND NON-ROTAVIRUS GASTROENTERITIS



LENGHORN COHORT: CLINICAL PRESENTATION OF ROTAVIRUS AND NON-ROTAVIRUS GASTROENTERITIS

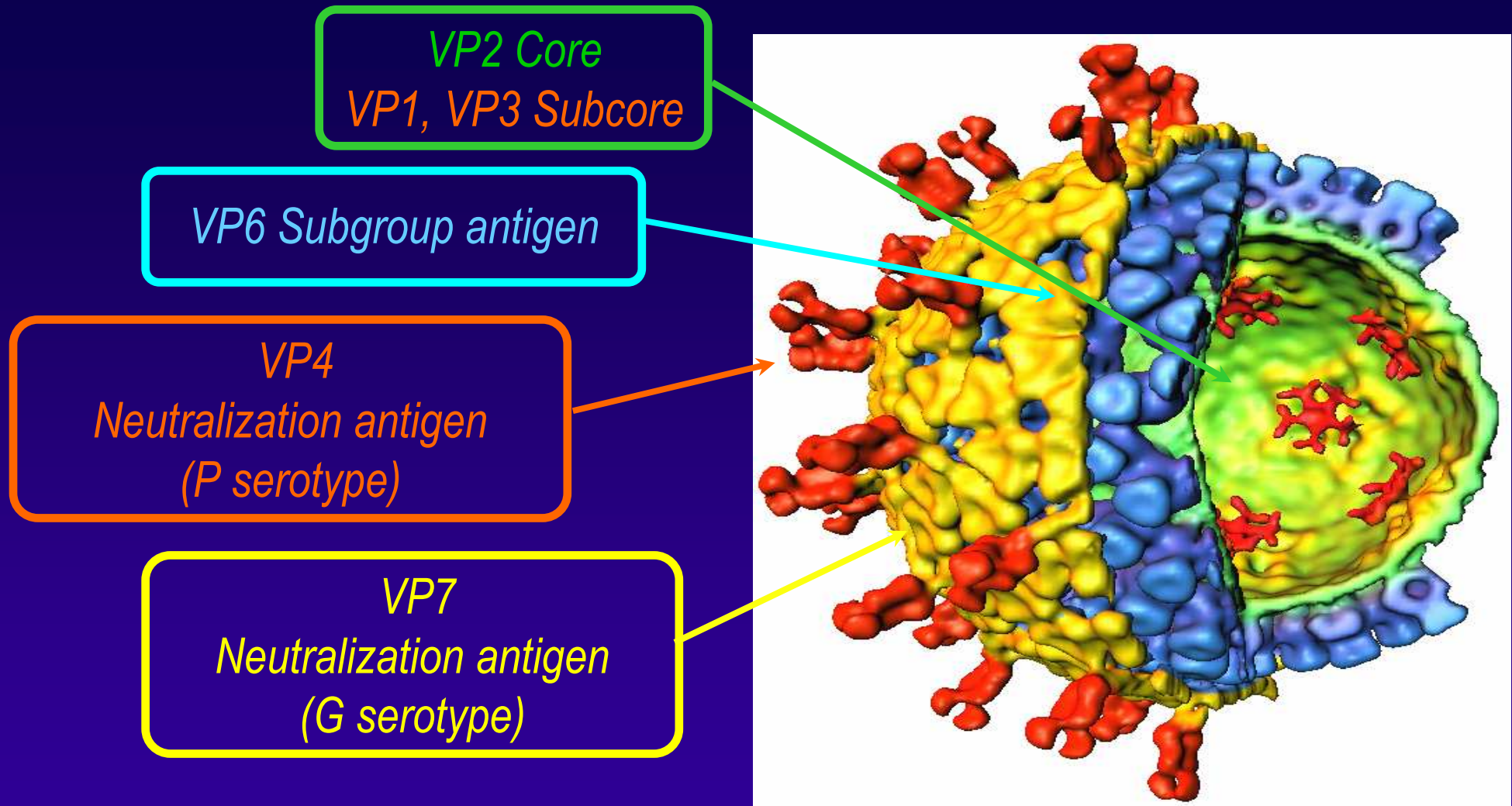
	<i>Univariate analysis</i>			<i>Multivariate anal.</i>	
	<i>Rotavirus pos</i>	<i>Rotavirus neg</i>	<i>p</i>	<i>O.R.</i>	<i>95% I.C.</i>
<i>Fever</i>	56.2%	31.8%	<0.01	2.6	1.8-3.7
<i>Abdominal pain</i>	51.6%	46.9%	NS		
<i>No of stools</i>	5.1±1.7	4.6±1.5	NS		
<i>Presence of mucus</i>	11.8%	10.3%	NS		
<i>Presence of blood</i>	0.5%	1%	NS		
<i>Dehydration</i>	18.7%	9.7%	<0.01	1.8	1.1-3

USA: CLINICAL PRESENTATION AND IMPACT OF ROTAVIRUS AND NON-ROTAVIRUS OUTPATIENT GASTROENTERITIS

(Coffin et al, PIDJ 2006)

	<i>Rotavirus pos</i>	<i>Rotavirus neg</i>	<i>p</i>
<i>Fever</i>	60%	43%	0.01
<i>Diarrhea and vomiting</i>	75%	50%	<0.01
<i>Vomiting without diarrhea</i>	7%	15%	NS
<i>Telephone calls (median, range)</i>	1, 0-9	0, 0-7	0.02
<i>Lost days of work (median, range)</i>	2, 0-10	0, 0-10	<0.01
<i>Lost days of day care (median, range)</i>	3, 0-7	1, 0-7	<0.01

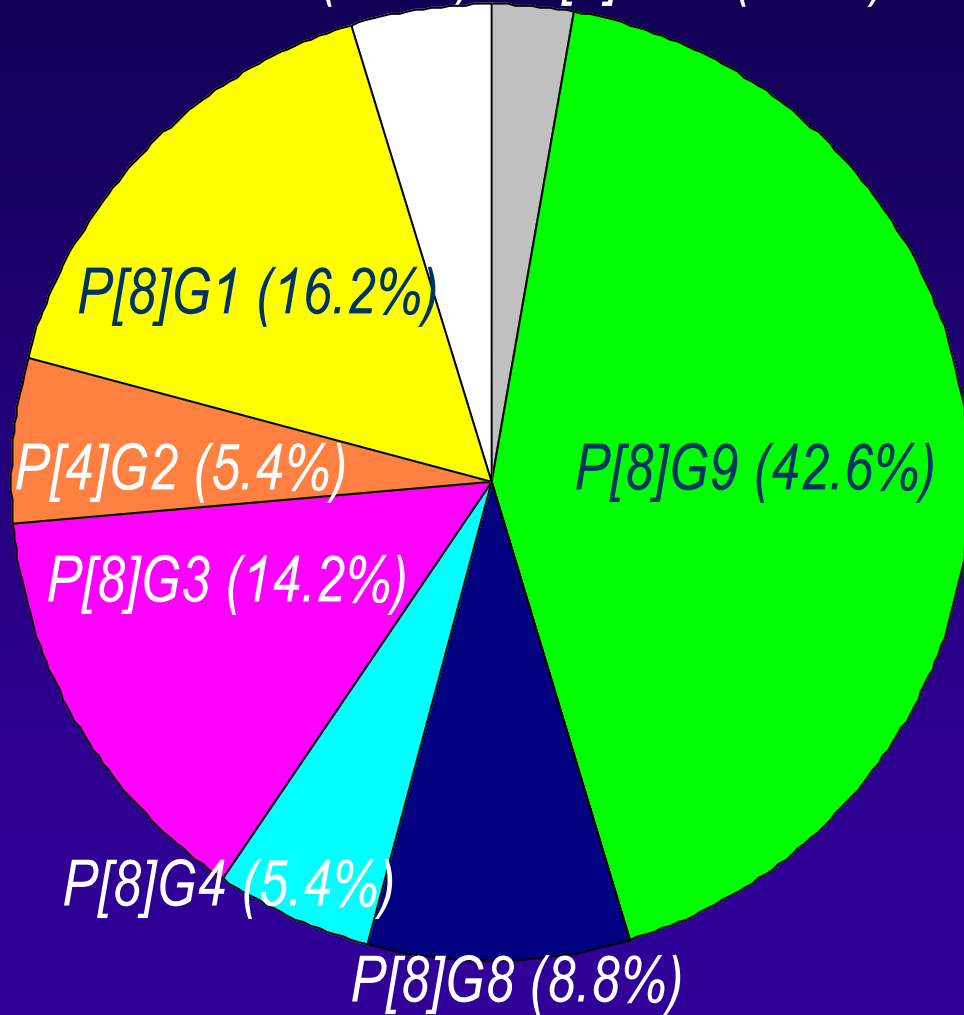
ROTAVIRUS: SEGMENTED RNA VIRUS WITH A WHEEL SHAPE



- Double-shelled capsid: outer (VP4, VP7) and inner (VP6)
- Genome: 11 segments of dsRNA

G- AND P-GENOTYPE DISTRIBUTION

Co-infections (4.7%) P[8]G10 (2.7%)



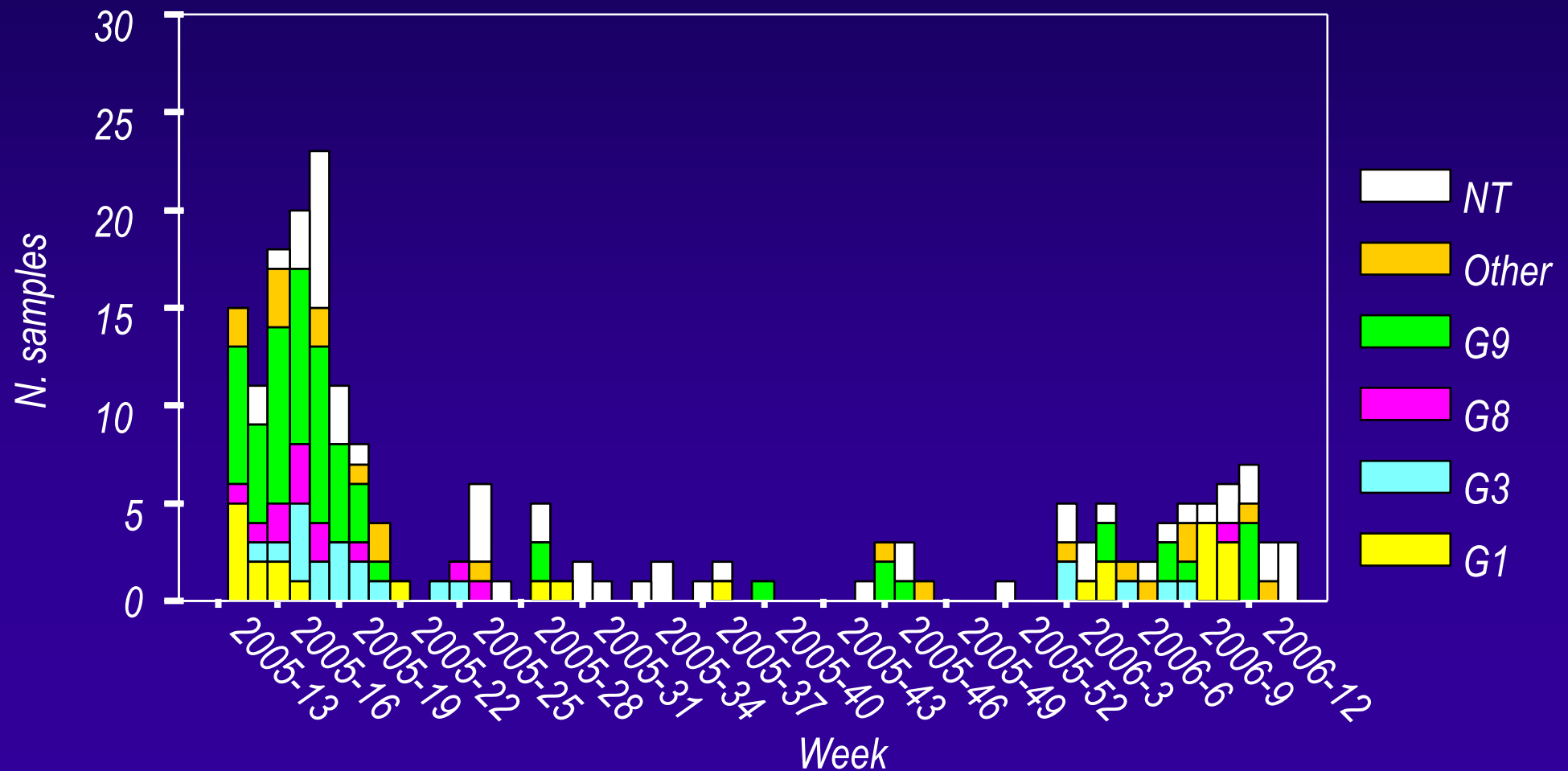
Is it expected?

P[8]G1 (16.2%)

Author	Country	Prevalence (%)*					
		G1	G2	G3	G4	G8	G9
Arista	Italy, 1999-00	43	-	2	34	-	19
Rahaman	Belgium, 1999-00	72	18	2	3	-	5
	Belgium, 2002-03	7	6	24	11	-	52
Cataloluk	Turck., 2000-02	30	11	2	48	-	3
Kang	Korea, 2002-03				27		11
Theamboonlers	Thail., 2002-04	6	69	-	-	-	25
Kirkwood	Australia, 2001	48	5	-	7	-	10

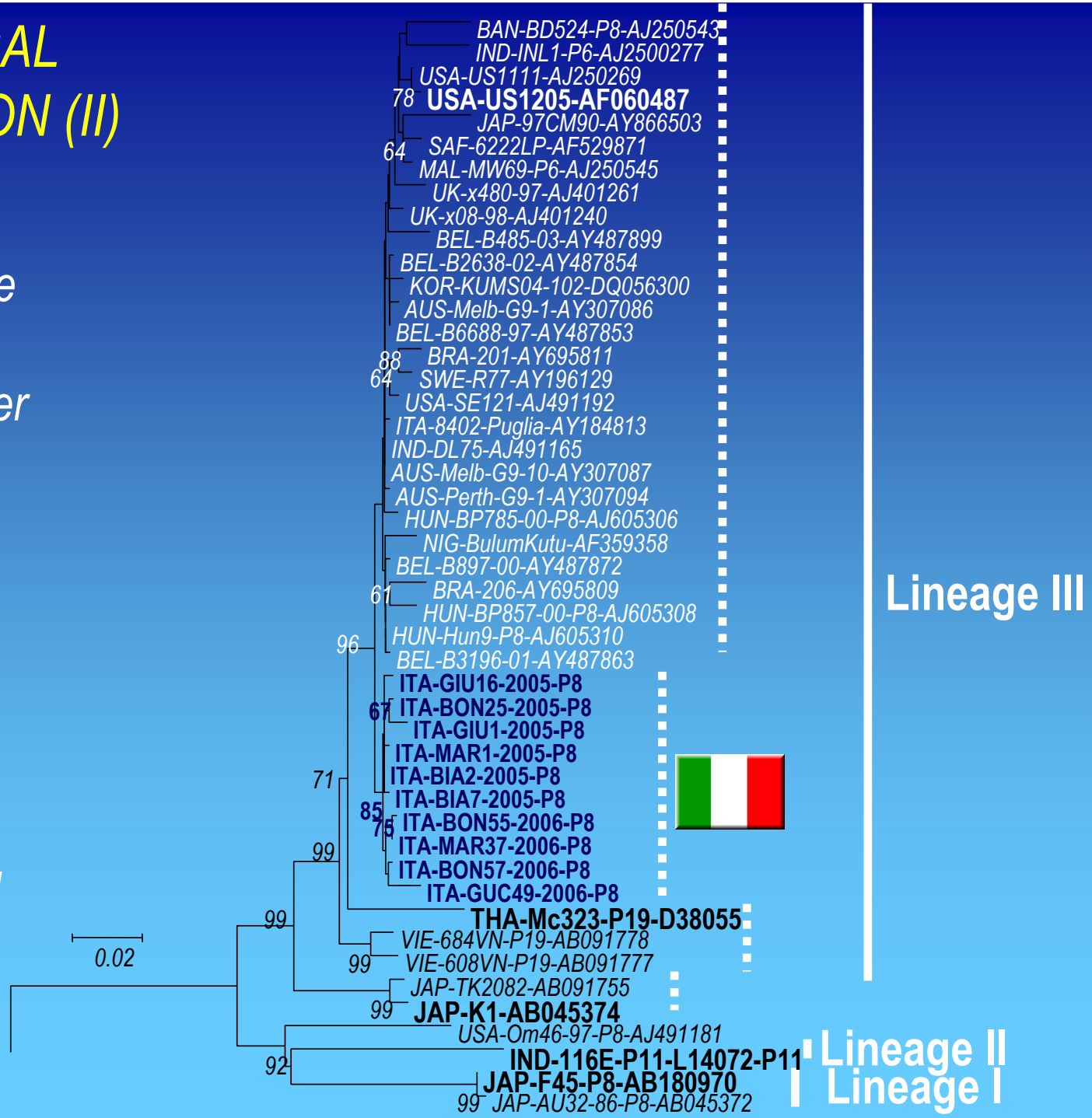
THE VIROLOGICAL CHARACTERIZATION (I)

- *the persistent circulation of rotavirus outside of the typical epidemic season such as summer and autumn*
- *the high heterogeneity of strains during the one-year surveillance with co-circulation of P[8]G1, P[8]G3, P[8]G8, P[8]G9 genotypes*



THE VIROLOGICAL CHARACTERIZATION (II)

- the very high incidence of P[8]G9 infections attributable to strains belonging to a closely related genetic cluster distinct from the other G9 strains recently isolated in other European countries, America and Asia¹⁴
- the possibility of VP4 exchange between G9 and G8 strains and G9 and G10 strains that circulated during the spring of 2005 and the winter of 2006, respectively



RATIONALE OF INTRODUCTION OF ROTAVIRUS VACCINE

- *The burden of RV gastroenteritis*
 - *Morbidity and mortality in developing countries*
 - *Morbidity in developed countries*
 - *High rate of hospitalization and economic burden in developed countries*
 - *The most important cause of nosocomial infections in childhood*
- *Other preventive measures are not effective*
- *Two new vaccines are licensed or submitted to FDA and EMEA*
- *The importance of virological surveillance of circulating RV to detect new variants and possible antigenic changes that might affect vaccines effectiveness*

PROGETTO SORVEGLIANZA ROTAVIRUS LIVORNO



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