



Viral Agents of Gastroenteritis : How Important are they?

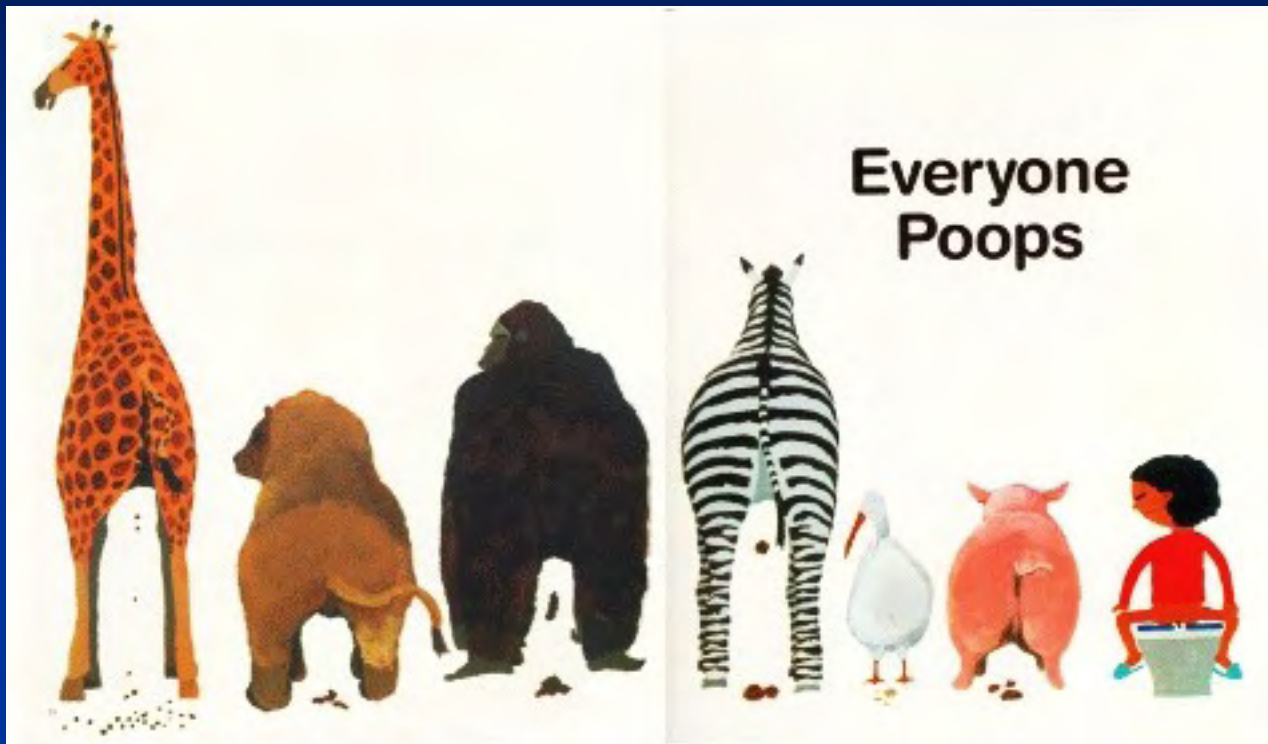
Roger I. Glass, M.D., Ph.D.
Director, Fogarty International Center
Associate Director for International Research, NIH

Dijon
June 14, 2007

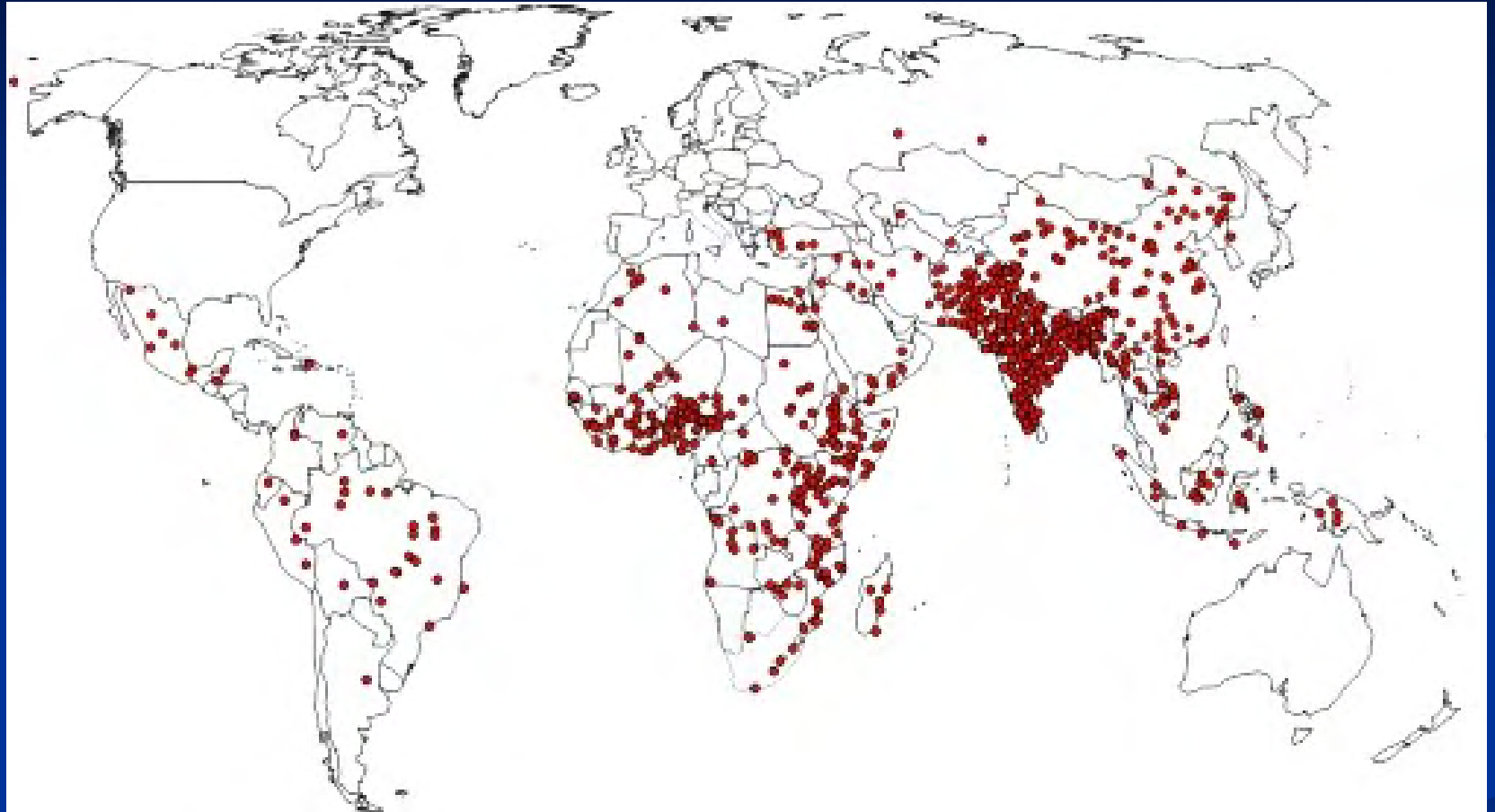


JOHN E. FOGARTY
INTERNATIONAL
CENTER





Estimated global distribution of the 2.2 million annual childhood deaths caused by diarrhea



1 dot = 5,000 deaths

20% of deaths < 5 yrs

The Estimated Burden of Gastroenteritis in the United States

Total

Children

Deaths

6,200

300

Hospitalizations

612,000

160,000 – (8-12%)

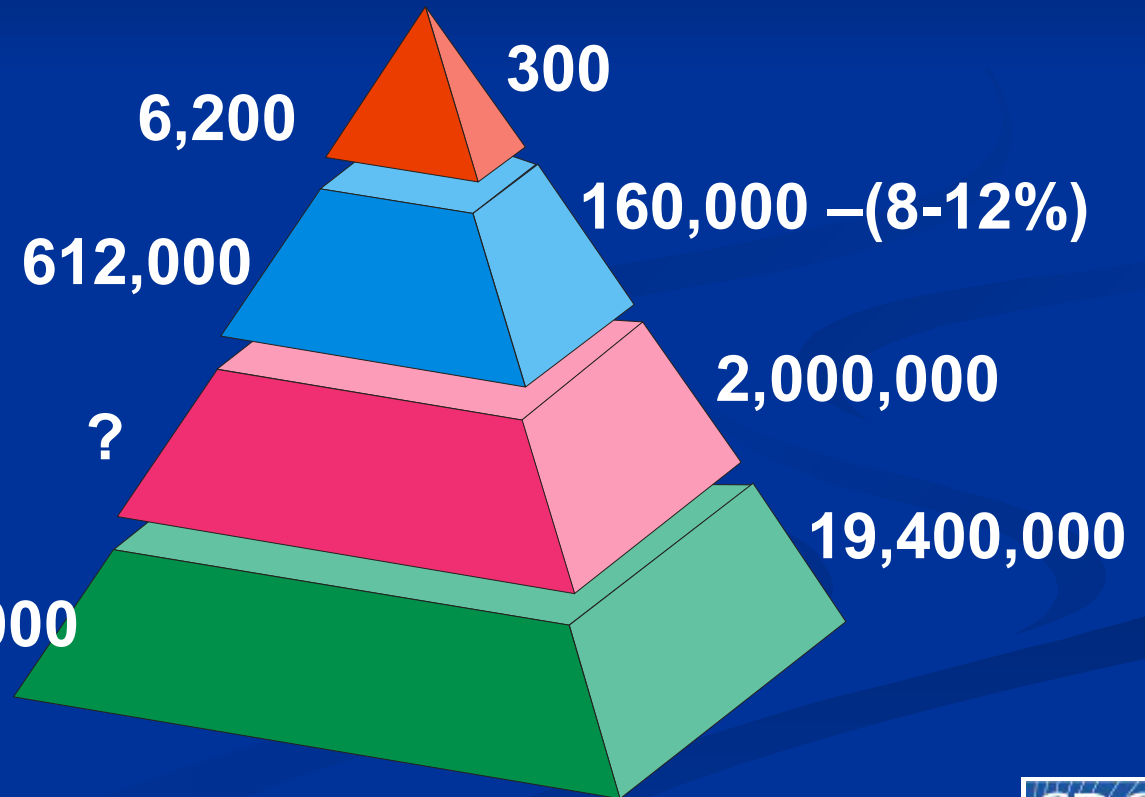
OPD Visits

?

2,000,000

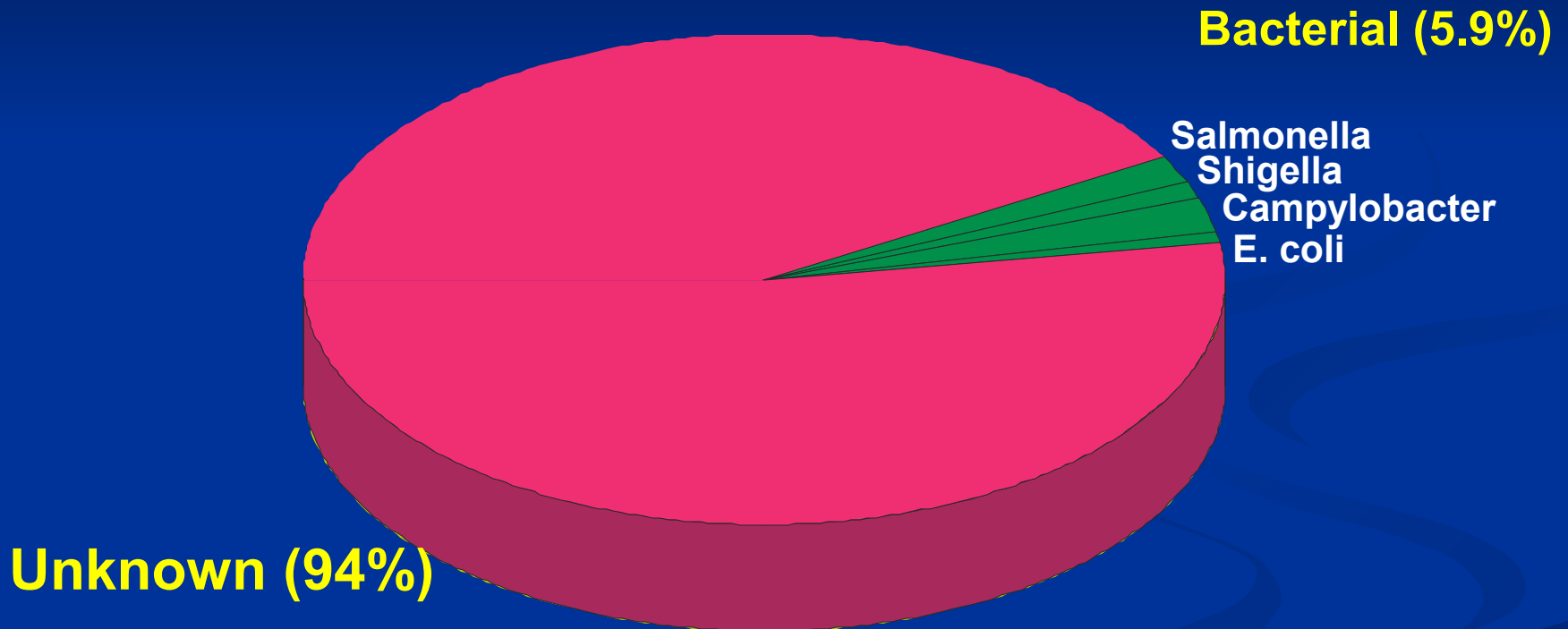
Episodes 267,000,000

19,400,000

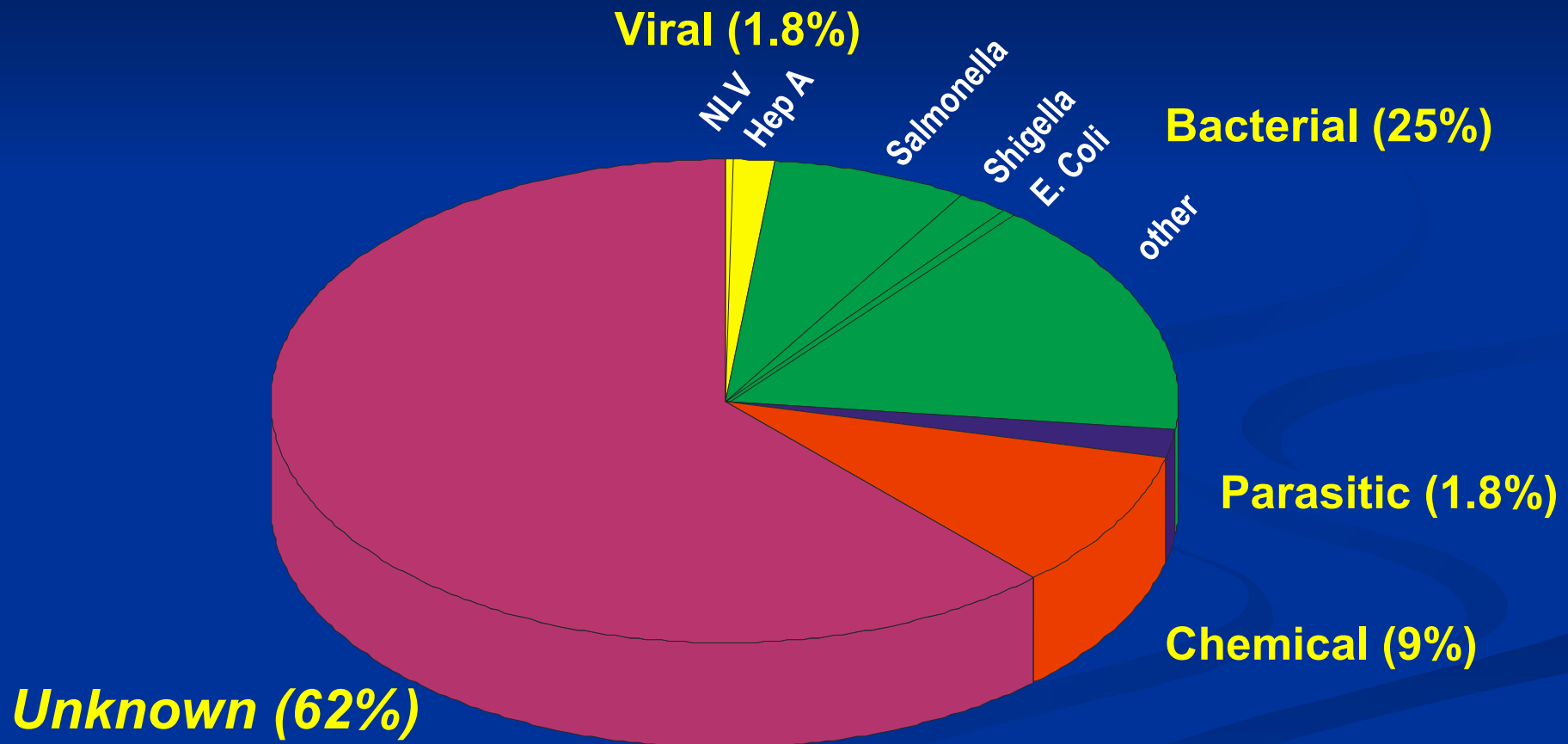


The "Diagnostic Void"

Survey of >30,000 specimens from 10 hospitals



Etiology of 7,458 Outbreaks of Gastroenteritis Reported to CDC, 1973-1987

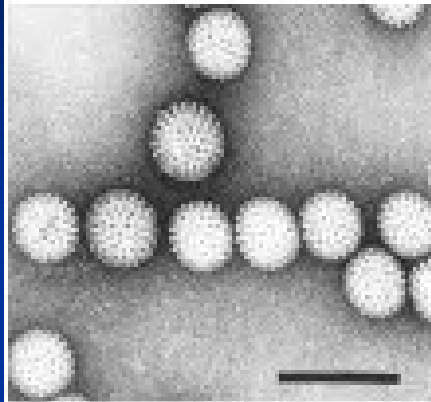


ref: Bean & Griffin, 1990

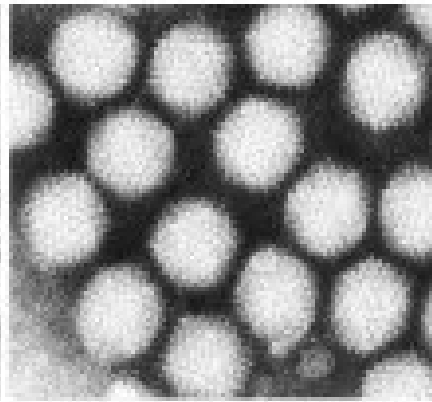


Viral Agents of Gastroenteritis

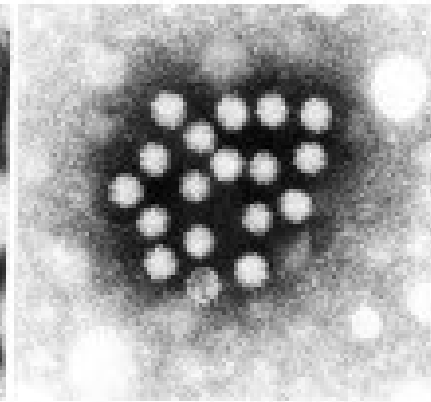
Rotavirus



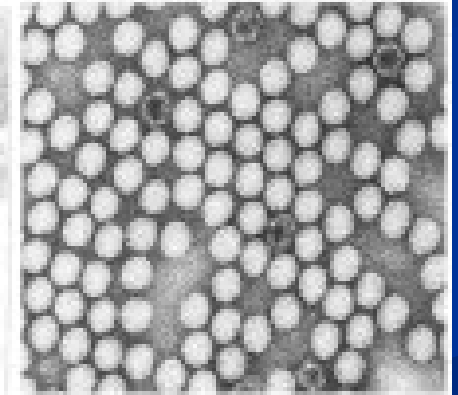
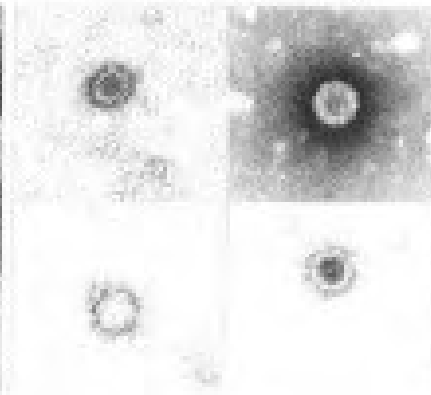
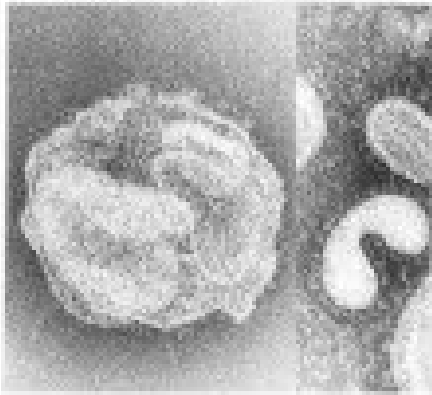
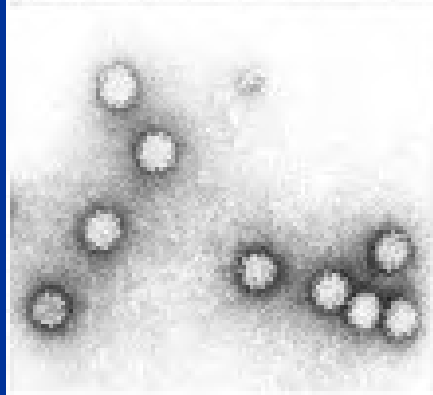
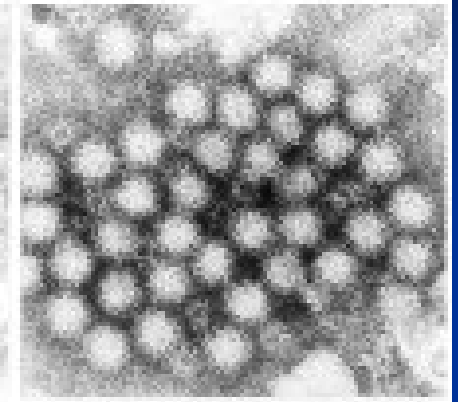
Adenovirus



Astrovirus



Calicivirus - NLV



Calicivirus - SLV

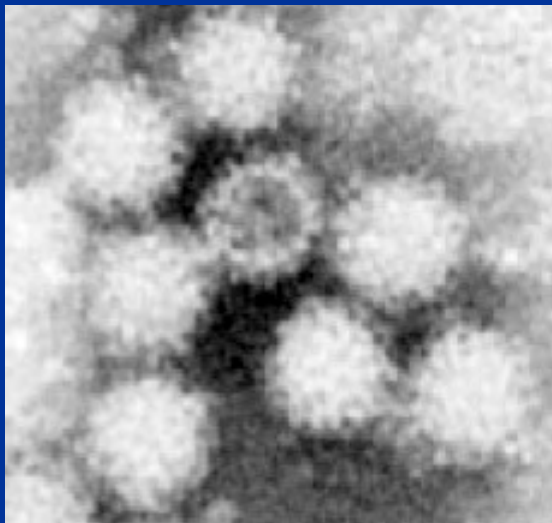
Torovirus

Picobirnavirus

Enterovirus 22

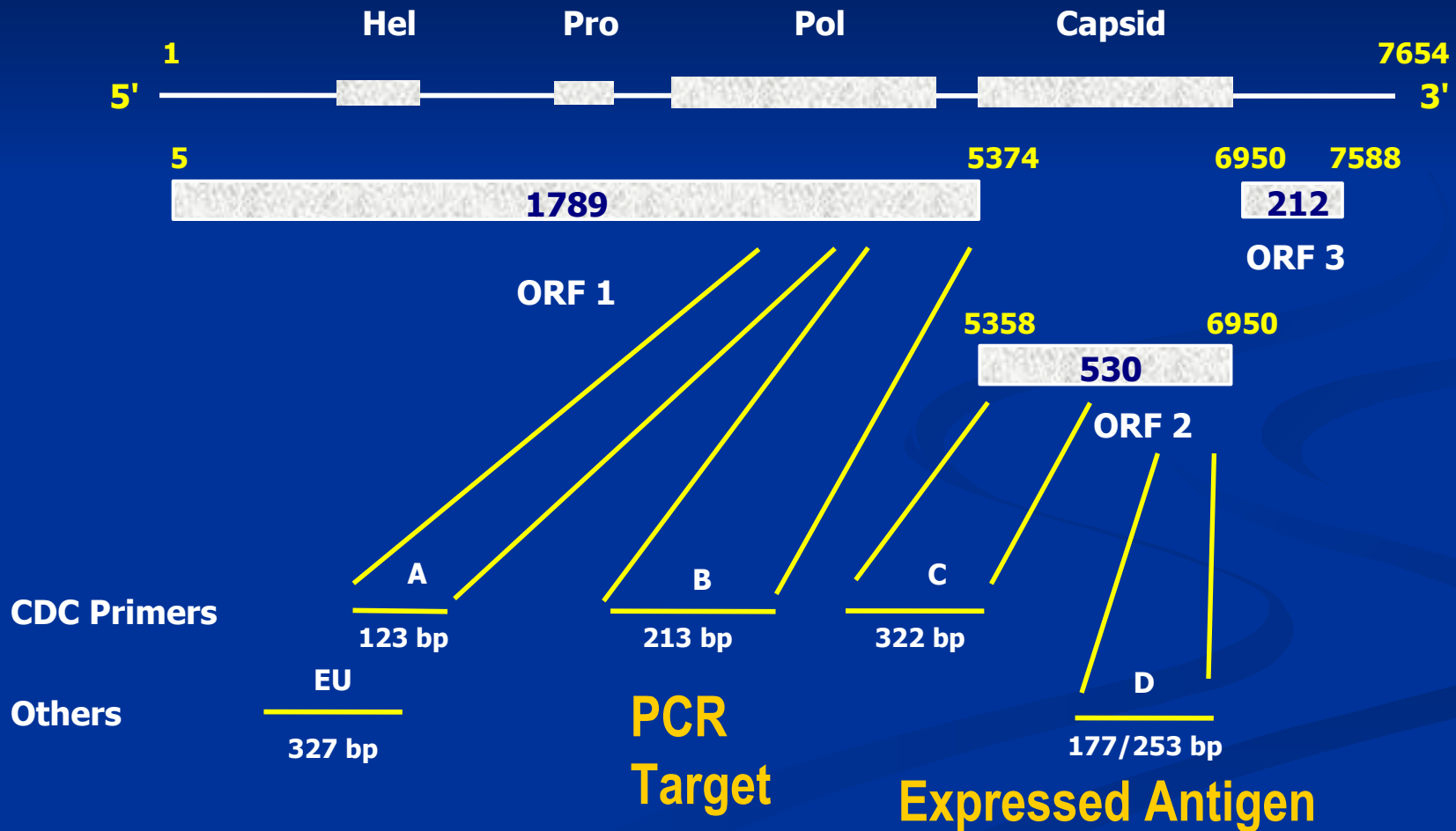
Noroviruses (a.k.a. Norwalk-like Viruses, human caliciviruses)

- Identified by electron microscopy (Kapikian)-1972
- Do not grow in cell culture; no animal model
- Commercial detection assays under development
- Molecular detection by RT-PCR
- Many different genotypes



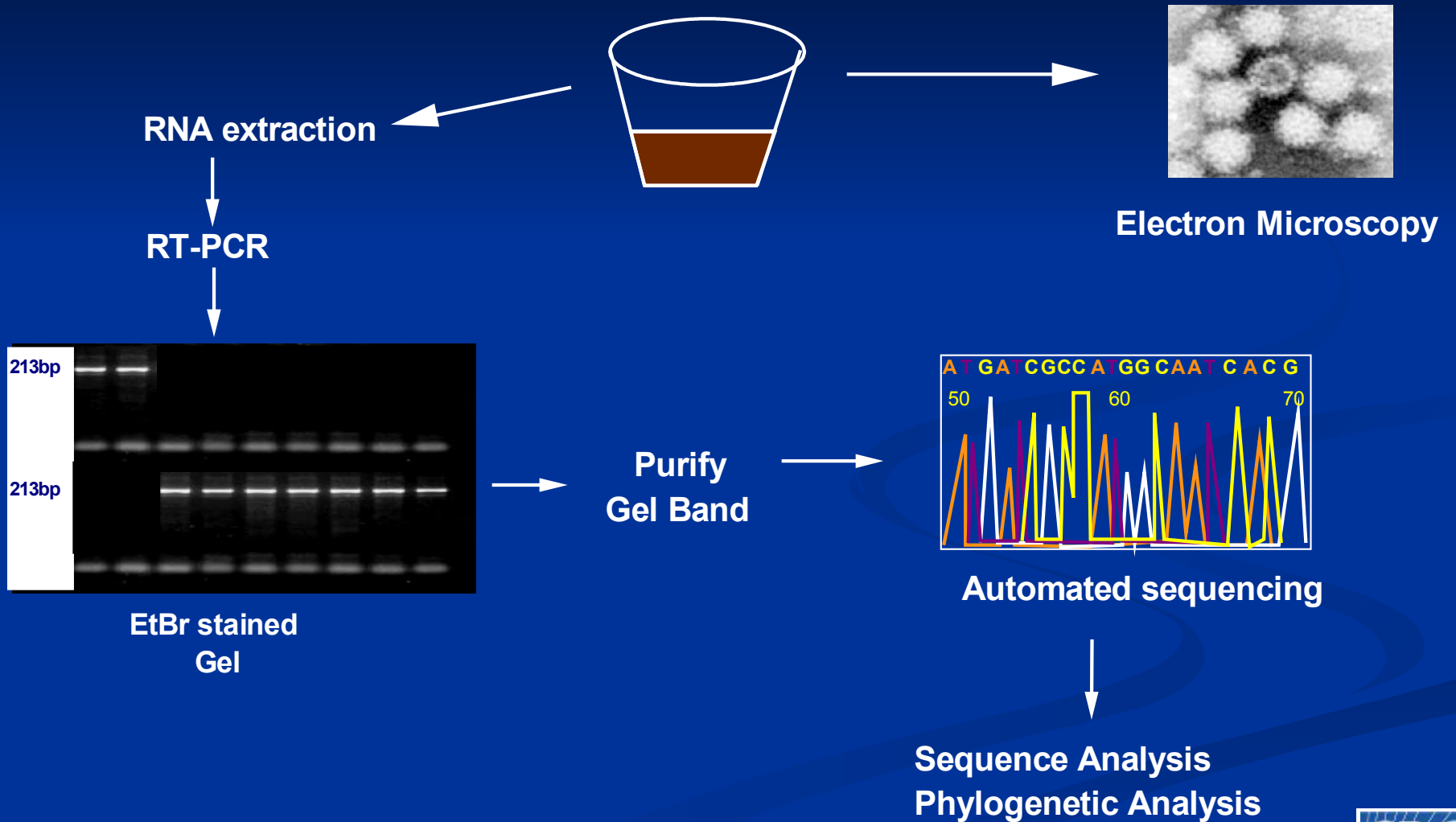
- Most common cause of outbreaks of nonbacterial acute gastroenteritis

Norovirus Detection by RT-PCR/EIA



Stool cup-to-Sequence

Detection & Characterization of NLVs



The New York Times

FRIDAY, JANUARY 25, 1991

F.D.A. Expected to Announce Tough Seafood-Safety Rules

The Food and Drug Administration is expected to announce new rules for seafood safety, including tougher standards for oysters, clams, and other shellfish. The agency is also expected to announce new rules for fish and shellfish products, including tougher standards for freshness and quality.

IS OUR FISH FIT TO EAT?

A six-month investigation of fresh fish and shellfish raises serious questions about their quality.



American are eating more fish. Over the last decade consumption per person in the U.S. has risen nearly 25 percent—about 12½ pounds a year. However, a six-month investigation by C.U. raises questions about the quality, abundance, and safety of the fish consumers are eating. Almost 40 percent of the fish we sampled was of fair or poor quality, and 30 percent was downright poor. Nearly half the fish we tested was... bacteria free.

Gov. Schaefer suggests oyster harvest ban

By DAN A. BALLESTERO
Capital News Service

BALTIMORE — Governor William Donald Schaefer said Friday that Maryland should consider a moratorium on oyster harvesting, citing the success of the 1980 ban on fishing for striped bass.

Schaefer made his remarks to more than 300 oystermen and restaurateurs during a public hearing for the Aquaculture Research Center.

"Our watermen are having a tough time," the governor said, referring to the current oyster season. "Maybe we ought to let harvesting for a while... We've proved that rockfish come back if you give them a chance to survive."

The governor's draft recommendations call for "oyster recovery areas" in several rivers and joint efforts among industry groups and scientists to create alternative approaches to harvesting, said Paul Muzzarelli, director of DNR's Waterway Administration and Roundtable coordinator.

Muzzarelli declined to comment on the specifics of the plan until it is signed. He expects approval by the legislature within two weeks.

Schaefer, in his speech at the hearing, said it was time for "some hard decisions" about the Bay's declining oyster population.

One such decision, he said, is

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

December 17, 1993 / Vol. 42 / No. 49

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

- 340 Multistate Outbreak of Viral Gastroenteritis Related to Consumption of Oysters — Louisiana, Maryland, Mississippi, and North Carolina, 1993
- 346 HIV Transmission Between Two Adolescent Brothers With Hemophilia — United States, 1993
- 352 Resurgence of Pertussis — Michigan, 1993
- 361 Estimates of Future Global Tobacco Use and Mortality
- 364 Notices to Readers

Epidemiologic Notes and Reports

Multistate Outbreak of Viral Gastroenteritis Related to Consumption of Oysters — Louisiana, Maryland, Mississippi, and North Carolina, 1993

On November 17, 1993, the state health departments of Louisiana, Maryland, and Mississippi notified CDC of several outbreaks of gastroenteritis occurring in their states since November 12. Preliminary epidemiologic investigations identified consumption of oysters as the primary risk factor for illness. On November 16, the Louisiana Department of Health and Hospitals (LDH) had identified the Grand Pra-

Uncooked shellfish suspected of making Festival visitors sick

WASHINGTON — More than 20 people reported becoming ill with gastroenteritis after eating at the Waterford Festival, according to the Talbot County Health Department.

Dr. John Ryan, the health officer for Talbot County, said 24 people in Talbot reported suffering from gastroenteritis during the festival on Sunday and Monday. All of the victims bought food from vendors at the Waterford Festival the weekend of Nov. 13-14, he said.

"The illness generally lasted less than three days, and no cases resulted in hospitalization, he said.

Officials have not determined exactly what she ate, or exactly what she drank, or what vendor's stand it originated in, Ryan said, adding that he believed uncooked shellfish was the most probable culprit.

Anyone who experienced these symptoms after eating at the Waterford Festival is asked to contact either Susan Deaton or Kim Comber at the Health Department in Eastern Shore at 410-326-1234.

Ryan said they need to know what the victims ate, when they ate, and when their symptoms began.

Which so cases have been previously served to her, officials should see a doctor if the illness lasts longer than three days or if the vomiting is especially severe.

La. oysters eaten in Md. tied to stomach complaint

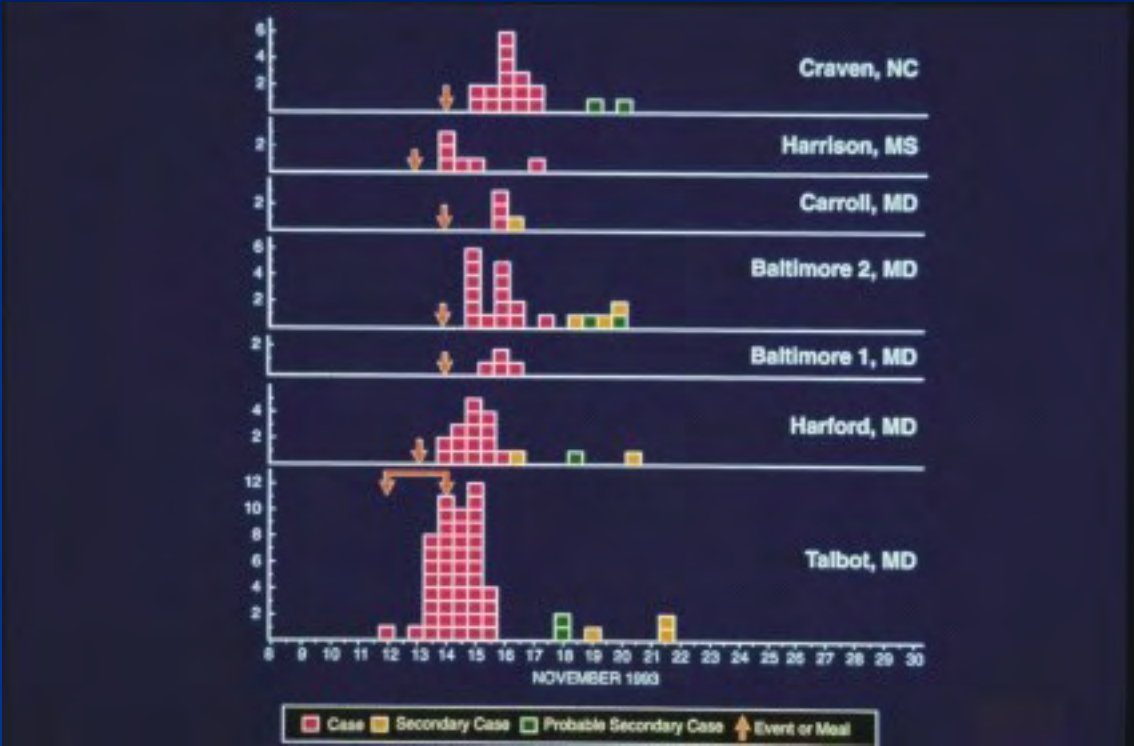
WASHINGTON — Oysters harvested from waters off Louisiana are tied to a mysterious stomach ailment and consumers should not eat them, the government said last night.

One person has been seriously hurt, and more than 100 people were hospitalized in Louisiana, Mississippi and Maryland, the Food and Drug Administration said.

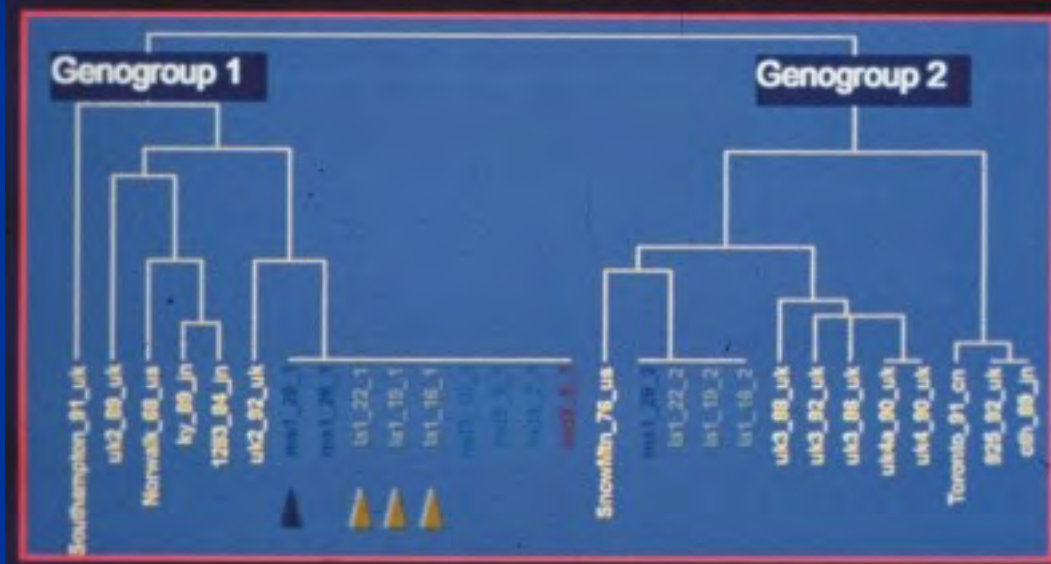
The ailment is caused by a virus-like illness.

The government said that oysters harvested from two areas of Louisiana were closed to harvesting Nov. 16.





Nucleotide Relatedness of SRSVs 104 bp within RNA Polymerase





Over a 3 day period,
one sick fisherman
contaminated 23,000
bushels of oysters sold
in about 14 states with a
single strain of norovirus



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Medical notes

Education

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Programmes

Friday, 3 January, 2003, 15:14 GMT

Vomiting bug cases at record high



The virus has closed hospital wards

The number of cases of the winter vomiting bug doubled over the last 12 months to reach their highest ever level, official figures have revealed.

See also:

- 22 Jan 02 | T-2
Winter vomiting virus
- 23 Jan 02 | Health
Gastric virus causing widespread misery
- 19 Nov 02 | Wales
Hospital identifies winter bug

Internet Links:

- Public Health Laboratory Service
- Norwalk-like virus information

The BBC is not responsible for the content of external internet sites

Top Health stories now:

- 'Cloned baby' DNA test delayed
- NHS moves to out doctors' hours

Related reports

There were 2,000 confirmed reports of the

Outbreaks aboard Cruise Ships, 2005

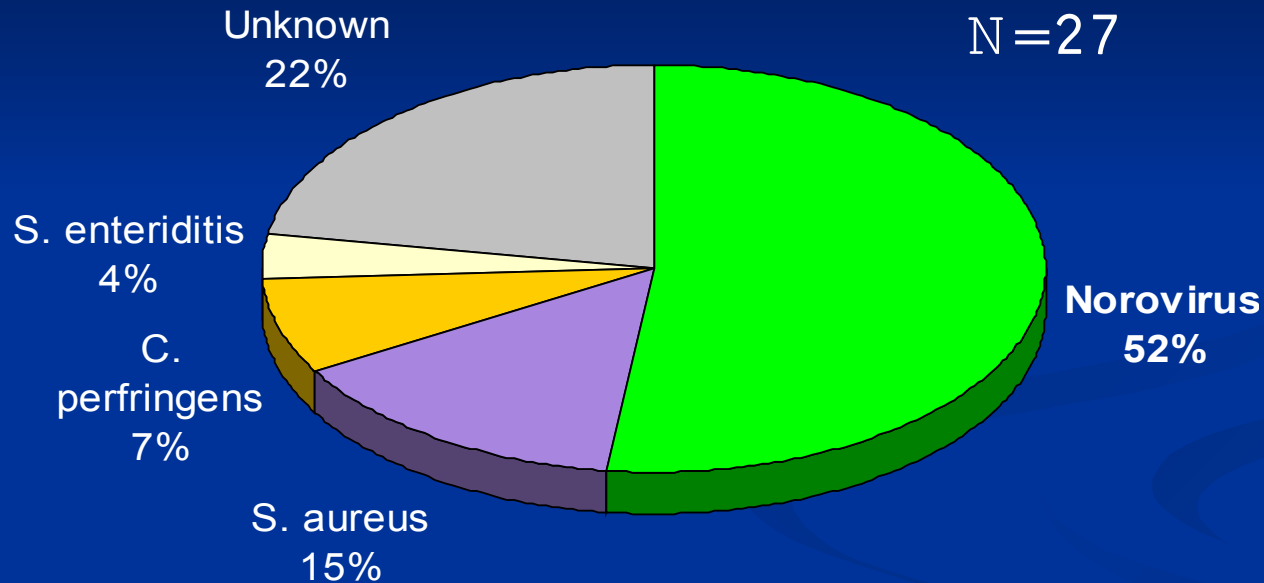


- 14 outbreaks on 10 ships
- Some repeated after cleanup
- By sequence, some linked to common sources
- Overcrowding –major risk
- Multiple modes of spread
 - Food, person- to-person

International Outbreaks of Norwalk like Virus



Enhanced Foodborne Outbreak Surveillance: CA, MD, TN; 2001-2002



- Active Outbreak Detection
- Aggressive sample collection (In-home kits)
- Comprehensive pathogen testing

Sporadic Norovirus Gastroenteritis in Adults: Emergency Department Patients

- 3 FoodNet sites (CT, NY, OR)
- 364 subjects enrolled
- 152 subjects with stool sample tested for all pathogens
- ***Norovirus most common pathogen detected***

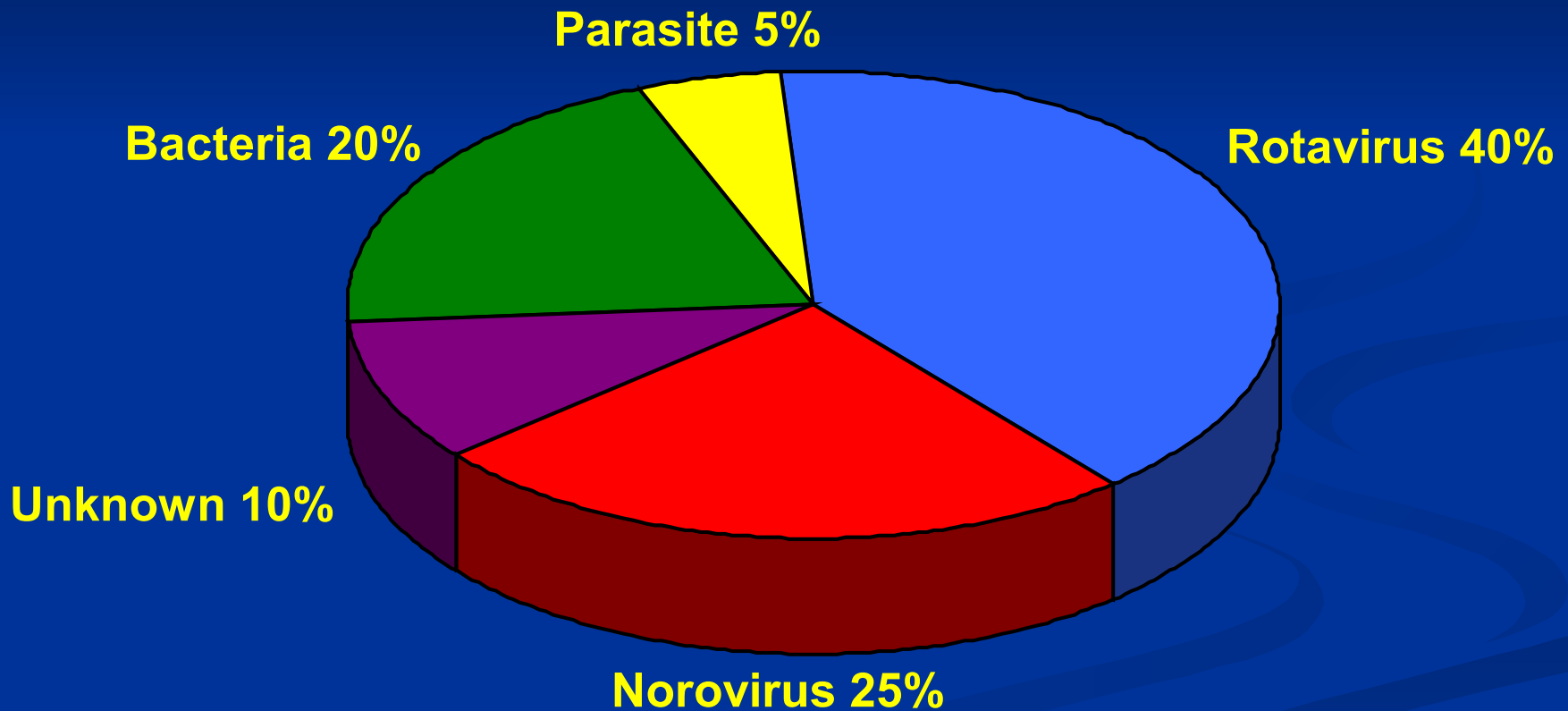
Pathogen	No. positive (%)
Viruses	49 (32%)
Norovirus	30 (20%)
Rotavirus	18 (12%)
Any bacteria	21 (14%)
Any parasite	3 (2%)
Any pathogen	73/152 (48%)
No pathogen	79/152 (52%)

The Global Challenge



Are noroviruses a problem in the developing world ?

Etiology of Severe Diarrhea in Peruvian Children

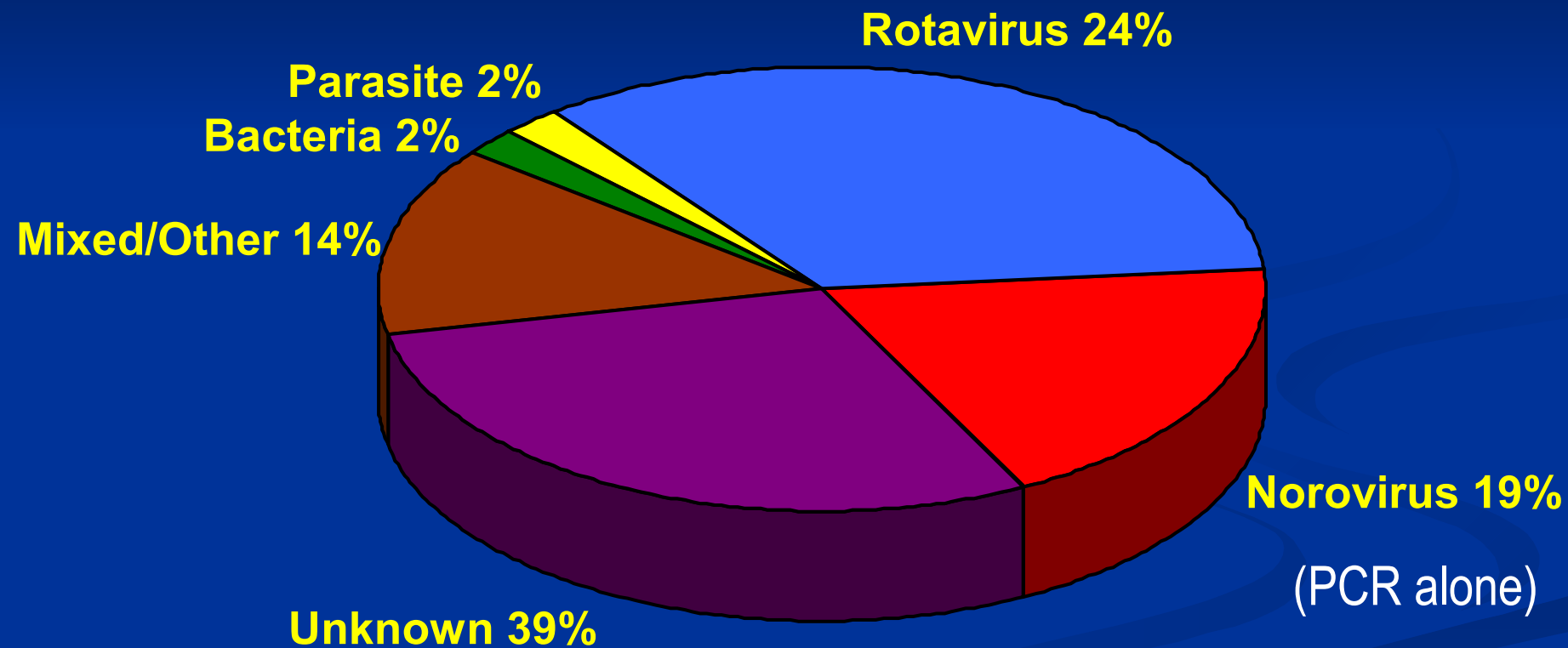


U. Parasher, 2003

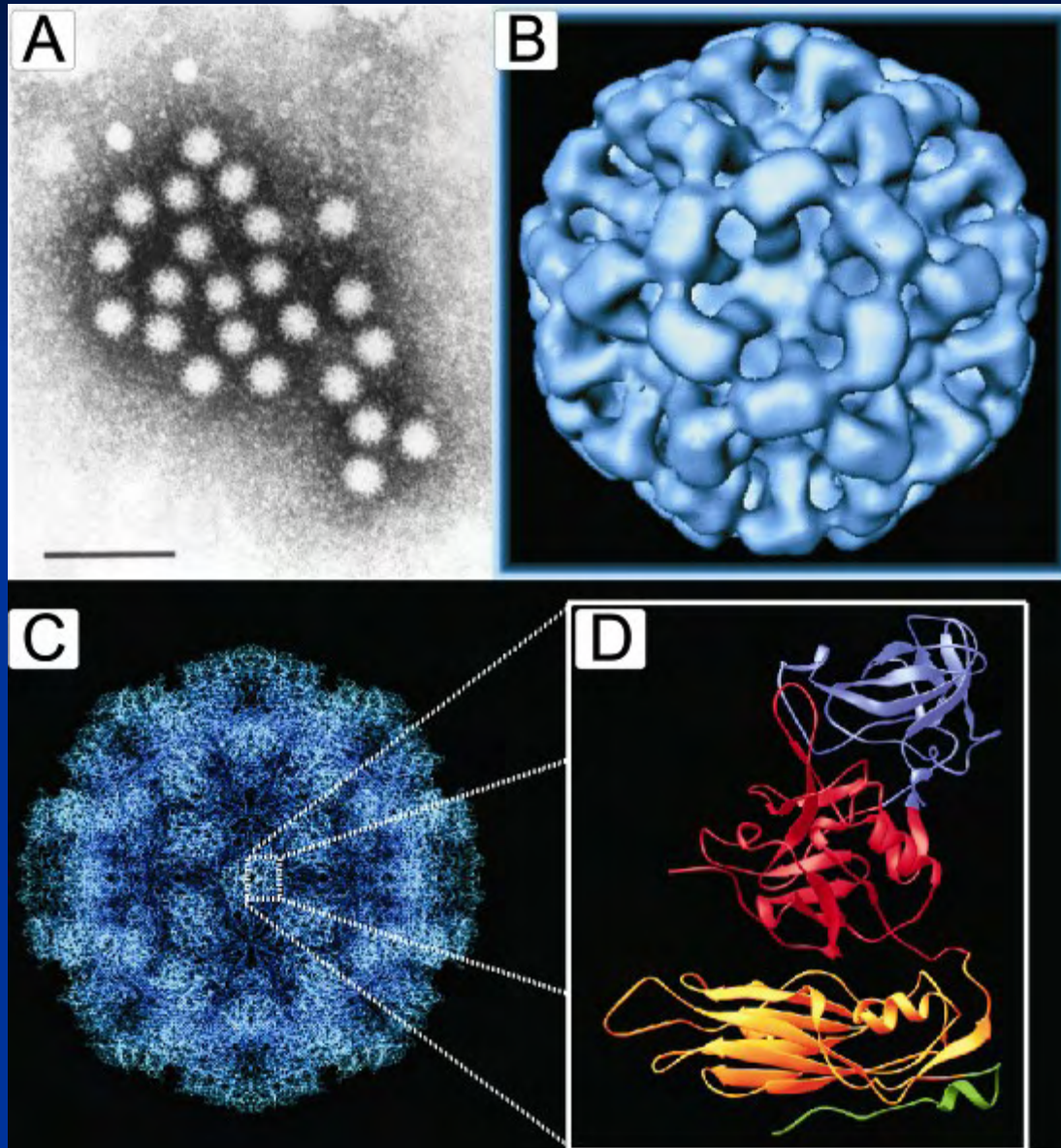
Will this translate into mortality?



Etiology of Diarrhea in Finnish Children



Research Challenges



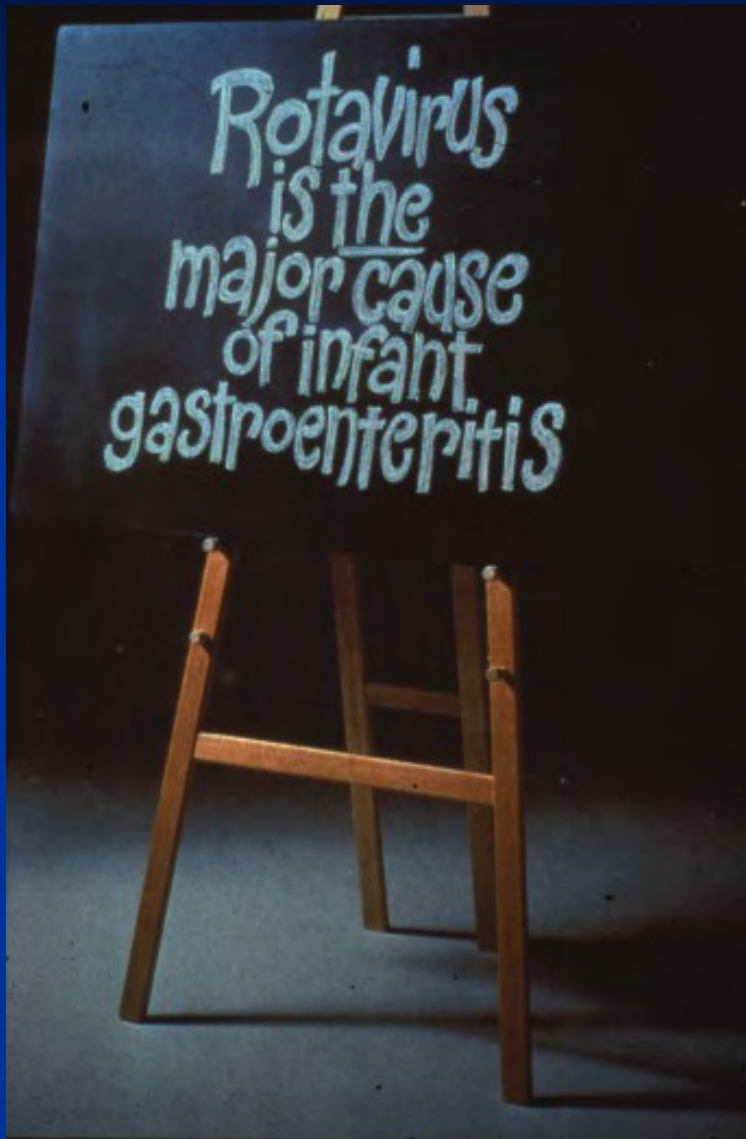
Diagnostics
Receptors
Vaccines
Cell Culture
Animal models

A Kapikian

B,C,D Prasad

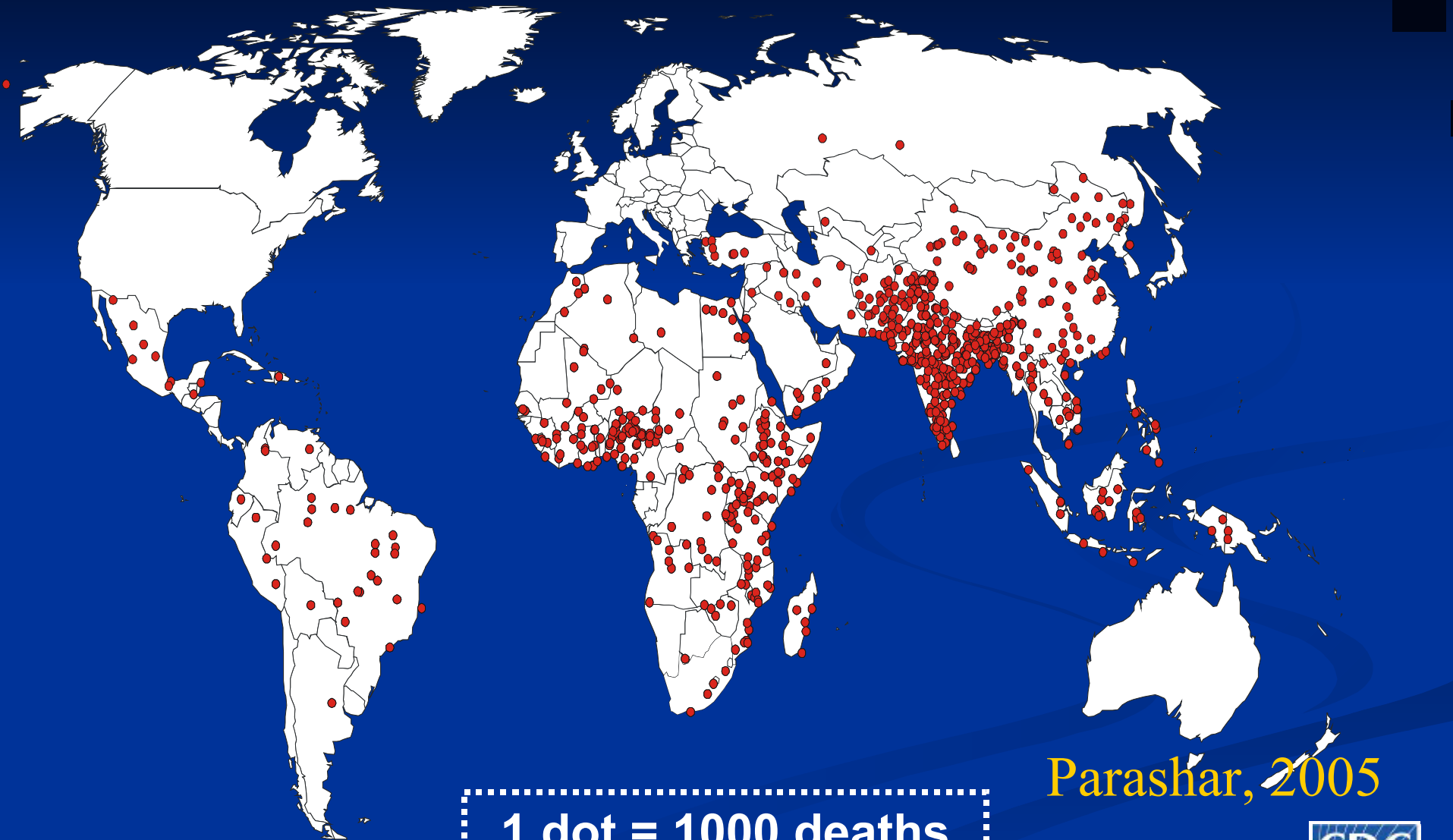


Histoire Naturelle des Infections a Rotavirus



- La cause la plus fréquente de diarrhée sévère chez l'enfant
- Touchera tous les enfants avant l'âge de 5 ans
- Un virus "Démocratique"
- La première infection est symptomatique
- Immunité naturelle est bonne
- Peu de souches circulantes
- L'amélioration de conditions d'hygiène n'influence pas l'infection

Distribution des 600,000 deces annuel dus au rotavirus



1 dot = 1000 deaths

Parashar, 2005



Importance de Rotavirus aux US

Risk

Events

1 : 10⁶

20-40 Deaths

1 : 80

60-70,000 Hospitalizations

1 : 7

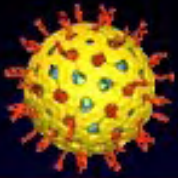
500,000 Outpatient visits

1 : 0.9

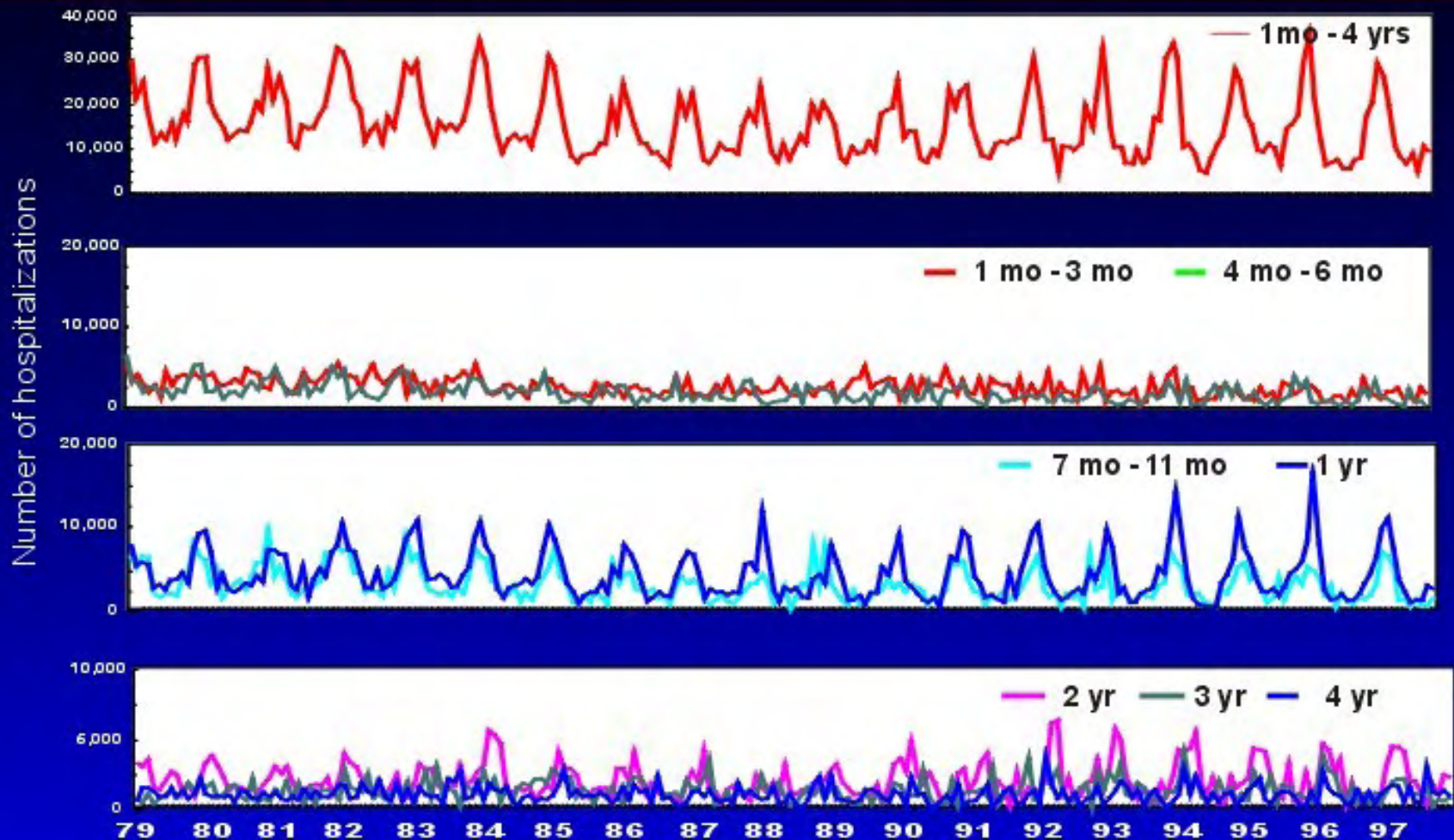
3.2 Million episodes

Cost: \$400 M medical; >\$1 B total

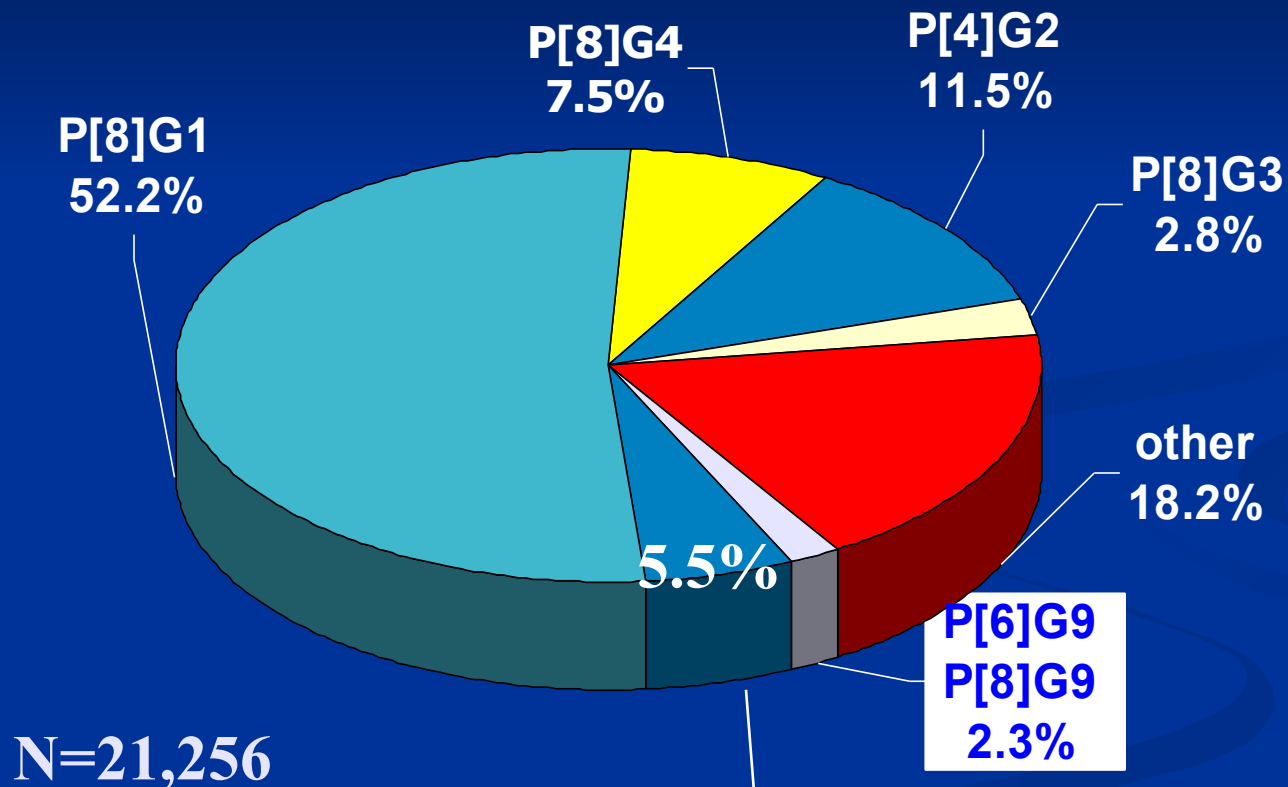




Diarrhea-associated hospitalizations by month & age among U.S. children < 5 years, 1979-1997



Genotypes de Rotavirus (1993-2003)



Rare or regionally common strains (23 strains total): P[4]G1 (1.3%), P[6]G2 (0.8%), P[6]G1 (0.6%), P[6]G8 (0.6%), P[4], G3 (0.5%)

INFECTIOUS DISEASES IN CHILDREN

THE ASSOCIATED PRESS AND UNIVERSITY MICROFILMS

Circulation: 28,000
Date: February 1997

Rotavirus vaccine shown to be cost effective

NEWS VS. HISTORY

Honor due to Kapikian

Question: Which Washington news figures have caused and led to more attention among the masses and the public — Virginia Lewandky, Kenneth Starr or Albert Kapikian? Now consider this: Which of these people is likely to have a more profound effect on the world's young children to hospitals each year and killing about 1 million children in other countries. Remember that the vaccine will wipe out rotavirus altogether, but it should greatly reduce hospitalizations of the disease and the dehydration that often becomes deadly.

Winston-Salem Journal
September 8, 1995

The Virginian-Pilot

New vaccine may tame common childhood virus

New Vaccine Passes Test For Disease In Children

The New York Times

F.D.A. Approves Vaccine for Childhood Diarrhea

By THE ASSOCIATED PRESS

Washington -- The Food and Drug Administration Monday approved the first vaccine against a leading cause of childhood diarrhea, a virus that hospitalizes 55,000 American children a year and kills one million in other countries.

HEALTHCARE REVIEW

Southern New England Edition (Massachusetts, Connecticut & Rhode Island)
Circulation: 52,000
Date: February/March 1997

Rotaviruses: Affecting children and healthcare costs across the globe

Vaccine offers way to prevent child diarrhea

Pediatric News

Circulation: 28,418
Date: November 1996

Rotavirus Vaccine Cuts Diarrhea Hospitalizations



Rhesus Rotavirus Vaccine

- Vaccins vivant oral
- 3 doses --2,4,6 mois
- Bien tolere
- Efficacite – >90% contre hospitalisations
- Efficacite evaluee au Venezuela
- Acceptabilite rapide aux USA malgre le prix (\$38/dose)

Calendrier Vaccinal aux USA --1999

Age ► Vaccine ▼	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4-6 yrs	11-12 yrs	14-16 yrs
Hepatitis B	Hep B										
		Hep B			Hep B					Hep B	
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP		DTaP		DTaP	Td	
<i>H. influenzae</i> type b			Hib	Hib	Hib	Hib					
Polio		IPV	IPV		Polio	Polio			Polio		
Rotavirus		<i>Rv</i>	<i>Rv</i>	<i>Rv</i>							
Measles, Mumps, Rubella						MMR			MMR	MMR	
Varicella						Var				Var	

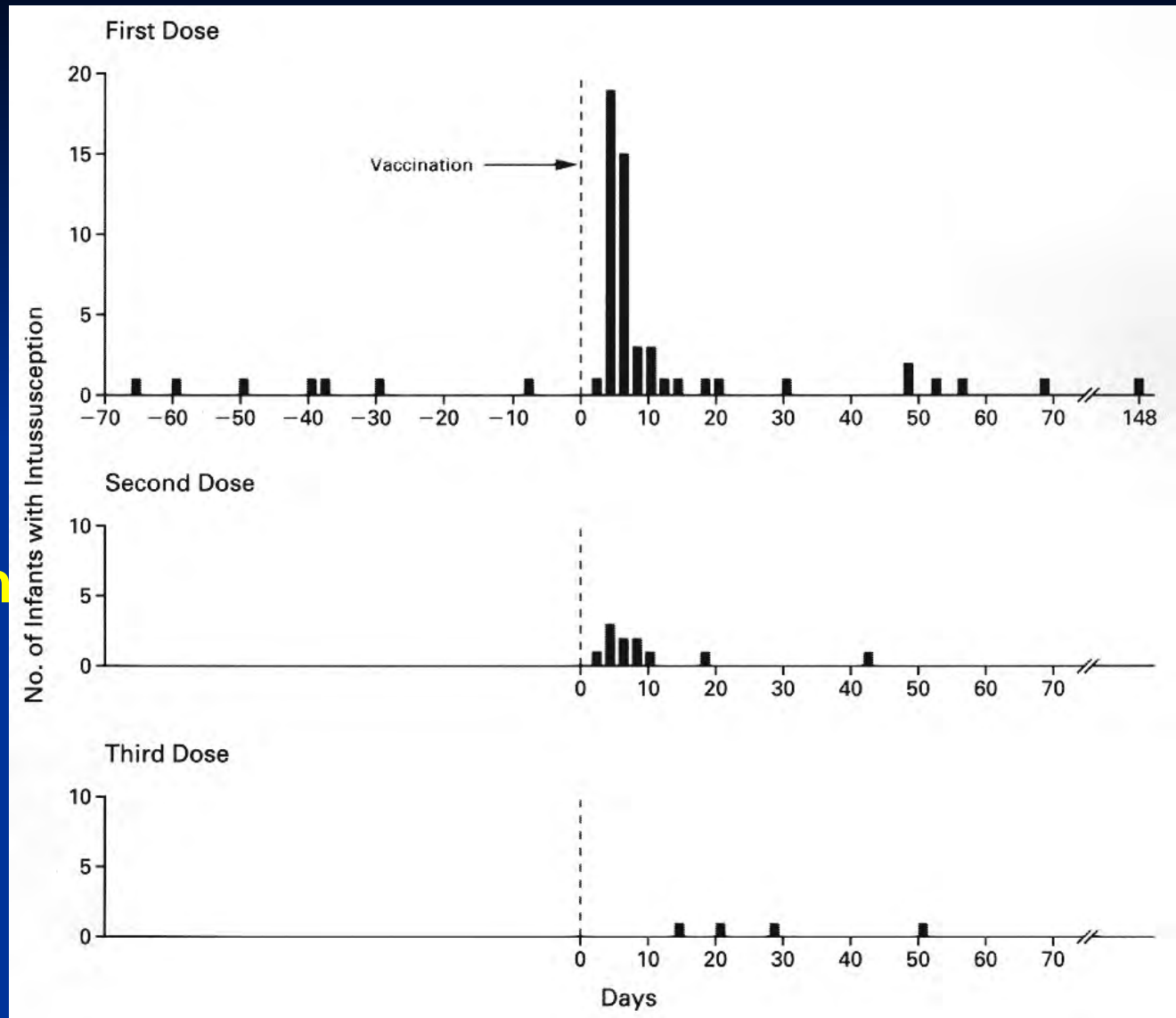
MMWRTM
**MORBIDITY AND MORTALITY
WEEKLY REPORT**

- 577 Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999
- 582 Outbreak of *Salmonella* Serotype Muenchen Infections Associated with Unpasteurized Orange Juice — United States and Canada, June 1999
- 585 Progress Toward Measles Elimination — Southern Africa, 1996–1998
- 590 Recommendations of the Advisory Committee on Immunization Practices: Revised Recommendations for Routine Poliomyelitis Vaccination

**Intussusception Among Recipients of Rotavirus Vaccine —
United States, 1998–1999**

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RotaShield^{®*}, Wyeth Laboratories, Inc., Marietta, Pennsylvania) (RRV-TV) was licensed in the United States for vaccination of infants. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians have recommended routine use of RRV-TV for vaccination of healthy infants (1,2). During September 1, 1998–July 7, 1999, 15 cases of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). This report summarizes the clinical and epidemiologic features of these cases and preliminary data from ongoing studies of intussusception and rotavirus vaccine.

Interval between Vaccine and Intussusception



Murphy TV, et al, 2001

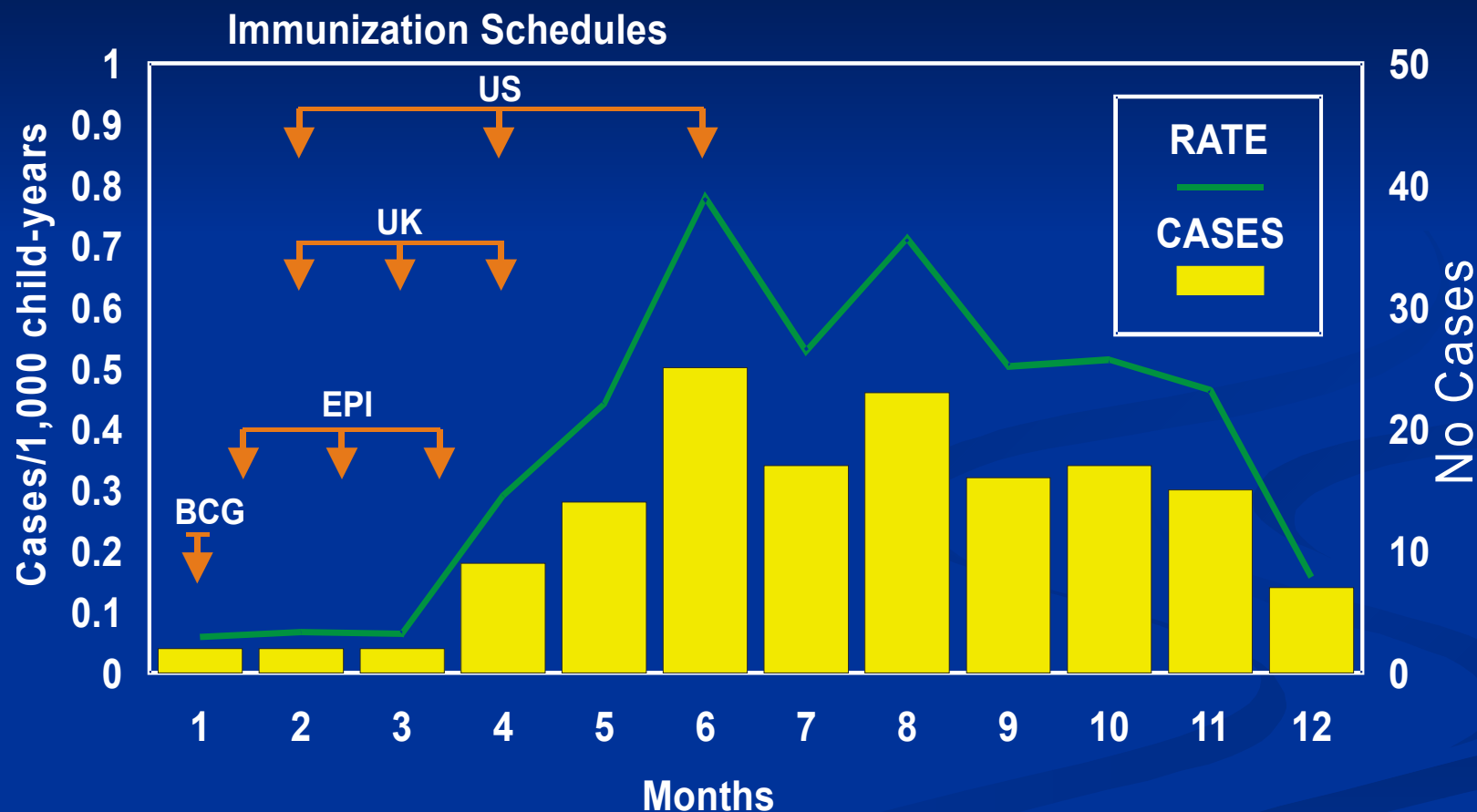


Evaluation du risque d'invagination intestinale apres RotaShield®

Study	Author	Risk	Excess Cases for US
Preliminary Data	Livengood-NIP	1 in 2500	1600
Reassessment	Livengood-NIP		888
Case Series	Murphy-NIP	1 in 4670	785
Case Control	Murphy-NIP	1 in 9474	361
Cohort Study	Kramarz-NIP	1 in 11,073	316
Ecologic Studies	Chang-NYS	<1 in 17 000	200
	Simonsen-NIH		
	all infants	-11%	0
	45-210 days	1 in 28,000	122



Taux d'incidence et nombre d'hospitalisations pour invagination intestinal par age (mois) VSD, 1991-1997

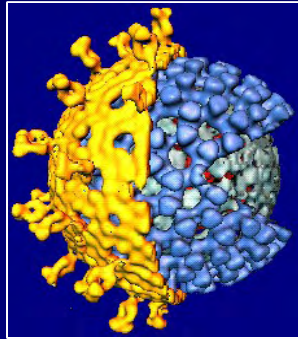


*80% des les inv. int. chez les enfants age de plus de 3 mois
lors de la premiere dose*



The next generation of rotavirus vaccines

Human rotavirus

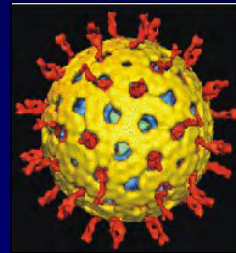


G1P[8]

GSK Bio

Rotarix

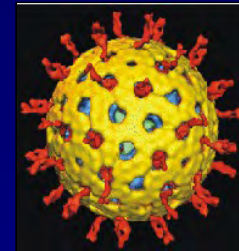
Bovine rotavirus with single human rotavirus gene substitution



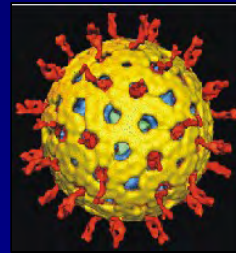
G1



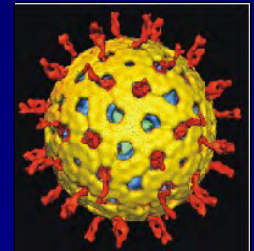
G3



P[8]



G2



G4

Merck

RotaTeq

Human-Bovine Reassortant Rotavirus Vaccine - RotaTeq® (Merck)

- *Pentavalent*
- *Liquid vaccine with buffer, stabilizer*
- *3 doses, 2ml/dose,*
- *easy to administer*
- *Grows poorly -high dose (10^{7-8}), low shedding*



Clinical Trials of Rotateq

	Vac / Placebo	Outcome	Vac Placebo	Efficacy (95%CI)
U.S., Finland	2834/2839	Any Severe	83 / 315 1 / 51	74 (67-80) 98 (88-100)
U.S.	650 /650	Any Mod/sev Severe	15 / 54 10 / 42 0 / 6	73 (51-86) 76 (52-89) 100 (13-100)

GSK Attenuated Human Rotavirus Vaccine, Rotarix®

- *Monovalent*
- *Lyophilized vaccine, needs reconstitution*
- *2 doses, 1 ml/dose*
- *Grows well -low dose ($10^{5.8}$); high shedding (>50%)*



Clinical Trials of Rotarix

	Vac/Placebo	Outcome	Vaccine Placebo	Efficacy (95%CI)
Finland,	245 / 123	Any Severe	13 / 23 2 / 10	72 (42-87) 85 (42-97)
Brazil, Mexico, Venezuela	464 / 454	Any Severe.	15 / 49 5 / 3434	70 (46-84) 86 (63-96)
Latin America	10,159 / 10,010	Severe Hosp.	<i>NA</i>	85 (72-92) 85 (77-94)

Efficacy of Rotarix

- 63,225 infants in 11 Latin American countries
- ~20,169 followed for severe GE until 12 mo.
- Efficacy - severe RVGE 85%
 - G1 disease 92%
 - non-G1 75%
 - (G2 ~50%

All GE hospitalizations 41%

Safety from Intussusception

	Followup	Vac/ Placebo	IS cases Vac/Pl	
Rotarix	31 days	31,500/ 31,500	Dose 1	1 / 2
			Dose 2	5/5
			Total	6 / 7
RotaTeq	42 days	35,150 35,150	Dose 1	0 / 1
			Dose 2	4/ 1
			Dose 3	2/ 3
			Total	6/ 5

Was Intussusception due to Rotashield alone ?

CDC Advisory Committee on Immunization Practices (ACIP) –Feb. 2006

Draft-- Recommendations for Pentavalent Bovine-Human Rotavirus Vaccine (PRV)

- Routine immunization of infants
- 3 doses at 2, 4, and 6 months of age
- Dose 1 between 6-12 weeks of age
- All doses by 32 weeks of age
- 4-10 week interval between doses



Status of Rotavirus vaccine licensure, as of 15 March 2007

GSK Rotarix® licensure (88 countries):

<i>WHO Region</i>	<i>Countries that have licensed Rotarix®</i>	
<i>Americas</i>	22	<i>Argentina, Aruba, Bolivia, Brazil, Chile, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Trinidad/Tobago, Venezuela</i>
<i>Africa</i>	17	<i>Burkina Faso, Cameroun, Central African Republic, Congo, DR Congo, Guinea, Ivory Coast, Kenya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Nigeria, Senegal, South Africa, Togo</i>
<i>Europe</i>	31	<i>Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK</i>
<i>Middle East</i>	8	<i>Bahrain, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, UAE, Yemen</i>
<i>Southeast Asia</i>	3	<i>Bangladesh, Sri Lanka, Thailand</i>
<i>Western Pacific</i>	7	<i>Australia, Hong Kong, Malaysia, New Zealand, Philippines, Singapore, Taiwan</i>



Status of Rotavirus vaccine licensure, as of 1 March 2007

Merck RotaTeq™ licensure (47 countries):

WHO Region	Countries that have licensed RotaTeq®	
Americas	12	Argentina, Canada, Curaçao, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Perú, Puerto Rico, USA
Africa	6	DRCongo, Guinea, Kenya, Niger, Rwanda, Togo
Europe	26	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Turkey, UK
Middle East	0	
Southeast Asia	0	
Western Pacific	3	Australia, Hong Kong, Taiwan



Les vaccins vivant oraux-- seront ils efficaces dans les pays en developpement ?

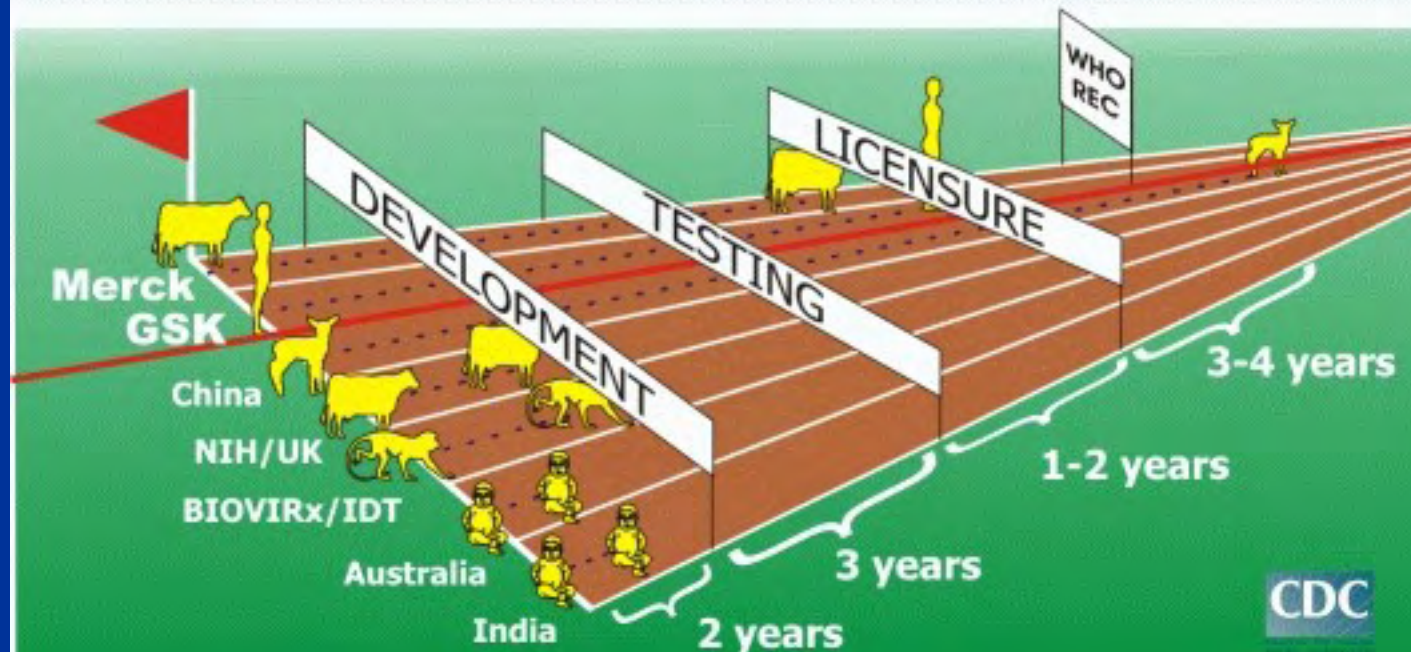
- OPV Less immunogenic/more doses needed for children in India (*T. Jacob Johns*)

- Cholera (Oralchol) Less immunogenic/higher titer needed in Thai/Indonesian studies (*Mike Levine*)

- Oral RV
 - RIT Failed in Africa/Peru
 - WC3 Failed in Africa
 - RRV Lower efficacy in Peru/Brazil
 - GSK Being tested in S.Africa/Bangladesh

Timelines

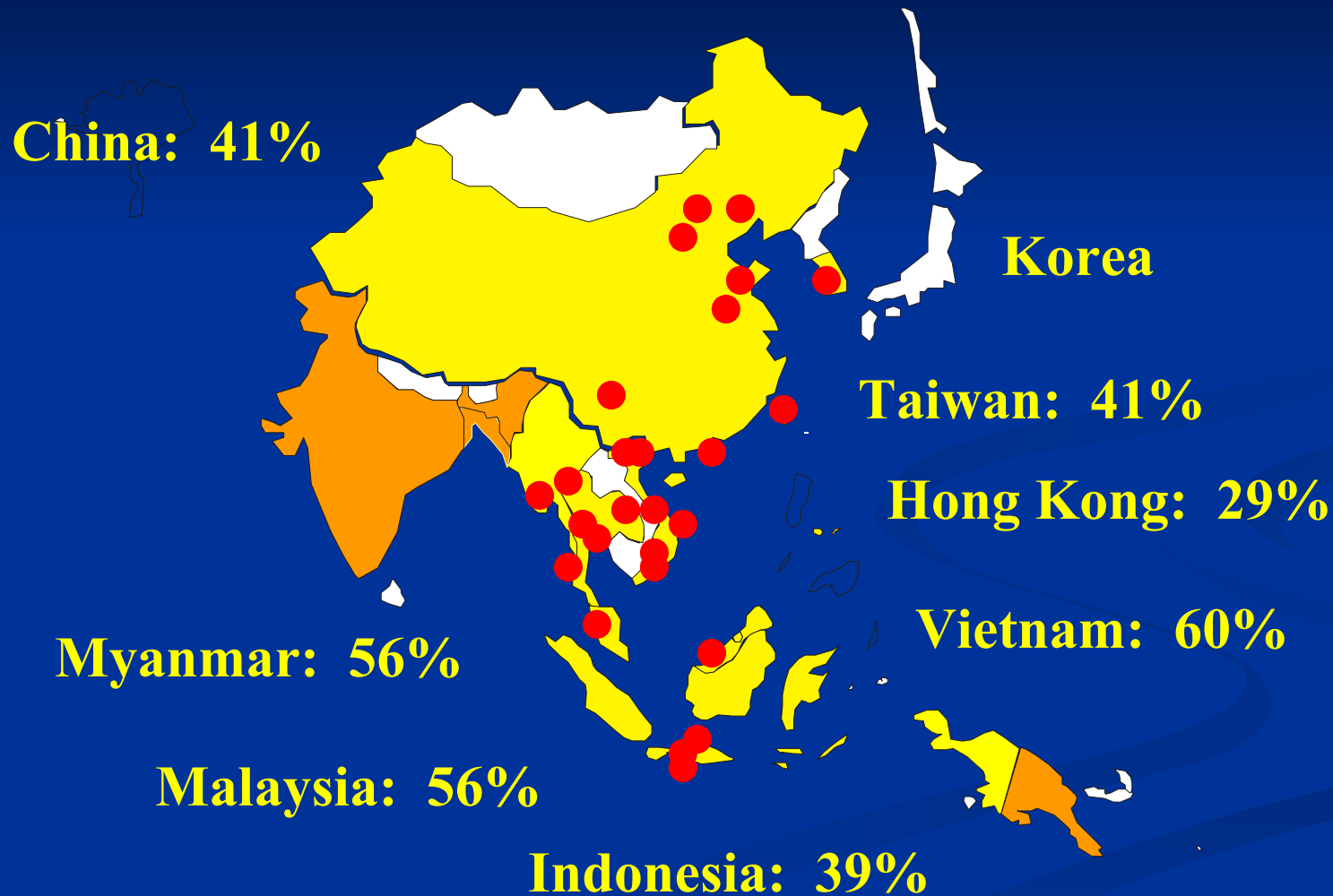
The Rotavirus Vaccine Agenda



CDC

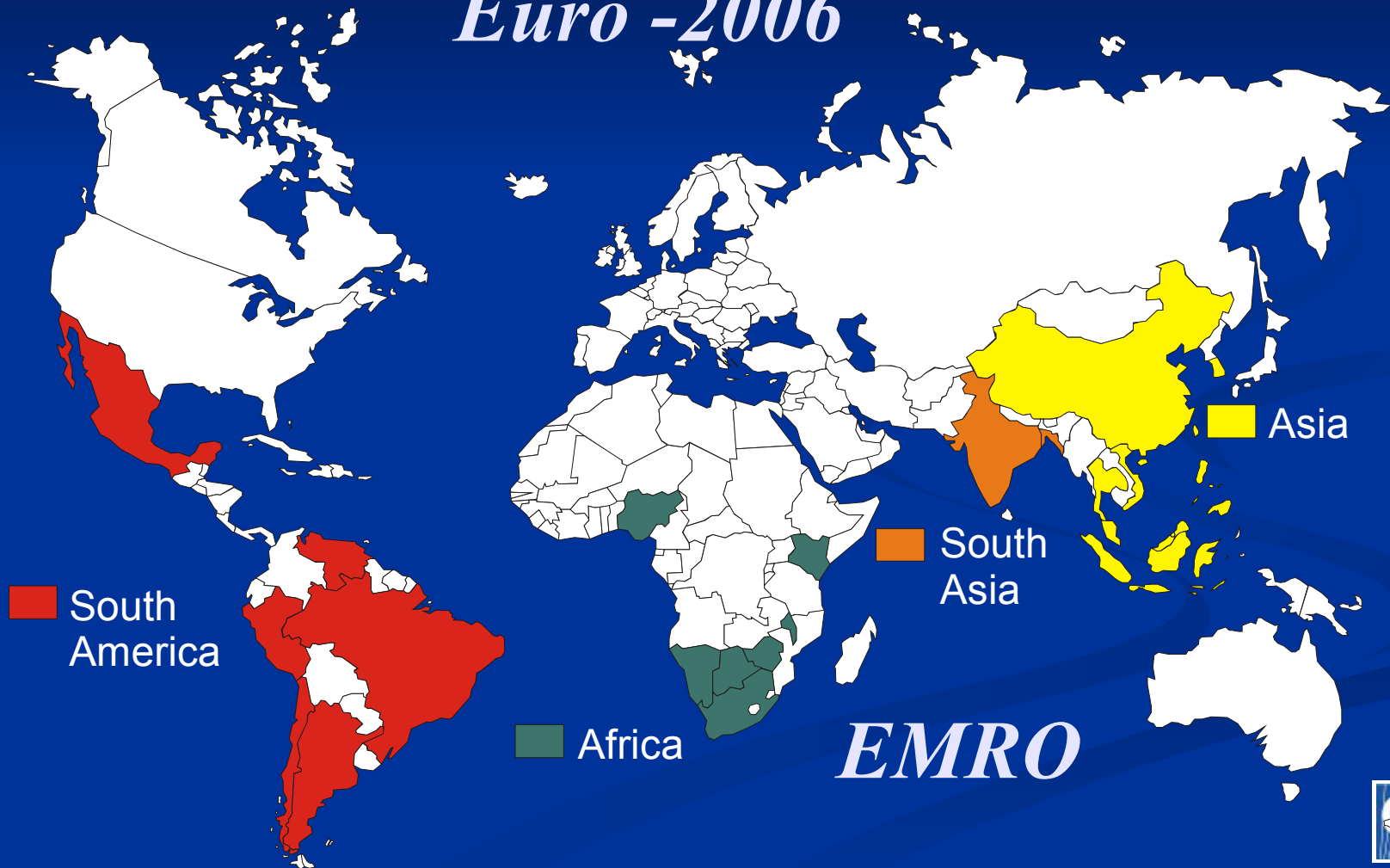


Reseau de rotavirus en Asie 2001-2003

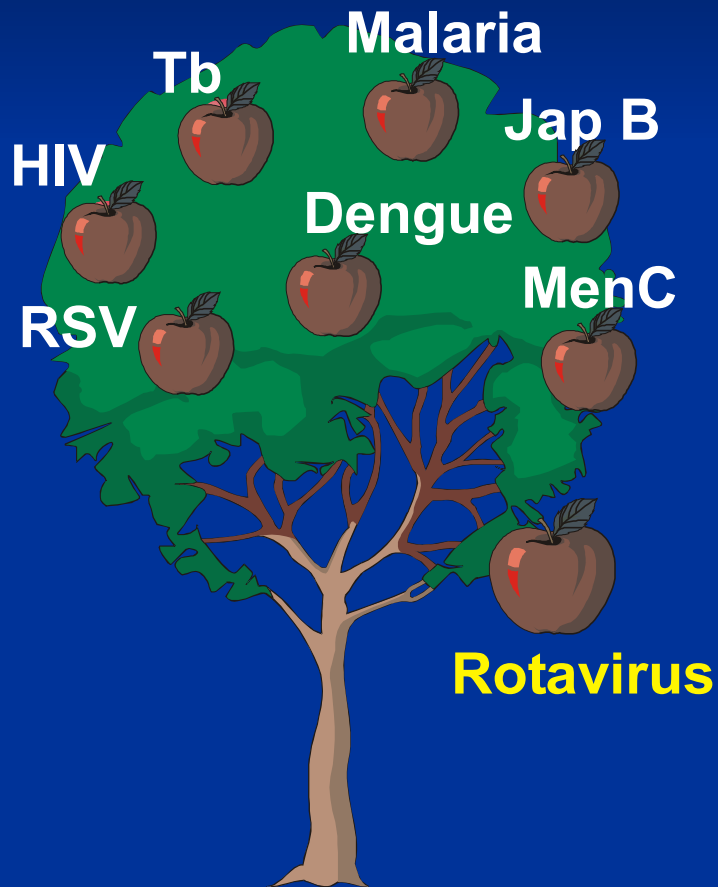


Reseaux regionaux de surveillance de rotavirus

Euro -2006

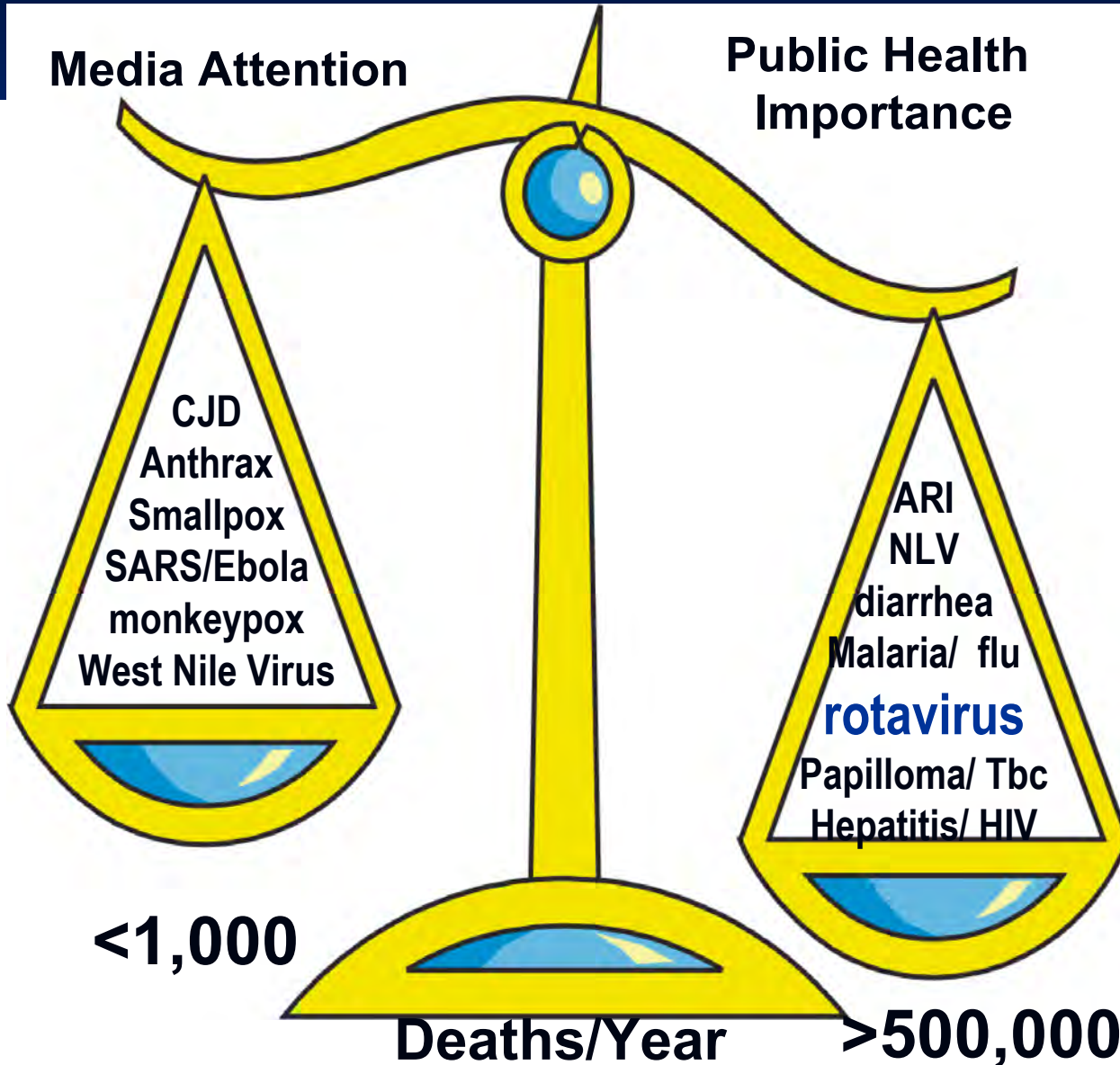


Vaccins rotavirus - “le fruit le plus mur” des vaccins en developpement



- 🍏 disease burden is large & global
- 🍏 principles to develop vaccines are well established
- 🍏 extensive past experience with clinical trials
- 🍏 achievable in 5-7 years
- 🍏 impact of vaccine should be measurable within one year

Celles qui font peur et celles qui tuent!





Utilisera-t-on le vaccin Rotavirus en Europe?

*Quelles seront les facteurs clés
de décision ?*