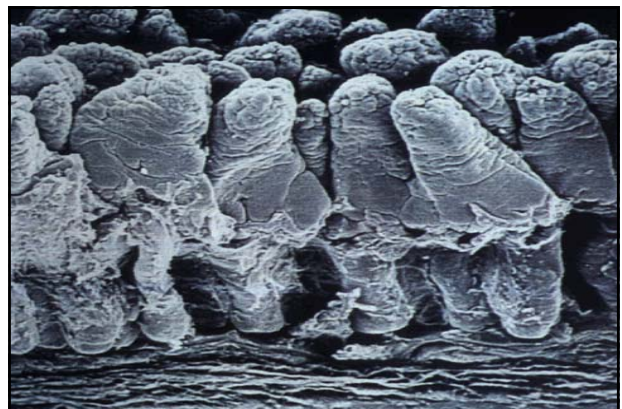
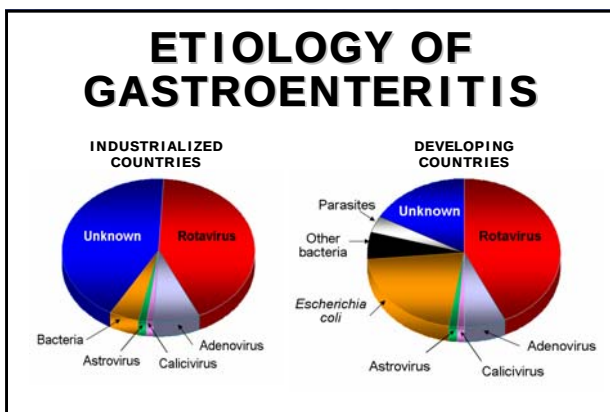


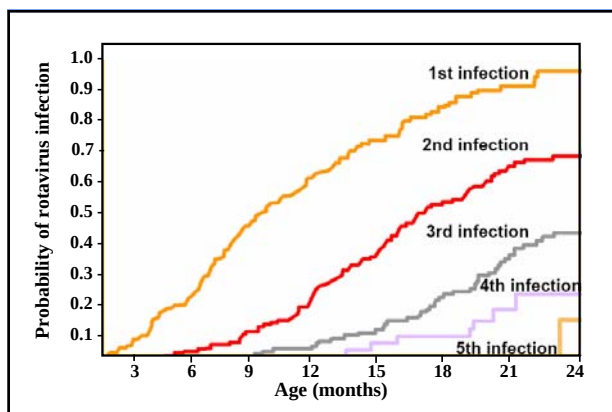


ROTAVIRUSES

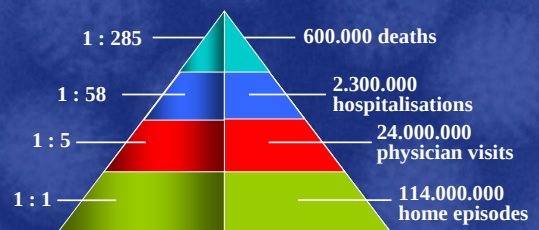
- **EPIDEMIOLOGY**
- **VIROLOGY**
- **VACCINATION**
 - Vaccine composition
 - Vaccine safety
 - Vaccine efficacy

ROTAVIRUS TRANSMISSION

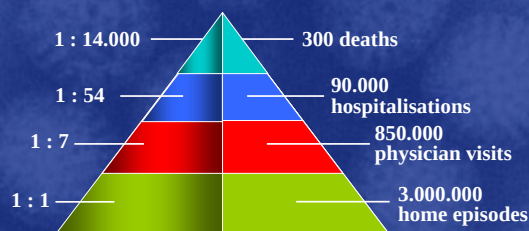
- Faecal-oral route predominant mode of transmission
 - up to one trillion viral particles shed in faeces
 - shedding begins before symptoms and persists after illness
 - fomites on contaminated objects (e.g. toys) retain infectivity for several days/weeks
- Transmission still occurs despite improved sanitation



WORLDWIDE INCIDENCE OF ROTAVIRUS-RELATED EVENTS



EUROPEAN INCIDENCE OF ROTAVIRUS-RELATED EVENTS

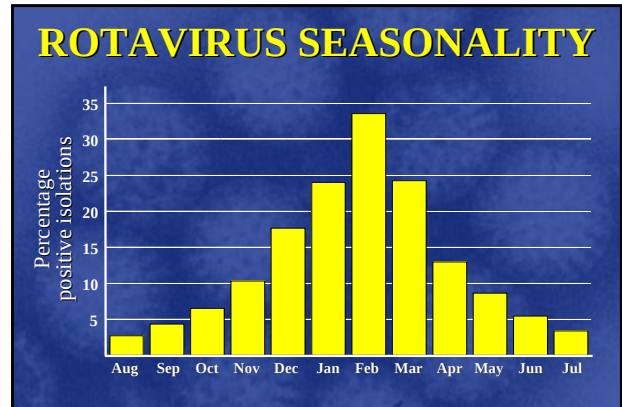
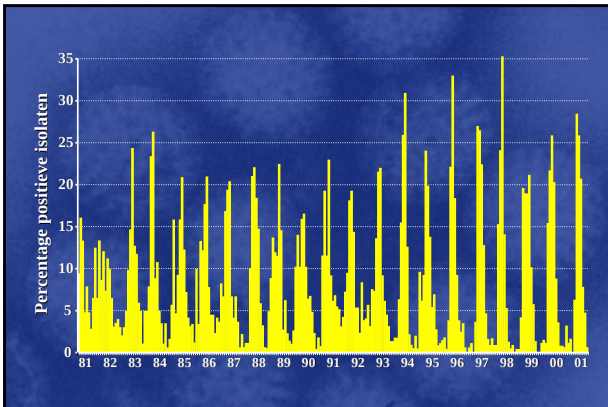


23 EU countries, 23.6 million children <5 years old

ROTAVIRUS HOSPITALISATION

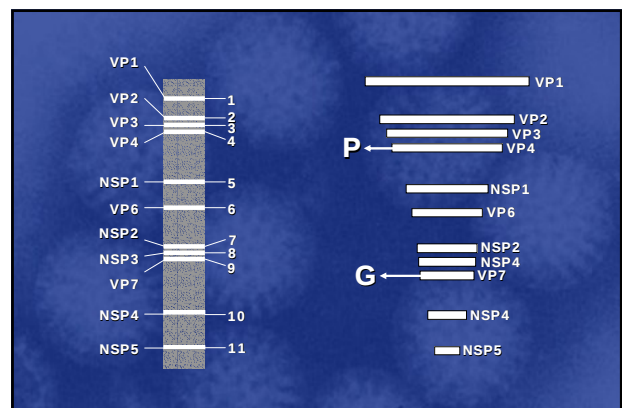
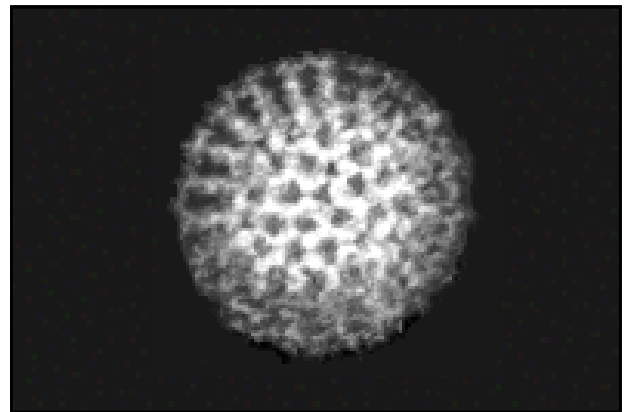
- Hospital stay for rotavirus gastroenteritis varies across countries
 - France¹ and Spain²: 4 days
 - UK: 2 days³
- Cumulative risk of hospitalisation due to rotavirus in children <5 years
 - 1/40 in UK³
 - 1/33 in Finland⁴
 - 1/20 in Poland⁵
 - 1/17 in Ireland⁶

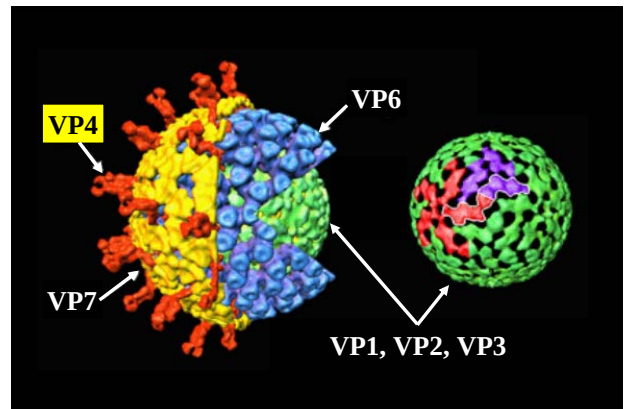
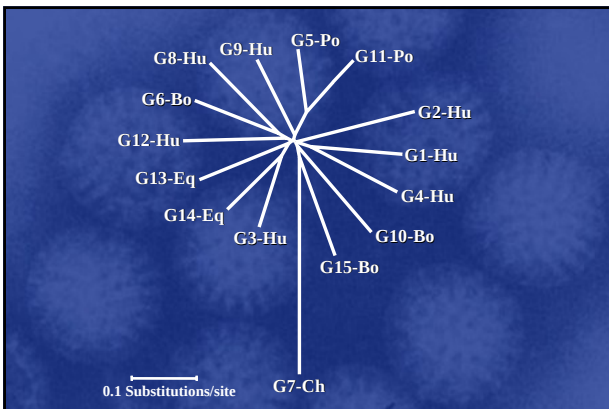
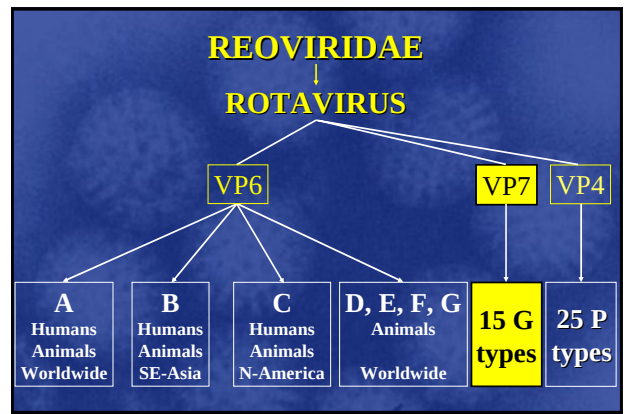
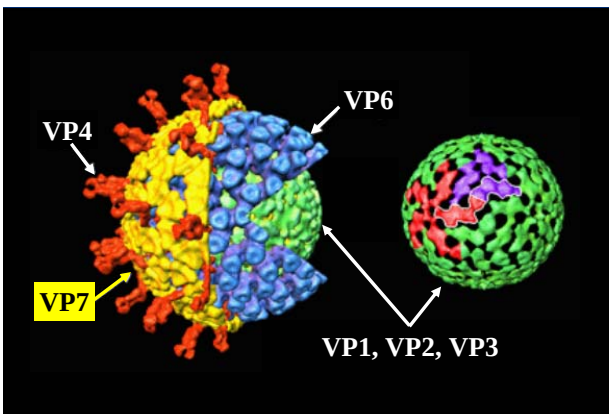
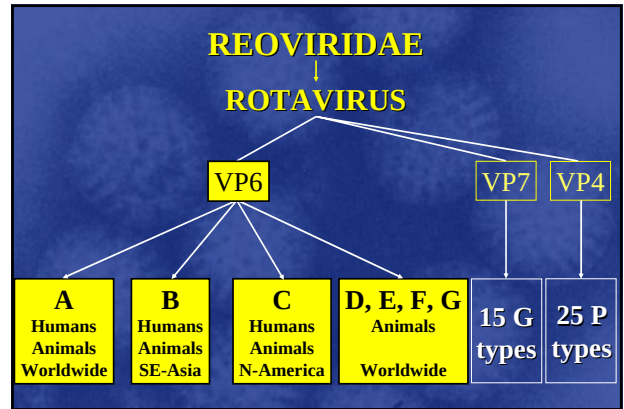
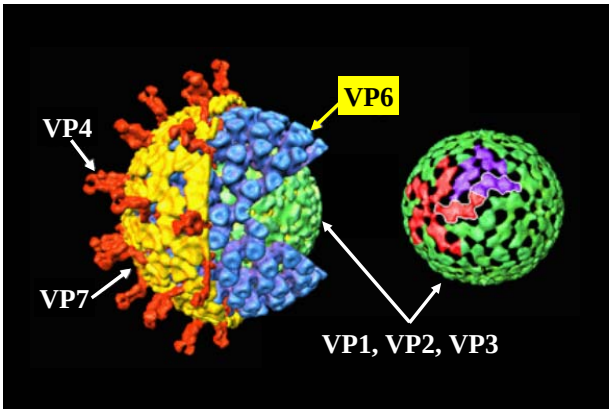
¹Marie-Cardine et al., Clin Infect Dis 2002;34(9):1170-8; ²Gil et al. Abstract, ESPID annual meeting, May 2002; ³M.J. Ryan et al., Journal of Infectious Diseases 1996;174(suppl 1):S12-6; ⁴Vesikari et al., Acta Paediatr 1999;S426:24-30; ⁵Winkiewicz et al. Abstract, JPECN 2003; ⁶M. Lynch et al., Pediatr Infect Dis J 2001;20:693-6

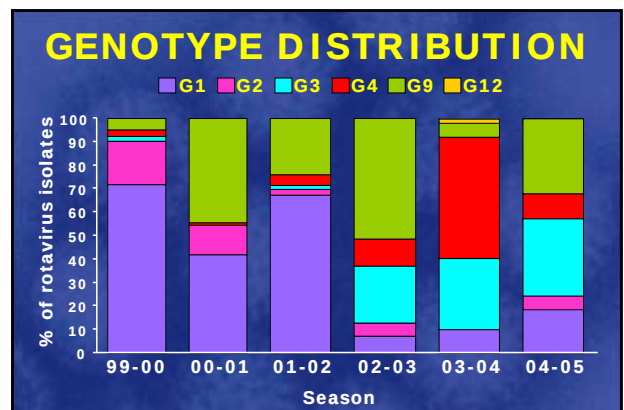
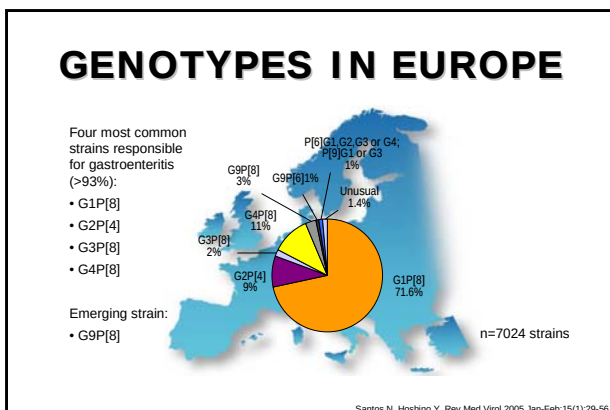
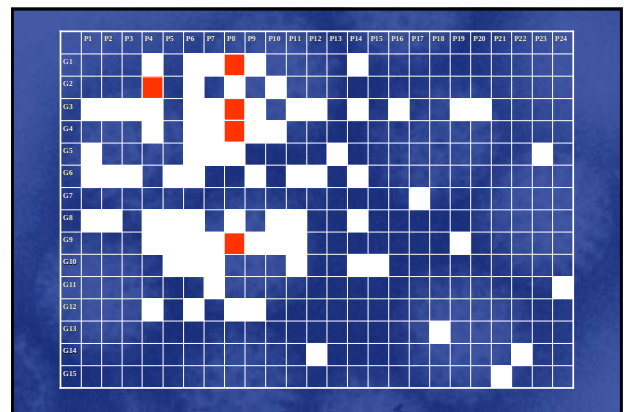
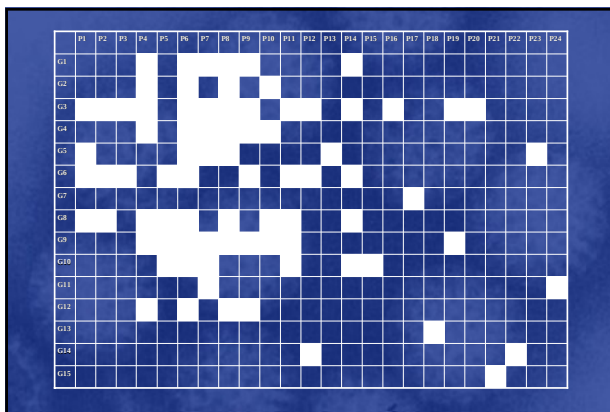
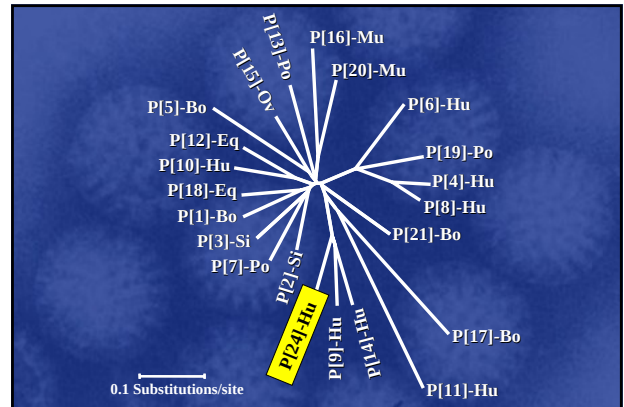
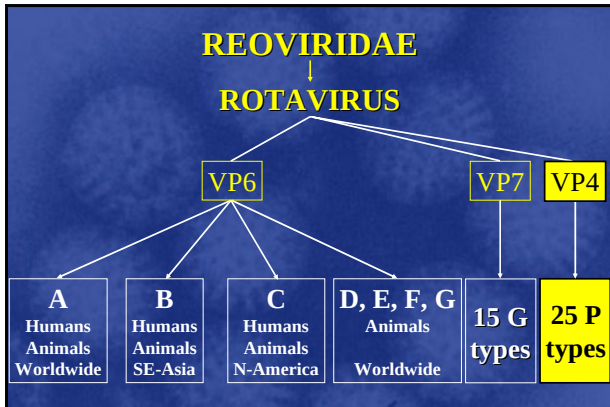


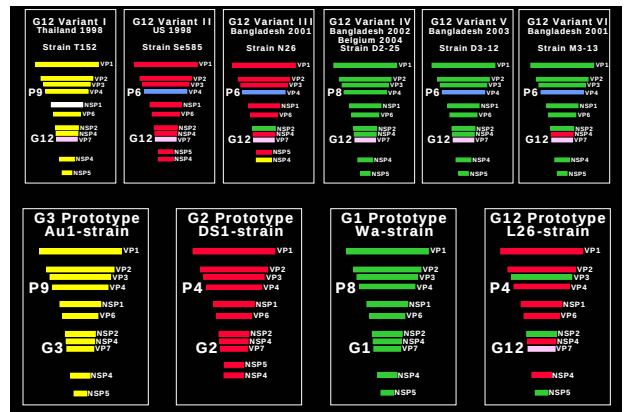
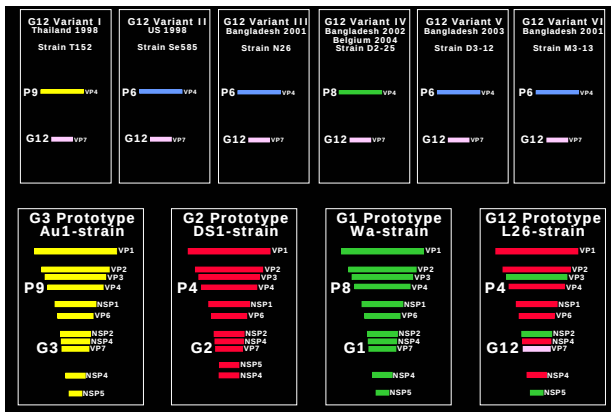
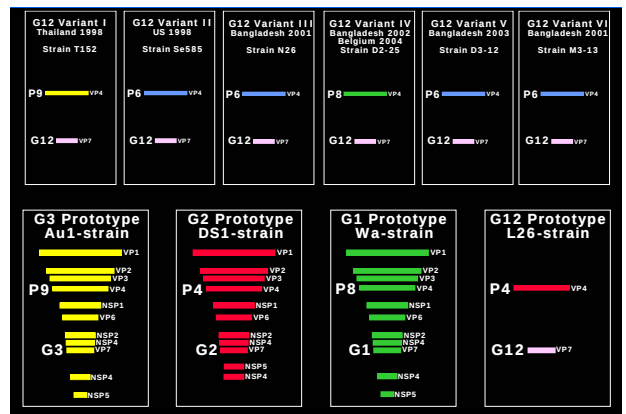
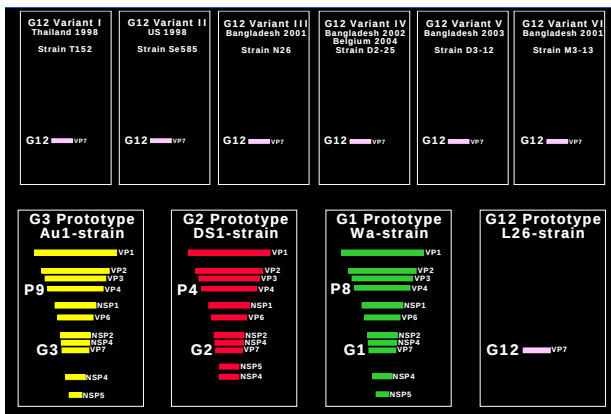
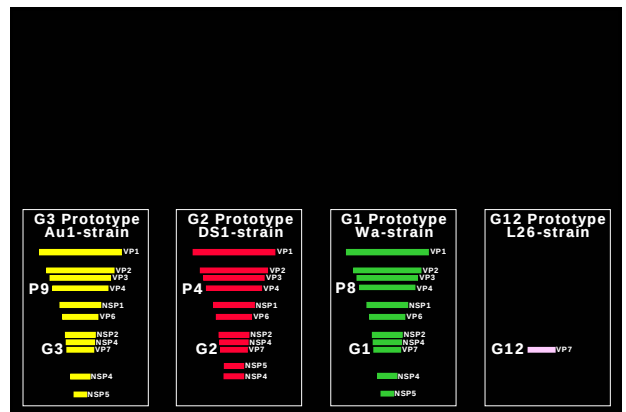
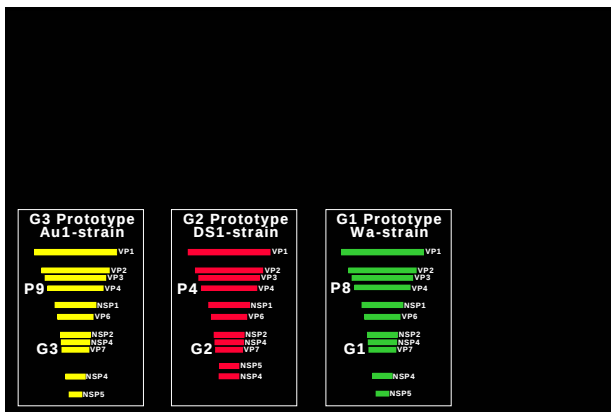
ROTAVIRUSES

- EPIDEMIOLOGY
- VIROLOGY
- VACCINATION
 - Vaccine composition
 - Vaccine safety
 - Vaccine efficacy









ROTAVIRUSES

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GOALS OF ROTAVIRUS VACCINATION

- Provide early protection, comparable to that conferred by natural rotavirus infection
- Protect against moderate/severe RVGE
- Prevent hospitalisation due to RVGE
- Reduce morbidity and socioeconomic burden

ROTAVIRUSES

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Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Guillermo M. Ruiz-Palacios, M.D., Irene Pérez-Schael, M.Sc., F. Raúl Velázquez, M.D., Hector Abate, M.D., Thomas Breuer, M.D., SueAnn Costa Clemens, M.D., Brigitte Cheuvart, Ph.D., Felix Espinoza, M.D., Paul Gillard, M.D., Bruce L. Innis, M.D., Yolanda Cervantes, M.D., Alexandre C. Linhares, M.D., Pio López, M.D., Mercedes Macías-Parra, M.D., Eduardo Ortega-Barria, M.D., Vesta Richardson, M.D., Doris Maribel Rivera-Medina, M.D., Luis Rivera, M.D., Belén Salinas, M.D., Noris Pavia-Ruz, M.D., Jorge Salmerón, M.D., Ricardo Rüttimann, M.D., Juan Carlos Tinoco, M.D., Pilar Rubio, M.D., Ernesto Nuñez, M.D., Lourdes Guerrero, M.D., Juan Pablo Yarzabal, M.D., Silvia Damaso, M.Sc., Nadia Tornieporth, M.D., Xavier Sáez-Llorens, M.D., Rodrigo F. Vergara, M.D., Timo Vesikari, M.D., Alain Bouckennooghe, M.D., Ralf Clemens, M.D., Ph.D., Béatrice De Vos, M.D., Miguel O'Ryan, M.D., for the Human Rotavirus Vaccine Study Group



Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine

Timo Vesikari, M.D., David O. Matson, M.D., Ph.D., Penelope Dennehy, M.D., Pierre Van Damme, M.D., Ph.D., Mathuram Santosham, M.D., M.P.H., Zoe Rodriguez, M.D., Michael J. Dallas, Ph.D., Joseph F. Heyse, Ph.D., Michelle G. Goveia, M.D., M.P.H., Steven B. Black, M.D., Henry R. Shinefield, M.D., Celia D.C. Christie, M.D., M.P.H., Samuli Vittal, M.D., Robbin F. Itzler, Ph.D., Michele L. Coia, B.A., Matthew T. Onorato, B.S., Ben A. Adeyi, M.P.H., Gary S. Marshall, M.D., Leif Gotheffors, M.D., Dirk Campens, M.D., Aino Karvonen, M.D., James P. Watt, M.D., M.P.H., Katherine L. O'Brien, M.D., M.P.H., Mark J. DiNubile, M.D., H. Fred Clark, D.V.M., Ph.D., John W. Boslego, M.D., Paul A. Offit, M.D., Penny M. Heaton, M.D., for the Rotavirus Efficacy and Safety Trial (REST) Study Team

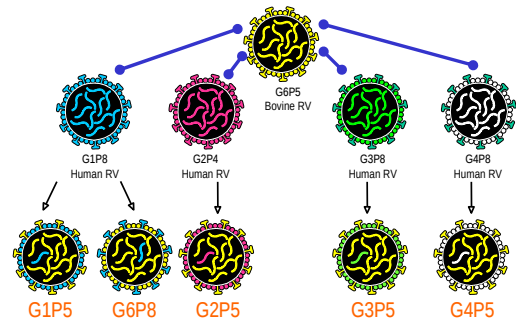
ROTARIX/ROTATEQ

Parameters	Rotarix	Rotateq
Company	GlaxoSmithKline Biologicals	Merck & Co.
Origin	Human	Human/bovine reassortant
Valency	Monovalent	Pentavalent
Serotypes	PI[8]G1	PI[8], G1, G2, G3, G4*
Number of doses	Two	Three
Phase III studies		
No. children	63,225 (safety) 20,169 (efficacy)	70,301 (safety) 5673 (efficacy)
Countries tested	Latin America, Finland	USA, Central America, Europe
Efficacy (95% CI)		
Any RV gastroenteritis	Unavailable	74% (66.8–79.9)
Severe RV gastroenteritis	84.7% (71.7–92.4)	98% (88.3–100.0)
Heterotypic protection	75.4% (50.0–89.0) [§]	Few non-G1 strains [§]
Intussusception	No increased risk	No increased risk
Vaccine status	Licensed in Mexico [§]	Submitted to FDA and EMEA

ROTARIX: MONOVALENT



ROTATEQ: PENTAVALENT



ROTARIX



TARGETS

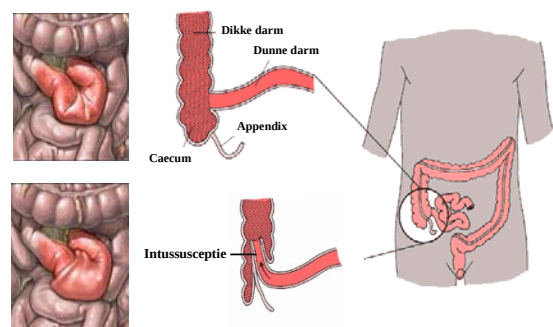


ROTATEQ



ROTAVIRUSES

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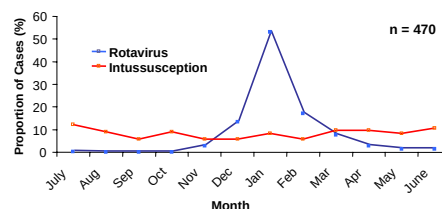
INTUSSUSCEPTION

Age of Rotashield vaccination and IS risk

Age at first dose	IS cases	Vaccinees	Incidence of IS per 100.000 doses
All	45	433.222	10
< 90 days	9	268.202	3
> 90 days	36	165.019	22

INTUSSUSCEPTION

Seasonal distribution in children <3 years



Chang et al Pediatr Infect Dis J 2002 21:97-102

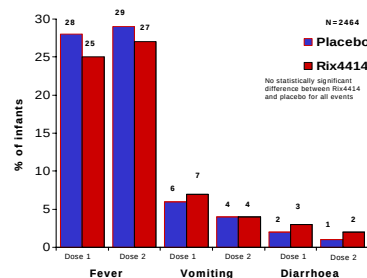
NO INTUSSUSCEPTION RISK

- Phase III trial involving over 60,000 subjects showed no increased risk of IS between Rix4414 & placebo¹

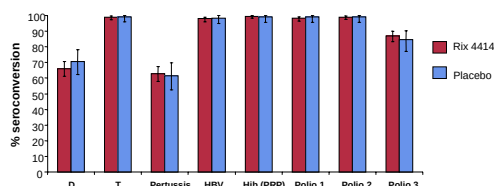
Timing of IS	Rix4414 n ~ 31,000	Placebo n ~ 31,000	Relative risk IS Rix4414 vs Placebo (95% CI)
IS cases within 31-day window	6	7	0.85 (0.30;2.42)
IS cases between dose 1 and 30-90 days post dose 2	9	16	0.56 (0.25;1.24)

¹Ruiz-Palacios GM et al. New Engl J Med 2006;354(1):11-22

REACTOGENICITY



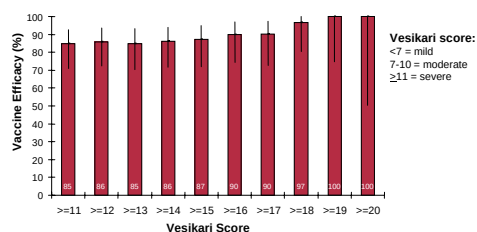
CO-ADMINISTRATION WITH OTHER VACCINES



ROTAVIRUSES

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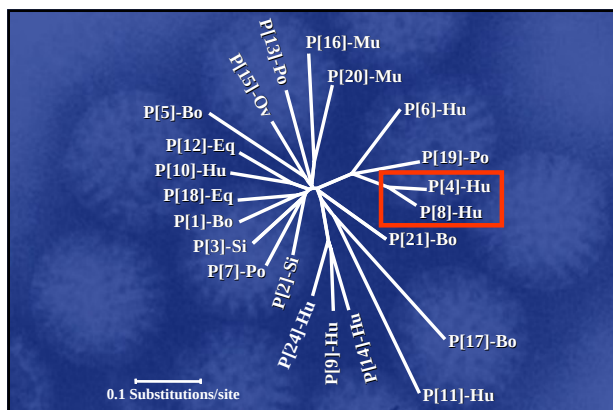
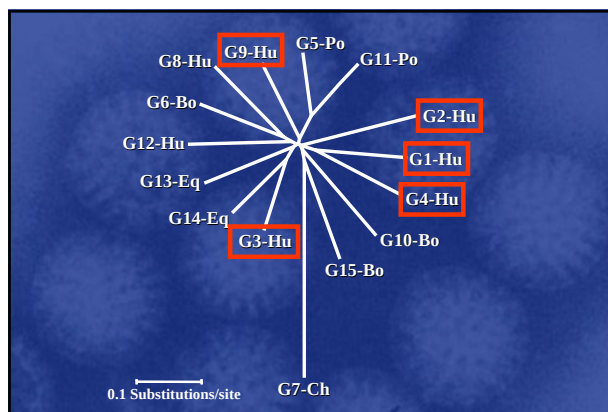
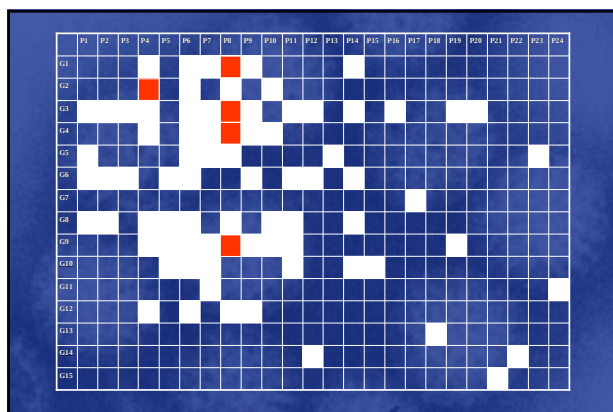
VACCINE EFFICACY



VACCINE EFFICACY

Endpoint	Vaccine efficacy % (CI)
RVGE	87 (79-92)
Severe RVGE	96 (90-99)
Hospitalisation RVGE	100 (82-100)

Rotarix : European efficacy study (036)



VACCINE EFFICACY

Group	N	n	%	P-value
G1 P8				
Rotarix	2572	2	96	<0.001
Placebo	1302	28		
G2 P4				
Rotarix	2572	1	75	0.263 N = too small
Placebo	1302	2		
G3 P8				
Rotarix	2572	0	100	0.004
Placebo	1302	5		
G4 P8				
Rotarix	2572	0	100	<0.001
Placebo	1302	7		
G9 P8				
Rotarix	2572	2	95	<0.001
Placebo	1302	19		

Rotarix : European efficacy study (036)

VACCINE EFFICACY

	Rotarix 023	Rotarix 036	Rotateq
Any RVGE	72	87	74
Severe RVGE	85	96	96
Hospitalisation	85	100	98

Rotarix : Latin America study (023)
European efficacy study (036)

VACCINATIE KALENDER

VACCIN	LEEF TIJD	2 MAAND	3 MAAND	4 MAAND	12 MAAND	15 MAAND	18 MAAND	5-7 JAAR	10-12 JAAR	14-16 JAAR
Poliomyelitis ⁽¹⁾	IPV	IPV	IPV		•	IPV	•	IPV		
Difterie- Tetanus- Diphtherie ⁽²⁾	DTPa	DTPa	DTPa		•	DTPa	•	DTPa		DT
Hepatitis B ⁽³⁾	HB	HB	HB		•	HB	•			
Hepatitis B ⁽³⁾	HBV	HBV	HBV		•	HBV	•		HBV	
Mazelen Dif Rubeola ⁽⁴⁾				MMR ₁	•			MMR ₂	MMR ₂	MMR ₂
Meningokok C ⁽⁵⁾					•	MenC	•			
Parusokok ⁽⁶⁾	Pa7V		Pa7V	Pa7V	•					
Rotavirus ⁽⁷⁾	ROTA	ROTA	(ROTA)							

