

The Oral Rotavirus Vaccine

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Interactive Session.....

- 1. Which age group has the highest incidence of confirmed rotavirus disease?
 - <1, 1-4, 5-14, 15-24, 25-44, 45-64, 65+
- 2. Which age group has the highest number of cases of confirmed rotavirus disease?
 - <1, 1-4, 5-14, 15-24, 25-44, 45-64, 65+y
- 3. Where do adults get rotavirus from? Who are these adults?
- 4. Where do toddlers (1-4 year-olds) get rotavirus from?
- 5. Where do infants (<1 year-olds) get rotavirus from?



2006 – Two Oral Rotavirus Vaccines







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Number 1

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., Brijtte 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., Plo López, M.D., Mercedes Macías-Parra, M.D., Eduardo Ortega-Barría, M.D., Vesta Richardson, M.D., Doris Maribel Rivera-Medina, M.D., Luis Rivera, M.D., Belén Salinas, M.D., Noris Pavía-Ruz, M.D., Jorge Salmerón, M.D., Ricardo Rüttimann, M.D., Juan Carlos Tinoco, M.D., Pilar Rubio, M.D., Ernesto Nuñez, M.D., M. Lourdes Guerrero, M.D., Juan Carlos Tinoco, Silvia Damaso, M.Sc., Nadia Tornieporth, M.D., Xavier Sáez-Llorens, M.D., Rodrigo F. Vergara,

The NEW ENGLAND JOURNAL of MEDICINE

Volume 354

January 5, 2006

Number 1

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.
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Figure 1. Number of positive and total rotavirus tests from 25 continuously reporting National Respiratory and Enteric Virus Surveillance System laboratories, by week of year and region, June 2000–July 2012, 3-week moving average.

Source: Rha et al., 2014



1 Number of hospitalisations* coded as rotavirus gastroenteritis (all ages) and infant rotavirus vaccine coverage,[†] Australia, July 2001 to June 2010



*By month of admission. † Coverage was calculated using data from the Australian Childhood Immunisation Register by 3-month birth cohorts born between 1 July 2007 and 31 March 2009, and the coverage assessment date was 12 months after the last birth date of each cohort.

Source: Dey et al., 2012



Indirect impact on older children

Age	Decline in rotavirus hospitalization rate (2008 vs. 2006)	Rotavirus vaccine coverage in 2008 (≥1 dose)					
<1 year	66%	56%					
1 - <2 years	95%	44%					
2 - <3 years	85%	<1%					
This age cohort was NOT eligible to receive rotavirus vaccine							



Lopman et al, JID 2011

First Dose Ś 20-Public Health intussusception England 15 Vaccination 10-5 No. of Infants with Intussusception Risk of IS -3030 50 148 -70 -60-50-40-20-1010 20 40 60 70 0 in infants Second Dose following 10-**Rotashield** 5 vaccination in the US 0 10 20 30 40 50 60 70 0 Third Dose 10-5 0 20 50 70 10 30 40 60 0 Days



Intussusception and rotavirus infection

Table 1: Seasonal Distribution of Rotavirus Disease and Intussusception in children < 3 yrs old (WHO Conference, 2000)



Intussusception Risk and Disease Prevention Associated With Rotavirus Vaccines in Australia's National Immunization Program

- Relative risk of IS for Rotarix® was
 - **6.8** (95% CI, 2.4–19.0; P<0.001) @ **1-7** days after first dose
 - **3.5** (95% CI, 1.3-8.9; P=0.01) @ 8-21 days after first dose
 - **2.8** (95% CI, 1.1-7.3; P=0.03) @ 1-7 days after second dose
- Relative risk of IS for Rotateq® was
 - 9.9 (95% CI, 3.7-26.4; P<0.001) @ 1-7 days after first dose
 - **6.3** (95% CI, 2.8-14.4; P<0.001) @ 8-21 days after first dose
 - **2.8** (95% CI, 1.2-6.8; P=0.03) @ 1-7 days after second dose
- Excess of 14 annual IS cases and >6500 fewer gastroenteritis hospitalizations
- Vaccine attributable risk for IS was
 - **4.3** (95% CI, 0.8–23.3) cases/100,000 infants vaccinated (Rotarix)
 - 7.0 (95% CI, 1.5–33.1) cases/100,000 infants vaccinated (Rotateq)



Rotavirus in the UK





Rotavirus: burden

- In England and Wales, in children <5 years of age:
- 90-133,000 GP consultations (25% of GP consultations for gastroenteritis)
- > 37,000 NHS Direct calls (27% of NHS direct calls for gastroenteritis)
- ➢ 30,000 A&E attendances
- 14,000 hospital admissions (45% of gastroenteritis admissions)

Estimated annual cost of £14.8 million

13



Rotavirus: Seasonal Variation



14

Admissions attributable to each organism

Episodes coded as "infectious intestinal disease"





Rotavirus infection: age in months





The UK infant immunisation schedule (changes in 2013)

- 2 monthsDTaP/IPV/Hib + PCV13 + Rotarix3 monthsDTaP/IPV/Hib + MenC + Rotarix
- 4 months DTaP/IPV/Hib + MenC + PCV13
- 12/13 months MMR + Hib/Men C CV13
- Pre-school DTaP-IPV (polio) + MMR

12-13 years HPV (girls)

13-18 years Td/IPV(polio)



More on RotaShield and Intussusception: The Role of Age at the Time of Vaccination

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¹National Institute of Allergy and Infectious Diseases, and ²Fogarty International Center, Care Research and Quality, Bethesda, Maryland

The Journal of Infectious Diseases 2005; 192:S36-43

Background. RotaShield, a vaccine intended to prevent severe rotavirus diarrhea, was withdrawn in July 1999, 9 months after it became available in the United States, because of a temporal association with intussusception events that occurred in vaccinated infants. We explore here the effect of age on the risk of intussusception.

Methods. We reanalyzed a case-control database of the Centers for Disease Control and Prevention by use of a 21-day window, to define vaccine-associated events. We obtained data on vaccine use from the National Immunization Survey and estimated the age-stratified background incidence of intussusception by use of Healthcare Cost and Utilization Project data. We combined these data to estimate how absolute risk varies with age and to model the projected population-attributable risk associated with 3 different vaccination schedules.

We found that the incidence of intussusception associated with the first dose of vaccine increased with age

the neonatal period projected L influssusception event/38.000-59.000 vaccine recipients.

Conclusion contributed di implemented i in the inciden

First dose: 6-15 weeks *Second dose:* <24 weeks

ch-up" vaccination, RotaShield. A fully most, a 7% increase



Coverage of Rotavirus Vaccination in infants

- Immunisation coverage:
 - CPRD data MHRA (Jan 2014, 6% E&W population)
 - > 89% by 3 months and 93% by 4 months: received at least one dose
 - 78% by 4 months, 81% by 5 months and 93% by 6 months: received two doses
 - Automated extracts from GP systems in England via ImmForm website (Feb 2014, 49% of GP practices in England)
 - > 93% by 25 weeks: received one dose
 - ➢ 88% by 25 weeks: received two doses



Weekly rate of laboratory-confirmed rotavirus infections (per 1,000,000) England and Wales, 2000-2014





Weekly rate of laboratory-confirmed rotavirus infections (per 1,000,000) by age group England and Wales, 2000/01-2012/13 (mean) vs. 2013/14





Weekly rate of AGE hospitalisations (per 1,000,000) by age group England and Wales, 2000/01-2012/13 (mean) vs. 2013/14









Laboratory-confirmed rotavirus infections										
Age group (years)	Mean 2000-01 to 2012-13 (minimum)	2013-14	RR (95% CI)	RR (95% CI)		Number averted				
<1	6,041 (5,310)	1,402	0.23 (0.16	-0.32)	<0.0001	4,810				
1	5,417 (4,895)	2,083	0.34 (0.23	-0.50)	<0.0001	4,026				
2	1,696 (1,402)	604	0.36 (0.24	-0.52)	<0.0001	1,087				
3	617 (534)	207	0.34 (0.23	-0.50)	<0.0001	405				
4	316 (257)	112	0.35 (0.23	-0.52)	<0.0001	210				
≥5†	788 (652)	343	0.50 (0.37	-0.67)	<0.0001	246				
All ages						10,884				
All-cause AG	All-cause AGE hospital admissions									
Age group	Mean	2013-14	RR (95% CI)		p value	Number				
(years)	2007-08 to 2012-13					averted				
	(minimum)									
<1	20,663 (20,131)	15,101	0.74 (0.65-0.84)		<0.0001	5,256				
1	14,678 (14,019)	10,078	0.67 (0.54-0.82)		<0.0001	4,648				
2	6,108 (5,760)	4,524	0.73 (0.61-0.88)		<0.0001	1,565				
3	3,490 (3,074)	2,986	0.81 (0.69-0.94)		<0.0001	710				
4	2,490 (2,197)	2,402	0.88 (0.77-1.00)		0.006	333				
5-14	11,426 (10,446)	11,782	0.92 (0.87-0.98)		<0.0001	1,020				
15-44	64,381 (56,408)	70,781	0.92 (0.90-0.94)		<0.0001	6,043				
45-64	64,734 (53,920)	71,082	0.88 (0.86-0.90)		<0.0001	9,484				
≥65	133,468 (121,978)	134,079	0.86 (0.83-0.90)		<0.0001	21,368				
All ages						50,427				

2

TES,



Laboratory-confirmed rotavirus disease England & Wales (up to 10 March 2016)



*Comparison is made with this ten year period as it is prior to the vaccine introduction.



The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Dose	Risk period (days)	Cases in risk period	RI (95% CI*)
1	1-7	15	13.81 (6.44-28.32)
	8-21	5	1.59 (0.34-3.75)
	1-21	20	3.94 (2.03-6.69)
2	1-7	5	2.20 (0.50-5.02)
	8-21	14	2.77 (1.36-5.32)
	1-21	19	2.48 (1.34-4.50)





The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Feature	1-7 days post first dose n/N (%)	Out of risk period- baseline** n/N (%)	Odds ratio (95%Cl)*	
Treatment				
Radiological	8/15 (53.3%)	30/56 (53.6%)	0.96 (0.24-3.91)	
Surgical	7/15 (46.7%)	22/56 (39.3%)	1.58 (0.38-6.59)	
Days from onset to admission				
Same day	5/15 (33.3%)	29/56 (51.8%)	1.04 (0.24-4.60)	
Mean (range) in days	0.71 (0-4)	0.77 (0-4)		
Duration of admission				
0-1 days	9/15 (60.0%)	32/56 (57.1%)	0.44 (0.11-1.85)	
Mean (range) in days	0.33 (0-8)	0.50 (0-12)		
Gender				
Male	10/15 (66.7%)	37/56 (66.1%)	0.54 (0.11-2.58)	



The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

	Period post dose 1			Period post dose 2				
Country	1-7 days	8-21 days	1-21 days	1-7 days	8-21 days	1-21 days		
Australia	6.76 (2.40-19.01)	3.45 (1.33-8.94)	4.55 (2.21-9.38)*	2.84 (1.10-7.34)	2.11 (0.97-4.62)	2.35 (1.28-4.33)*		
Mexico	5.30 (3.00-9.30)	0.99 (0.52-1.91)	2.43 (1.51-3.90)*	1.8 (0.90-3.80)	2.20 (1.40-3.45)**	2.07 (1.41-3.04)*		
Singapore	8.36 (2.42-28.96)	0.00	2.85 (1.13-7.19)*	3.09 (0.41-12.37)	1.54 (0.20-11.69)	2.06 (0.47-8.94)*		
England	13.81 (6.44-28.32)	1.59 (0.34-3.75)	3.94 (2.03-6.69)	2.20 (0.50-5.02)	2.77 (1.36-5.32)	2.48 (1.34-4.50)		
Pooled [^]	7.50 (5.07-11.09)	1.41 (0.87-2.30)	3.17(2.32-4.33)	2.21 (1.35-3.61)	2.29 (1.64-3.19)	2.21 (1.67-2.93)		



Rotavirus & Seizures

- Ueda et al. Clinical characteristics of seizures associated with viral gastroenteritis in children. Epilepsy Res. 2015 Jan;109:146-54.
- Lee et al. Neonatal seizures accompanied by diffuse cerebral white matter lesions on diffusion-weighted imaging are associated with rotavirus infection. Eur J Paediatr Neurol. 2014 Sep;18(5):624-31.
- Park et al. Incidence of benign convulsions with mild gastroenteritis after introduction of rotavirus vaccine. Brain Dev. 2015 Jun;37(6):625-30.
- Yeom et al. Impact of rotavirus vaccine introduction on rotavirus-associated seizures and a related possible mechanism. J Child Neurol. 2015 May;30(6):729-34
- Yeom et al. Distinctive pattearn of white matter injury in neonates with rotavirus infection. Neurology. 2015 Jan 6;84(1):21-7.
- Oh et al. Association of Rotavirus With Seizures Accompanied by Cerebral White Matter Injury in Neonates. J Child Neurol. 2015 Oct;30(11):1433-9.



Protective Association Between Rotavirus Vaccination and Childhood Seizures in the Year Following Vaccination in US Children

Daniel C. Payne,¹ James Baggs,² Danielle M. Zerr,^{3,4} Nicola P. Klein,⁵ Katherine Yih,⁶ Jason Glanz,⁷ Aaron T. Curns,¹ Eric Weintraub,⁸ and Umesh D. Parashar¹

Data on 250 601 infants, including 186 502 children fully vaccinated (74.4%) and 64 099 (25.6%) not vaccinated with rotavirus vaccine.

After adjusting for covariates, a statistically significant protective association was seen between a full rotavirus vaccination course vs no vaccination:

➢ First-ever seizures: risk ratio [RR] = 0.82; 95% CI, 0.73–0.91

➤All seizures (RR = 0.79; 95% CI,).71-.88).

Conclusions: rotavirus vaccination was statistically associated with an 18%–21% reduction in risk of seizure requiring hospitalization or A&E care in the year following vaccination,



th Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures

Jacobo Pardo-Seco, *† Miriam Cebey-López, *† Nazareth Martinón-Torres, MD, PhD, *† Antonio Salas, PhD, *† José Gómez-Rial, MSc, † Carmen Rodriguez-Tenreiro, PhD, *† José María Martinón-Sánchez, MD, PhD, *† and Federico Martinón-Torres, MD, PhD*†

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Rotavirus Vaccine in the UK: Summary of the programme

- 1. The **oral** rotavirus vaccine (Rotarix®) was introduced into the UK national infant immunisation programme on 01 July 2013
- 2. All infants born from 01 May 2013 onwards are eligible
- 3. Aim was to protect as many infants as possible before the next rotavirus season (January-April 2014)
- 4. No catch-up programme for older infants and children
- 5. First dose must be given between 6 and 15 weeks chronological age
- 6. Second dose must be given before 24 week chronological age (<6 mths)
- 7. Surveillance data indicate a massive impact on disease burden across all age groups



Rotavirus Vaccine in the UK: LESSONS LEARNT

- 1. Stool samples in 2 & 3 MONTH olds coming to A&E with Diarrhoea
- 2. Small but significant increase is the risk of intussusception after both doses, but especially in the first 7 days after the first dose of vaccine
- 3. Suspect early \rightarrow refer quickly \rightarrow radiological reduction
- Previous intussusception is a contra-indication to rotavirus vaccination – 10 infants with IS were vaccinated, no complications



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- PHE Virus Reference Department: David James Allen, Sameena Nawaz, David Brown
- Medicines and Healthcare Products Regulatory Agency: Katherine Donegan
- PHE Sentinel Sites
- GP surgeries





Rotavirus Surveillance: England & Wales

- Laboratory-confirmed cases through LabBase2
 - Linkage of HES and LabBase2: nosocomial infections
- Molecular epidemiology of rotavirus isolates and impact of routine vaccination (hospital laboratories & PHE VRD)
- Vaccine Effectiveness: using cases reported through LabBase2 and isolates submitted to PHE VRD
- Data sources for GP consultations: GPRD, RCGP, etc.
- Safety using data linkage: intussusception



The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Historical cases for age effect	Dose	Risk period (days)	Cases in risk period	RI (95% CI*)
Yes	1	1-7	15	13.81 (6.44-28.32)
		8-21	5	1.59 (0.34-3.75)
		1-21	20	3.94 (2.03-6.69)
	2	1-7	5	2.20 (0.50-5.02)
		8-21	14	2.77 (1.36-5.32)
		1-21	19	2.48 (1.34-4.50)
No	1	1-7	15	8.50 (3.27-28.75)
		8-21	5	1.18 (0.28-3.99)
		1-21	20	3.00 (1.48-6.44)
	2	1-7	5	1.74 (0.37-5.16)
		8-21	14	2.74 (1.22-5.89)
		1-21	19	2.33 (1.23-4.75)



Global Burden of Rotavirus infection (2008)







Rotavirus mortality in children younger than 5 years, 2008









Infant Rotavirus Vaccination May Provide Indirect Protection to Older Children and Adults in the United States

Ben A. Lopman, Aaron T. Curns, Catherine Yen, and Umesh D. Parashar

Cause-unspecified discharges

Rotavirus discharges

Age (years)	Median 2000–2006 (minimum)	2008	RR (95% CI)ª	Admissions averted, ^b thousands (95% CI)	Median 2000–2006 (minimum)	2008	RR (95% Cl) ^a	Admissions averted, ^b thousands (95% Cl)	Median costs (2008 USD) ^d	Median length of stay (days)
0–4	78 930 (75 924)	50 51	0.61 (.52–.71)	30.8 (22.8–37.6)	32 086 ^f (23 548)	9852	0.22 (.14–.34)	25.0 (21.4–27.6)	2897	2
5–14	24 946 (23 179)	17 884	0.71 (.65–.78)	7.2 (5.4–8.8)	1801 ^f (1274)	747	0.29 (.19–.45)	1.28 (.99–1.46)	3750	2
15–24	20306 ^f (18073)	21 76	0.92 (.86–.98)	1.6 (.36–2.7)	127 ^f (81)	70	0.35 (.15–.82)	0.08 (.023–.108)	5925	2
25–64 ^e	146000 ^f (132729)	174 56	0.99 (.95–1.03)		288 ^f (231)	279	0.74 (.47–1.16)		7481	3
≥65	118332 ^f (108917)	147 906	1.03 (.96–1.1)		266 ^f (168)	390	0.79 (.49–1.26)		10260	4
All ages				39.6 (28.5–49.1)				26.4 (22.4–29.2)		

Decline in Childhood Diarrhoea Deaths After Rotarix Introduction, Mexico



RAPID COMMUNICATIONS

Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination

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- Centre for Epidemiology and Surveillance (EPI), Centre for Infectious Diseases Control (CIb), National Institute for Public Health and the Environment (RIVM), the Netherlands
- 2. NIVEL (Netherlands Institute for health services research), the Netherlands
- Centre for Infectious Diseases Research, Diagnostics and Screening (IDS), Centre for Infectious Diseases Control (CIb), National Institute for Public Health and the Environment (RIVM), the Netherlands
- 4. Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, the Netherlands

Weekly rotavirus detections^a (August 1999–August 2014) and general practice gastroenteritis consultation rate for children under five years old (August 2006–August 2014), the Netherlands





Sentinel site reports of samples tested & numbers positive



Confirmed rotavirus reports by age in months Public Health **England & Wales** England



%