Rotavirus Vaccine Effectiveness in Hong Kong Children

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Overview

- Previous studies
- Test-negative Case-Control Study
- Results

Estimates of Rotavirus Disease Burden in Hong Kong: Hospital-Based Surveillance

E. Anthony S. Nelson,[1] John S. Tam,[2] Joseph S. Bresee,[6] Kin-Hung Poon,[3] Chi-Hang Ng,[4] Kin-Sing Ip,[5] T. Christopher Mast,[7] Paul K.-S. Chan,[2] Umesh D. Parashar,[6] Tai-Fai Fok,[1] and Roger I. Glass[6]

- Incidence of RV hospitalisation:
  - 880 per 100,000 children < 5yrs (2001 – 2003)

1 in 24

cumulative risk of hospitalisation for RV by age 5 yrs

Rotarix vaccine efficacy & safety to 2 yrs (Singapore, Hong Kong, Taiwan)

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: Randomised, double-blind, controlled study

K.B. Phua[a,*], F.S. Lim[b], Y.L. Lau[c], E.A.S. Nelson[d], L.M. Huang[e], S.H. Quak[f], B.W. Lee[g], Y.L. Teoh[b,h], H. Tang[h], I. Boudville[h], L.C. Oostvogels[h], P.V. Suryakiran[h], I.V. Smolenov[h], H.H. Han[h], H.L. Bock[h]

- From 2 weeks post-dose 2 to 2 years of age, vaccine efficacy was 96.1% (95%CI: 85.1-99.5) against severe rotavirus gastroenteritis

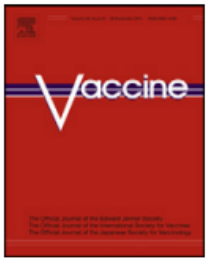
K.B. Phua et al. / Vaccine 27 (2009) 5936–5941

Rotarix vaccine efficacy sustained to 3 yrs (Singapore, Hong Kong, Taiwan)

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: A randomized clinical trial in an Asian population

Kong Boo Phua[a,*], Fong Seng Lim[b], Yu Lung Lau[c], Edmund Anthony Severn Nelson[d], Li Min Huang[e], Seng Hock Quak[f], Bee Wah Lee[g], Leen Jan van Doorn[h], Yee Leong Teoh[b,i], Haiwen Tang[i], P.V. Suryakiran[i], Igor V. Smolenov[i], Hans L. Bock[i], Htay Htay Han[i]

- From 2 weeks post-dose 2 to 3 years of age, vaccine efficacy was 96.9% (95%CI: 88.3-99.6) against severe rotavirus gastroenteritis

Rotarix vaccine efficacy in Hong Kong

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: A randomized, controlled trial

Yu-Lung Lau[a,1], E. Anthony S. Nelson[b,*,2], Kin-Hung Poon[c], Paul K.S. Chan[d], Susan Chiu[a], Rita Sung[b], Chi Wai Leung[e], Daniel Ng[f], Yee Man Ma[g], Desmond Chan[h], Tsz Leung Lee[i], Joyce Tang[j], Yat Wah Kwan[e], Patricia Ip[h], Marco Ho[i], Lai-Wah Eva Fung[b], Haiwen Tang[k], P.V. Suryakiran[l], Htay Htay Han[m], Hans Bock[n], Hong Kong Rotarix Study Group

- Vaccine efficacy against severe rotavirus gastroenteritis from 2 weeks post-dose 2 to
  - 2 years of age, was 95.6% (95%CI: 73.1-99.9)
  - 3 years of age, was 96.1% (95%CI: 76.5-99.9)

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Rotavirus incidence in hospitalised Hong Kong children: 1 July 1997 to 31 March 2011

Grace P.K. Chiang[a], E. Anthony S. Nelson[a,*], Timothy J.H.S. Pang[b], Shu Kei Law[c], W. Goggins[c], Johnny Y.C. Chan[d], Margaret Ip[e], Paul K.S. Chan[e]

- Incidence of RV hospitalisation:
  - 542 - 1093 per 100,000 person-years (1997 - 2011)

1 in 33

cumulative risk of hospitalisation for RV by age 5 yrs

Hong Kong universial Government Childhood Immunisation Programme

- Does not yet include rotavirus vaccine
- Vaccine has been available in private sector since 2006

Methodology

- 2014/ 2015 rotavirus season
- Test-negative case-control study
- 6 public hospitals:
  KWH, PWH, QEH, QMH, TMH, UCH
- Acute gastroenteritis (AGE)
  - Occurrence of 2 or more episodes of vomiting and/ or 3 or more episodes of diarrhoea (stools of a less formed character than usual) within a 24-hr period

Inclusion & Exclusion criteria

- Inclusion
  - Admitted to one of the study hospitals for treatment of AGE during the study period
  - Aged from 30 days to below 5 years
  - Onset of diarrhoea or vomiting started less than or equal to 14 days before admission
  - Normally receive vaccination and/ or medical care in Hong Kong
  - Written informed consent obtained from parents or guardians
- Exclusion
  - Patients with parents or guardians unable to speak Chinese (Cantonese or Mandarin) or English

Definition of case and control

- Case
  - AGE recruited subjects with stool specimens obtained during the first 48 hours of hospitalisation testing positive for rotavirus
- Control
  - AGE recruited subjects with stool specimens obtained during the first 48 hours of hospitalisation testing negative for rotavirus

Data collection

- Standardised WHO questionnaire modified for local use
- Interviews with guardians
  - Demographic information
  - Birth and medical history
- Medical records
  - Admission details
  - Disease severity
  - Final diagnoses
  - Laboratory results
- Immunisation record (copies / verbal report)

Enrolment

- 2189 potential subjects admitted
- 1616 potential AGE approached
  - 575 not eligible on initial screening
  - 129 Refused
  - 45 Discharge before consent
- 867 enrolled
- 525 confirmed AGE with stool <48hr
- 404 with immunisation record seen
  - Rotavirus positive (n = 126)
  - Rotavirus negative (n = 278)

Vaccine effectiveness

(1 – odds ratio) x 100

Statistical analysis

	Group 1	Group 2	Group 3
Unmatched	✓	x	x
Matched by date of birth (+/- 30 days)	NA	✓	✓
Matched by date of admission (+/- 30 days)	NA	x	✓

- Group 1: unconditional logistic regression, adjusting for age on admission and month of admission
- Groups 2 and 3: conditional logistic regressions
- Odds ratio for rotavirus vaccination rate (at least one dose and full series)
  - Patients were regarded as fully or partially vaccinated if the vaccines were administered at least 14 days before admission

Comparison between rotavirus-positive and rotavirus-negative patients with immunisation records seen (n=404)

	Rotavirus positive (n=126) n (%)	Rotavirus negative (n=278) n (%)	P-value
Age on admission (months), median (range)	20 (1.6-58)	13 (1.2-59)	<0.0001 *
Ever exclusively breastfed, n (%)	44 (48)	154 (67)	0.0026 *
Diarrhoea severity on admission, n (%) #			0.0007 *
Mild (Vesikari Score: <7)	0 (0)	0 (0)	
Moderate (Vesikari Score: 7-10)	1 (0.8)	31 (11)	
Severe (Vesikari Score: ≥11)	125 (99)	247 (89)	
Received intravenous fluids during hospital stay, n (%)	98 (78)	115 (42)	<0.0001 *
Ever received rotavirus vaccination, n (%)	3 (2.4)	67 (24)	<0.0001 *
Ever received RV1, n (%)	1	51	
Ever received RV5, n (%)	2	16	

RV1 = Rotarix® (GlaxoSmithKline Biologicals)
RV5 = RotaTeq® (Merck Research Laboratories)
•P-value < 0.05
•# Not all parameters of the Vesikari score were available for all patients, necessitating assigning a minimal score of 1 for some missing variables and estimating durations of vomiting and diarrhoea from the discharge date and vomit/ diarrhoea start date

Vaccine effectiveness against AGE hospitalisation (1 of 2)

	Received at least one dose	
	% (n/Total)	VE (95% CI) (%)
Unconditional Analyses		
Cases	**2.4%** (3/126)	
Controls	**24%** (67/278)	
Unadjusted		**92** (75, 98)
Adjusted for age		**92** (75, 98)
Adjusted for age and month of admission		**92** (75, 98)
Conditional Analyses		
Matched by date of birth		
Cases	2.1% (2/97)	
Controls	25% (48/191)	**96** (72, 100)
Matched by date of birth and date of admission		
Cases	2.5% (2/79)	
Controls	23% (31/135)	**89** (51, 97)

VE = vaccine effectiveness; CI = Confidence interval

Vaccine effectiveness of at least one dose of rotavirus vaccine against hospitalisation in children at different ages

	≤ 2 years old		≤ 3 years old		≤ 4 years old	
	% (n/Total) #	VE (95% CI) (%)	% (n/Total) #	VE (95% CI) (%)	% (n/Total) #	VE (95% CI) (%)
Unconditional Analyses						
Cases	3.9% (3/77)		2.9% (3/102)		2.5% (3/118)	
Controls	25% (51/206)		24% (58/241)		25% (64/261)	
Unadjusted		**88** (59, 96)		**90** (69, 97)		**92** (74, 98)
Adjusted for age		**88** (61, 97)		**90** (68, 97)		**92** (75, 98)
Adjusted for age and month of admission		**88** (60, 97)		90 (68, 97)		**92** (75, 98)
Conditional Analyses						
Matched by date of birth						
Cases	3.5% (2/57)		2.5% (2/79)		2.2% (2/93)	
Controls	24% (33/136)	**94** (50, 99)	25% (40/162)	**95** (63, 99)	25% (45/177)	**96** (71, 100)
Matched by date of birth and date of admission						
Cases	3.8% (2/52)		2.9% (2/69)		2.6% (2/77)	
Controls	23% (23/100)	**85** (32, 96.5)	24% (29/123)	**88** (48, 97)	23% (31/133)	**89** (51, 97)

VE = vaccine effectiveness; CI = Confidence interval

% (n/Total) = proportion of subjects ever received rotavirus vaccine

Published articles about rotavirus vaccine effectiveness against hospitalisation in high income countries

Article	Location	Sample size	Vaccine type	Vaccine effectiveness (95% CI) (%)	Dosage completed	Adjustment
Field et al.	Australia	28 cases, 350 controls	RV5	89 (76, 95)	Full series	-
Braeckman et al.	Belgium	215 cases, 276 controls	RV1 and RV5	91 (82, 95)	At least one dose	-
Muhsen et al.	Israel	111 cases, 216 controls	RV1 and RV5	89 (52, 98)	At least one dose	Matched by month and year of birth
Martinon-Torres et al.	Spain	467	RV1 and RV5	96 (86, 99)	At least one dose	-
Castilla et al.	Spain	756 cases, 6036 controls	RV1 and RV5	78 (70, 84)	At least one dose	Adjusted for age, sex, residence, area, major risk conditions and health care setting
Desai et al.	United States	42 cases, 80 controls	RV1 and RV5	94 (55, 99)	At least one dose	Adjusted for ethnicity, gender, and tobacco exposure
Boom et al.	United States	79 cases, 108 controls	RV5	89 (70, 96)	Full series	Adjusted for age
Staat et al.	United States	184 cases, 613 controls	RV5	95 (48, 99)	Full series	-
Cortese et al.	United States	140 cases, 280 controls	RV5	92 (86, 96)	Full series	-
Payne et al.	United States	RV1: 22 cases, 34 controls RV5: 130 cases, 372 controls	RV1 and RV5	RV1: 32 (-156, 82) RV5: 86 (74, 91)	-	Adjusted for month and year of birth, month and year of symptom onset, and surveillance site
Cortese et al.	United States	165 cases; 428 controls	RV1 and RV5	RV1: 98 (90, 100) RV5: 97 (77, 100)	Full series	-

CI = Confidence interval; RV1 = Rotarix® (GlaxoSmithKline Biologicals); RV5 = RotaTeq® (Merck Research Laboratories)

Limitations ~ not all potential subjects could be recruited

- Potential differences between the non-recruited & recruited subjects could affect estimates of vaccine effectiveness

Limitations ~ no rotavirus results

- AGE patients without a rotavirus test result more likely to have vomiting only & milder illness
- These patients more likely to have rotavirus vaccine
- Could have under-estimated vaccine effectiveness

Limitations ~ immunisation record not seen

- Immunisation records for only 77% of 525 eligible subjects ~ reduced the sample size
- Similar VE obtained on verbal immunisation report
- 98% (397/404) of immunisation records seen confirmed guardians' verbal report
- ? Verbal reports could be used in studies where obtaining confirmation of vaccination status is difficult

Limitation ~ serious response level (S2) alert due to H7N9 concern

- All Hong Kong infectious disease research suspended
- 26 Dec 2014 to 15 Jan 2015 (peak of 2014/2015 rotavirus season)
- Reduced sample size

Limitations ~ RT-PCR to identify rotavirus at 2 Hospitals

- May detect low level of rotavirus in the stool
- May underestimate vaccine effectiveness

Key points

- Rotavirus vaccine was 89% – 96% effective in preventing rotavirus hospitalisations
- Vaccine effectiveness in Hong Kong is similar to that in other high-income settings
- Universal rotavirus vaccination could significantly benefit Hong Kong children

Acknowledgement

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- Jackie Tate, US CDC

Thank you

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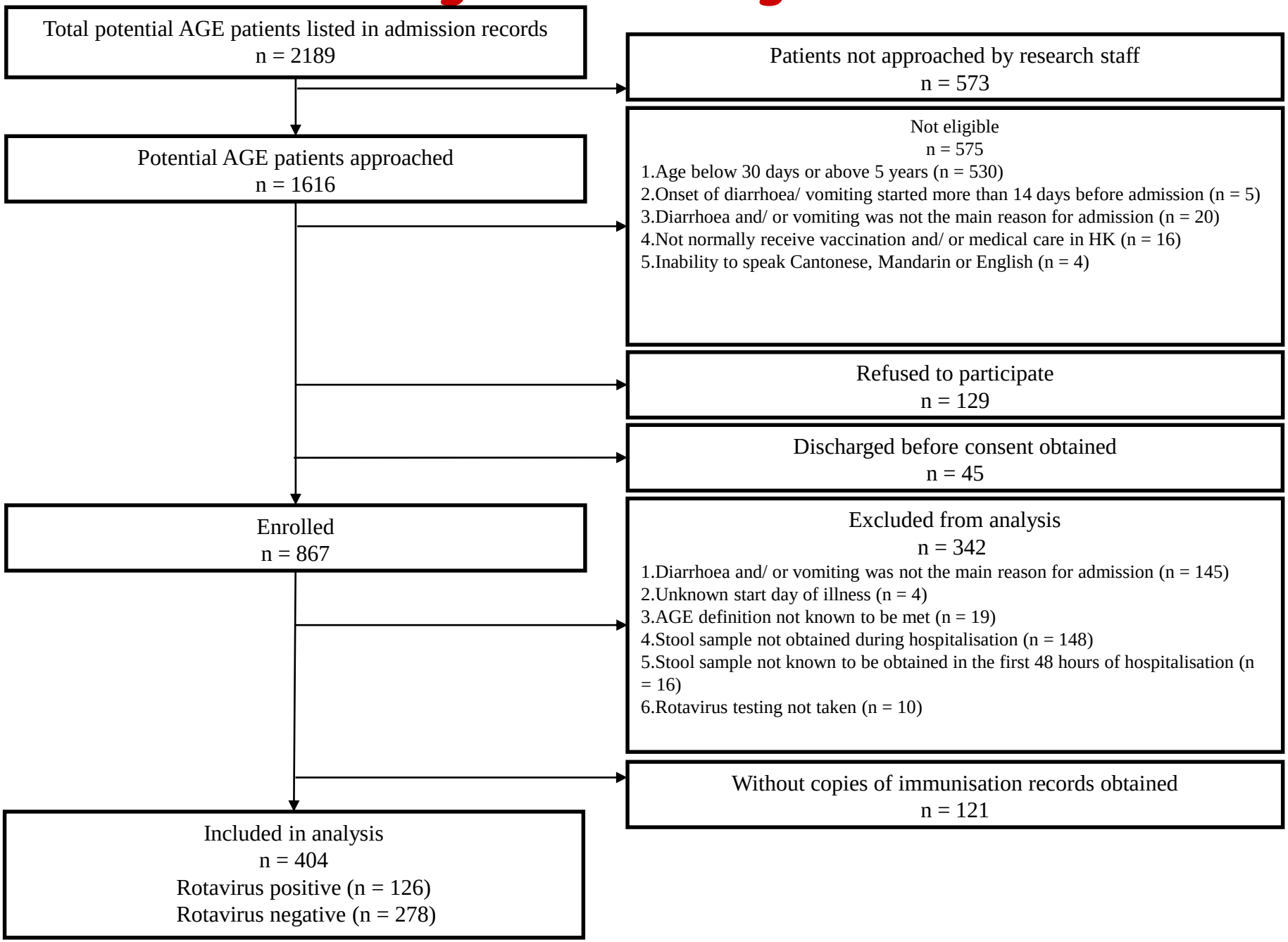
Backup slides

Ethics approvals

- Institutional Review Boards of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Ref.: UW 14-508)
- Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Ref.: CRE-2014.142)
- Kowloon West Cluster Research Ethics Committee (Ref.: KW/EX-14-193(80-13))
- New Territories West Cluster Clinical & Research Ethics Committee (Ref.: NTWC/CREC/1377/14)
- Research Ethics Committee (Kowloon Central/ Kowloon East) (Ref.: KC/KE-14-0178/FR-1)

Flow Diagram Showing Enrolment



Comparison between rotavirus-positive and rotavirus-negative patients with immunisation records seen (n=404)

	Rotavirus positive (n=126) n (%)	Rotavirus negative (n=278) n (%)	P-value
Background			
Age on admission (months), median (range)	20 (1.6-58)	13 (1.2-59)	<0.0001 *
Gender, n (%)			0.1994
Male	65 (52)	164 (59)	
Female	61 (48)	114 (41)	
Number of rooms for sleeping in household, median (range)	2 (1-6)	2 (1-5)	0.1696
Number of children in household, median (range)	0 (0-3)	0 (0-5)	0.9807
Ever breastfed, n (%)	93 (74)	232 (84)	0.0333 *
Ever exclusively breastfed, n (%)	44 (48)	154 (67)	0.0026 *
Month of admission, n (%)			<0.0001 *
October - November 2014	5 (4)	51 (18)	
December 2014	23 (18)	59 (21)	
January 2015	40 (**32**)	30 (11)	
February 2015	31 (25)	49 (18)	
March 2015	19 (15)	50 (18)	
April 2015	8 (6)	39 (14)	

* P-value < 0.05

Comparison between rotavirus-positive and rotavirus-negative patients with immunisation records seen (n=404)

	Rotavirus positive (n=126) n (%)	Rotavirus negative (n=278) n (%)	P-value
Severity and Symptoms			
Length of hospital stay (days), median (range)	2.7 (1-23)	2.1 (0.3-15)	0.0002 *
Highest body temperature during illness (C), median (IQR)	38.7 (38.2, 39.4)	38.6 (37.4, 39.5)	0.2035
Vomiting only, n (%)	1 (0.8)	11 (4)	0.1560
Diarrhoea only, n (%)	8 (6)	77 (28)	<0.0001 *
Diarrhoea and vomiting, n (%)	117 (93)	190 (68)	<0.0001 *
Diarrhoea severity on admission, n (%) #			0.0007 *
Mild (Vesikari Score: <7)	0 (0)	0 (0)	
Moderate (Vesikari Score: 7-10)	1 (0.8)	31 (11)	
Severe (Vesikari Score: ≥11)	125 (99)	247 (89)	
Treatments			
Received antibiotics before admission, n (%)	18 (15)	45 (16)	0.7622
Received oral rehydration solution before admission, n (%)	25 (21)	45 (17)	0.4206
Received intravenous fluids during hospital stay, n (%)	98 (78)	115 (42)	<0.0001 *
Vaccination			
Awareness of rotavirus vaccine before 6 months, n (%)	66 (52)	189 (69)	0.0023 *
Ever received rotavirus vaccination, n (%)	3 (2.4)	67 (24)	<0.0001 *
Ever received RV1, n (%)	1 (0.8)	51 (20)	<0.0001 *
Ever received RV5, n (%)	2 (1.6)	16 (7)	0.0472 *

IQR = Interquartile range presented in (lower quartile, upper quartile); RV1 = Rotarix® (GlaxoSmithKline Biologicals); RV5 = RotaTeq® (Merck Research Laboratories)

- P-value < 0.05
- # Not all parameters of the Vesikari score were available for all patients, necessitating assigning a minimal score of 1 for some missing variables and estimating durations of vomiting and diarrhoea from the discharge date and vomit/ diarrhoea start date

Vaccine effectiveness against AGE hospitalisation

	Received at least one dose		Fully vaccinated	
	% (n/Total)	VE (95% CI) (%)	% (n/Total)	VE (95% CI) (%)
Unconditional Analyses				
Cases	2.4% (3/126)		2.4% (3/126)	
Controls	24% (67/278)		21% (58/278)	
Unadjusted		92 (75, 98)		91 (70, 97)
Adjusted for age		92 (75, 98)		91 (69, 97)
Adjusted for age and month of admission		92 (75, 98)		91 (69, 97)
Conditional Analyses				
Matched by date of birth				
Cases	2.1% (2/97)		2.1% (2/97)	
Controls	25% (48/191)	96 (72, 100)	22% (42/191)	96 (70, 100)
Matched by date of birth and date of admission				
Cases	2.5% (2/79)		2.5% (2/79)	
Controls	23% (31/135)	89 (51, 97)	22% (29/135)	88 (48, 97)

VE = vaccine effectiveness; CI = Confidence interval

Vaccine effectiveness Vs breastfeeding experience

Unconditional vaccine effectiveness for at least one dose of rotavirus vaccine

Never breastfed	Ever breastfed
91% (95% CI: 28%, 99%)	93% (95% CI: 70%, 98%)