Appendices I-V

Koch J, Wiese-Posselt M, Remschmidt C, Wichmann O, Bertelsmann H, Garbe E, Hengel H, Meerpohl JJ, Mas Marques A, Oppermann H, Hummers-Pradier E, von Kries R, Mertens T. Background paper to the recommendation for routine rotavirus vaccination of infants in Germany. Bundesgesundheitsblatt 2013 56:957–984.
http://www.rki.de/EN/Content/Prevention/Vaccination/recommandations/BP_Rotavirus_recommendation.pdf?__blob=publicationFile

This appendix has been provided by the authors to give readers additional information about their work.
01.07.2013

Contents

Appendix I: Patient-relevant outcomes, literature search, inclusion and exclusion criteria, flow charts

Table 1: Hierarchy of patient-relevant outcomes for the evaluation of efficacy and safety of RV vaccines

Benefits	Vaccine efficacy	Initial ranking	Re-ranking	Importance of endpoints [*1]
1	RVGE requiring hospitalisation	8.6	8.8	critical
2	RVGE, severe	7.8	6.8	critical
3	Death due to RVGE	9	6.2	important
4	RVGE, nosocomial	5.5	6	important
5	All cause diarrhoea, severe	4.6	6	important
6	RVGE, any severity	5.6	4.8	important
7	Intussusception	8.8	7.6	critical
8	Kawasaki-Syndrome	6.8	6.4	important
9	Reactogenicity (fever, diarrhoea, vomiting)	6.5	5	important

[*1] classification according to the GRADE methodology

RVGE: Rotavirus gastroenteritis

Table 2: Literature search for efficacy of RV vaccines (Rotarix®, RotaTeq®), date of research: 28 September 2011

Search set	Search strategy	Number of results
1	CCTR93 CDSR93 ME60 EM74 BA70 IS74	93878660
2	FT=rotavirus OR (CT D "rotavirus" OR UT="rotavirus" OR IT="rotavirus" OR SH="rotavirus")	41531
3	FT=vaccin*	861467
4	(CT D "vaccination" OR UT="vaccination" OR IT="vaccination" OR SH="vaccination") OR (CT D "vaccine" OR UT="vaccine" OR IT="vaccine" OR SH="vaccine")	356587
5	3 OR 4	861856
6	FT=immunization	802408
7	(CT D "immunization" OR UT="immunization" OR IT="immunization" OR SH="immunization")	315624
8	6 OR 7	920904
9	5 OR 8	1492486
10	2 AND 9	11840
11	FT=RCT	176472
12	(CT D "RANDOMIZED CONTROLLED TRIAL" OR UT="RANDOMIZED CONTROLLED TRIAL" OR IT="RANDOMIZED CONTROLLED TRIAL" OR SH="RANDOMIZED CONTROLLED TRIAL")	311049
13	(CT D "RANDOMIZED CONTROLLED TRIAL" OR UT="RANDOMIZED CONTROLLED TRIAL" OR IT="RANDOMIZED CONTROLLED TRIAL" OR SH="RANDOMIZED CONTROLLED TRIAL")	311049
14	(CT D "CLINICAL TRIAL" OR UT="CLINICAL TRIAL" OR IT="CLINICAL TRIAL" OR SH="CLINICAL TRIAL")	911263
15	(CT D "CONTROLLED CLINICAL TRIAL" OR UT="CONTROLLED CLINICAL TRIAL" OR IT="CONTROLLED CLINICAL TRIAL" OR SH="CONTROLLED CLINICAL TRIAL")	314573
16	11 OR 12 OR 13 OR 14 OR 15	1081995
17	10 AND 16	718
18	17 AND PY=2004 to 2011	518
19	**check duplicates: unique in s=18**	**479**

Table 3: Inclusion and exclusion criteria for literature screening regarding efficacy of RV-vaccines (Rotarix®, RotaTeq®)

PICO-criteria	Inclusion criteria	Exclusion criteria
P	Children <5 years of age	Other age groups
P	Healthy children	Children with underlying disease
P	Study population from industrialized or newly industrialized countries (Europe, Australia, Canada, USA, Latin-America, (high-income countries of) Asia)	Study population from developing countries
I	Immunization with Rotarix or RotaTeq-Vaccine, dosage as licensed	Different vaccine or different dosage
I	Immunization schedule according to approval	Immunization schedule differing to approval
I	No co-administration with OPV (oral Polio vaccine)	Co-administration with OPV (oral Polio vaccine)
I	Study objective: RV immunization completed	Study objective: RV immunization not completed
I	Formulation of the vaccine according to approval	Vaccine formulation differing from licensed product
I	Study about efficacy and/or safety of RV vaccine	Different topics
C	Control group receives placebo or no vaccine	Different comparison groups
O	Outcomes as with regard to items formulated by the working group	different outcomes (e.g. immunogenicity data)
S	Efficacy study of RV vaccines	Other study objectives
S	Study completed	Study ongoing
S	Study design: randomized controlled trials (RCT), interventional studies, reviews	Other study designs, observational studies (e.g. Case control studies, cohort studies)
Time period	Publication date: 2004-2011	

P: population, **I:** Intervention, **C:** Comparison, **O:** Outcome, **S:** Study characteristics

Figure 1: Flow chart of literature search for Rotavirus vaccine efficacy (Rotarix®, RotaTeq®)

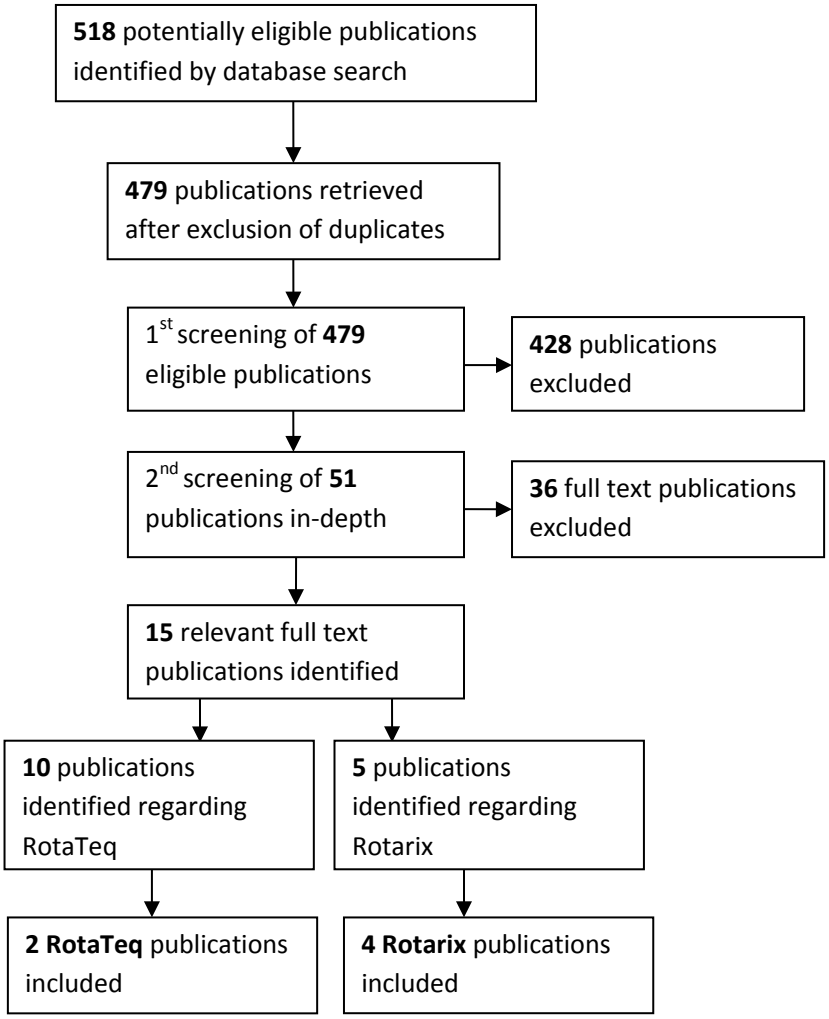


Table 4: Search method for literature-search of effectiveness of Rotavirus vaccines (Rotarix®, RotaTeq®), date of research: 29 December 2011

Search set	Search strategy	Number of results
1	CCTR93 CDSR93 ME60 EM74 BA70	62314343
2	FT=rotavirus OR (CT D "rotavirus" OR UT="rotavirus" OR IT="rotavirus" OR SH="rotavirus")	32633
3	FT=vaccin	699562
4	(CT D "vaccination" OR UT="vaccination" OR IT="vaccination" OR SH="vaccination") OR (CT D "vaccine" OR UT="vaccine" OR IT="vaccine" OR SH="vaccine")	332374
5	3 OR 4	699971
6	FT=immunization	744276
7	(CT D "immunization" OR UT="immunization" OR IT="immunization" OR SH="immunization")	303338
8	6 OR 7	864502
9	5 OR 8	1303640
10	2 AND 9	9462
11	(CT D "vaccine effectiveness" OR UT="vaccine effectiveness" OR IT="vaccine effectiveness" OR SH="vaccine effectiveness")	155
12	FT=vaccine effectiveness	2119
13	29 OR 30	2119
14	FT=IMPACT	1139889
15	(CT D "IMPACT" OR UT="IMPACT" OR IT="IMPACT" OR SH="IMPACT")	3874
16	14 OR 15	1139889
17	13 OR 16	1141666
18	10 OR 17	941
19	check duplicates: unique in s=34	469

Figure 2: Flow chart of literature search for Rotavirus vaccine effectiveness (Rotarix®, RotaTeq®)

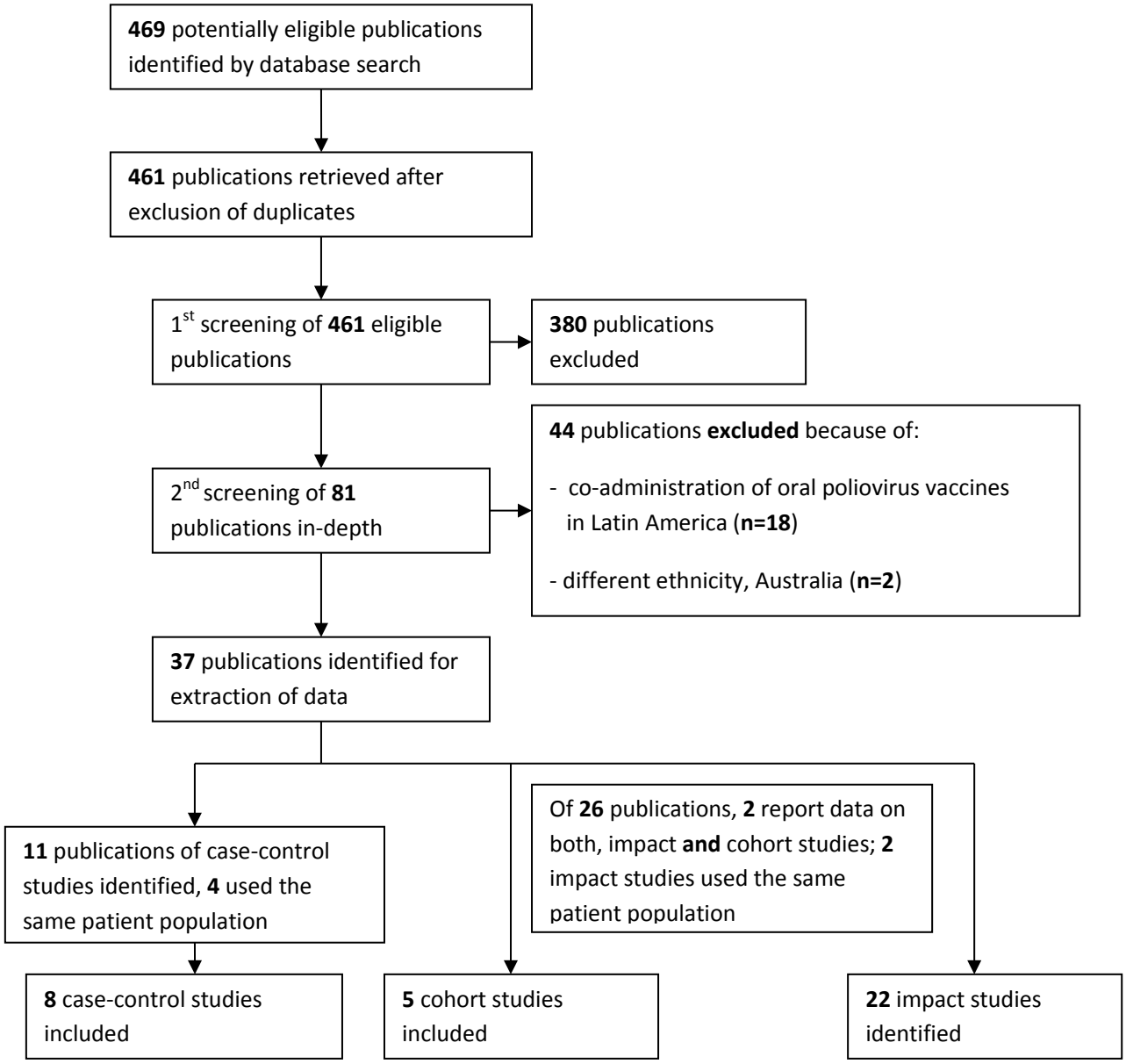
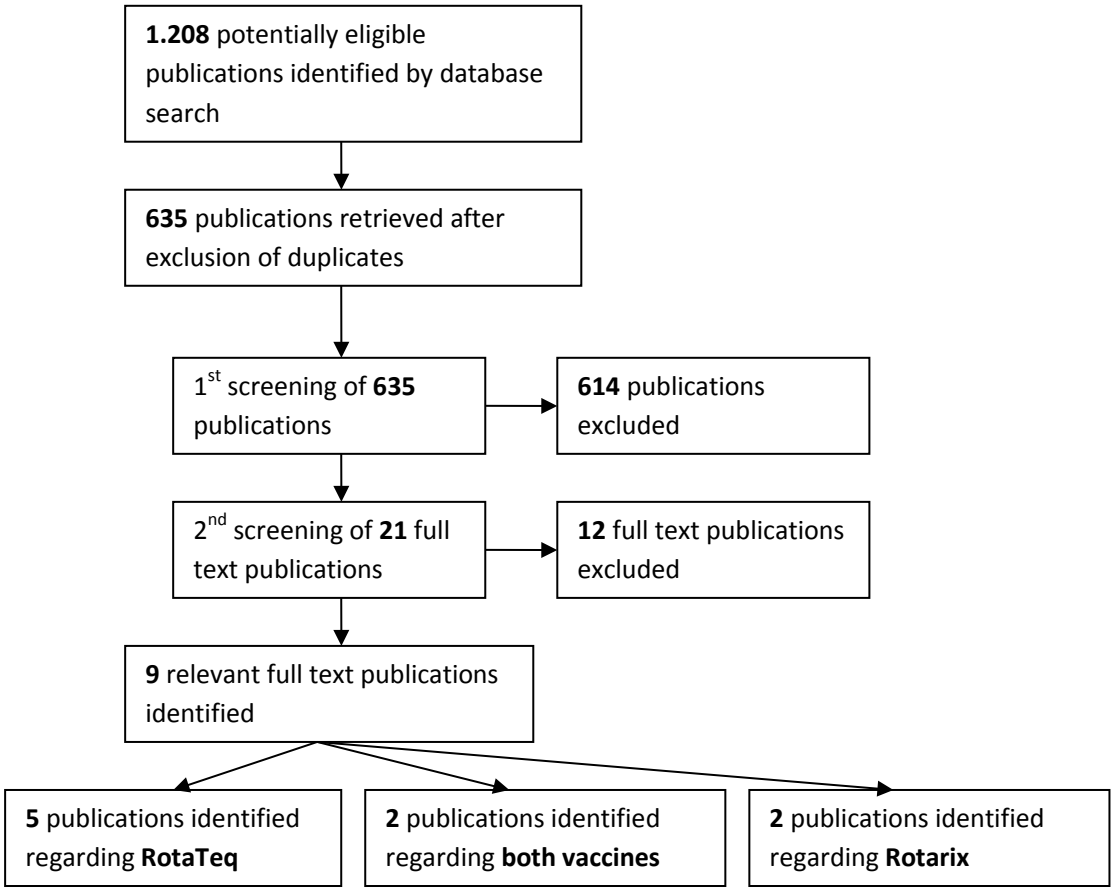


Table 5: Search method for literature-search regarding Intussusception risk due to Rotavirus vaccines (Rotarix®, RotaTeq®), date of research: 10 January 2012

Search set	Search strategy	Number of results
1	CCTR93 CDSR93 ME60 EM74 BA70 IS74	95000682
2	FT=rotavirus OR (CT D "rotavirus" OR UT="rotavirus" OR IT="rotavirus" OR SH="rotavirus")	42243
3	FT=vaccin*	877264
4	(CT D "vaccination" OR UT="vaccination" OR IT="vaccination" OR SH="vaccination") OR (CT D "vaccine" OR UT="vaccine" OR IT="vaccine" OR SH="vaccine")	364078
5	3 OR 4	877677
6	FT=immunization	807077
7	(CT D "immunization" OR UT="immunization" OR IT="immunization" OR SH="immunization")	320315
8	6 OR 7	927525
9	5 OR 8	1509802
10	2 AND 9	12195
11	FT=intussusception	22169
12	(CT D "intussusception" OR UT="intussusception" OR IT="intussusception" OR SH="intussusception")	12560
13	11 OR 12	22169
14	FT=invagination	18588
15	(CT D "invagination" OR UT="invagination" OR IT="invagination" OR SH="invagination")	1045
16	14 OR 15	18588
17	13 OR 16	33393
18	10 AND 17	1208
19	**check duplicates: unique in s=34**	**633**

Figure 3: Flow chart of literature search for intussusception risk due to Rotavirus vaccines (Rotarix®, RotaTeq®)



Appendix II: Characteristics of included efficacy studies

Study	**Vesikari-2007-RX [104]**
Vaccine	**Rotarix**
Objectives	To evaluate the efficacy, immunogenicity and safety of 2 doses of RV-vaccine in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the RV-vaccine.
Study period	September 2004 - August 2006
Study site	6 European countries; Finland (74%), France (4%), Germany (7%), Czech Republic (7%), Spain (8%), Italy (1%)
Methods	Randomized controlled trial (2:1); Length of follow-up: 2 years Efficacy analysis was undertaken for 3 periods: 1st: from 2 weeks post-dose two up to the end of the first rotavirus epidemic season 2nd: from the end of the 1st rotavirus epidemic season to the end of the 2nd epidemic season; 3rd: the combined period. Data analysis was planned for the total vaccinated cohort (TVC) from the 1st dose onwards for all participants who received at least 1 dose.
Participants	**Number:** 3,994 randomised; 3,848 completed Vaccine group: 2,646 randomised; 2,554 completed Control group: 1,348 randomised; 1,294 completed **Inclusion:** healthy infants aged 6 – 14 weeks who weighed >2000 g at birth **Exclusion:** acute disease at the time of enrolment, a history of chronic administration of immunosuppressants since birth, received any vaccines or treatments prohibited by the protocol, or had any disorders or illnesses excluded by the protocol.
Intervention	1. Rotarix (RIX4414) vaccine contained $10^{6.5}$ PFU; 2 doses given 1 or 2 months apart 2. Placebo: same constituents as vaccine but without virus; 2 doses given 1 or 2 months apart 1st vaccine dose given at 6 - 12 weeks of age; vaccination was postponed if temperature ≥ 37.5 (ax) or ≥ 38 (rectal) or gastroenteritis (GE) within 7 days before planned vaccination. Except OPV other routine childhood vaccines could be administered concomitantly.
Outcomes	**Efficacy:** Primary outcome: RVGE caused by wild-type RV of any severity during the first follow-up period Secondary outcomes measured in different time periods: - any and severe RVGE (Vesikari-severity score ≥11) caused by wild-type RV - any RVGE requiring medical attention (medical provider contact, advice, visit) - hospitalization admission due to RVGE caused by wild-type RV

	Vesikari-severity score used for assessment of severity **Safety:** Serious adverse events (SAE) (intussusception) recorded throughout the whole study period. Reactogenicity: (Day 0-7) Diarrhoea, Fever, Vomiting	
Funding	GlaxoSmithKline Biologicals	
Risk of bias	**Assessment**	**Description**
Adequate sequence generation	adequate	GSK Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list
Allocation concealment	adequate	Randomisation was done by a central internet randomisation system. Infants were randomly allocated in a 2:1 ratio two doses of either RIX4414 or placebo.
Blinding	adequate	Treatment allocation remained concealed from investigators and the parents of participating infants throughout the study.
Missing output data	no	Missing data adequately presented
Selective reporting	no	Data are provided for all RVGE outcomes and for all cause GE (severe and with hospitalisation)
Other bias	unclear	No information
Comments	Information about distribution and kind of included study centres missing (generalizability/ representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g. socio economic differences, siblings). No placebo-intervention arm without irrigating ingredients (glucose). Evaluation of surveillance regarding gastroenteritis episodes not presented (e.g., number of not successful parent contacts, missing stool samples). Efficacy analysis was almost exclusively presented per protocol; analysis of total vaccinated cohort (TVC) for RVGE of any severity (1^{st} + 2^{nd} year) and for severe RVGE (1^{st} + 2^{nd} year).	
References:	**Vesikari, T., A.** Karvonen, et al. (2007). "Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study." Lancet 370(9601): 1757-1763.	

Study	Ruiz-Palacios-2006-RX [100, 107]
Vaccine	**Rotarix**
Objectives	To evaluate the safety, immunogenicity and efficacy of Rotarix in healthy infants approximately 2-3 months of age at the time of the first dose.
Study period	August 2003 - October 2005
Study site	Multicentre study conducted at multiple sites in 10 countries in Latin America (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama and Venezuela) and Finland. Follow up in the 2nd year after vaccination only in Latin America
Methods	Randomized, placebo-controlled trial (1:1), multi-country and multi-centre study; Length of follow up: For efficacy: from 2 weeks post dose 2 until 2 years of age For safety: from dose 1 till the end of the study.
Participants	**Number:** 63,225 randomised for safety; 59,308 completed for safety; from the safety cohort 20,169 randomised for efficacy; 17,882 completed 1st year efficacy and 14,615 2nd year efficacy Vaccine group safety: 31,673 randomised; 29,616completed Control group safety: 31,552 randomised; 29,465completed Vaccine group efficacy: 10,159 randomised; 9,009completed Control group efficacy: 10,010 randomised; 8,858 completed **Inclusion criteria:** Healthy infants 6 - 13 weeks old at dose 1 with written informed consent. **Exclusion criteria:** Allergic reaction to vaccine components; clinically significant history of chronic GI disease or GI malformation or other serious medical condition or received vaccines or treatment prohibited by the protocol; or immunocompromised condition.; use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the 1st dose of study vaccine, or planned use during the study period; acute disease at time of enrolment; gastroenteritis within 7 days preceding the study vaccine administration; previous confirmed occurrence of RVGE; HIV moderately and severely symptomatic: stages III and IV.
Intervention	1. Rotarix (RIX4414) vaccine contained $10^{6.5}$ PFU; 2 doses given 4 to 8 weeks apart 2. Placebo: same constituents as vaccine but without virus; 2 doses given 4 to 8 weeks apart 1st vaccine dose given at 6 - 13 weeks of age. Except OPV other routine childhood vaccines could be administered concomitantly.
Outcomes	- Severe Adverse Events (SAE) (e.g., confirmed intussusception) - Severe all-cause diarrhoea - All-cause diarrhoea; from 2 weeks after 2nd dose up to 2 years' follow-up

	- RVGE; from 2 weeks after 2nd dose up to 2 years' follow up - Severe RVGE; from 2 weeks after 2nd dose up to 2 years' follow-up - RVGE requiring hospitalization - Reactogenicity; up to 30 days after vaccination	
Funding	GlaxoSmithKline Biologicals	
Risk of bias	**Assessment**	**Description**
Adequate sequence generation	adequate	GSK provided vaccine supplies that were numbered with a computer-generated randomisation list; a blocking scheme randomisation was used. GSK did the masking and concealment.
Allocation concealment	adequate	Randomisation was done by a central internet randomisation system.
Blinding	adequate	Treatment allocation remained concealed from investigators and parents of participating infants throughout the study. GSK did the masking and concealment.
Missing output data	unclear	Insufficient description of attrition in the 2nd year follow up.
Selective reporting	yes	Not all prespecified outcomes reported (data about RVGE of any severity is missing).
Other bias	unclear	No information.
Comments	Information about distribution and kind of included study centres missing (generalizability /representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g., socio economic differences, siblings). No placebo-intervention arm without irrigating ingredients (glucose). Evaluation of surveillance regarding gastroenteritis episodes not presented (e.g., number of not successful parent contacts, missing stool samples). Efficacy analysis was almost exclusively presented per protocol (except severe RVGE1st year).	
References:	**Ruiz-Palacios, G. M.,** I. Perez-Schael, et al. (2006). "Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis." New England Journal of Medicine 354(1): 11-22. (Data about 1st year) **Linhares, A. C.,** F. R. Velázquez, et al. (2008). "Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study." The Lancet 371(9619): 1181-1189. (2nd year)	

Study	Phua-2009-RX [103]
Vaccine	**Rotarix**
Objectives	Aim to assess efficacy of Rotarix against severe RVGE during the 1st 2 years of life in high-income countries of Southeast and East Asia (Focus on VE assessment against the G2 type).
Study period	December 2003-July 2007
Study site	21 study centres in 3 Asian countries (Hong Kong, Singapore, Taiwan)
Methods	Randomized, placebo-controlled trial, multi-country and multi-centre study; (1:1) Length of follow up: 2 weeks post dose 2; up to 2 years
Participants	**Number**: (Hong Kong (n=3,025), Singapore (n=6,542), Taiwan (n=1,141)) Total cohort: 10,708 randomised; 10,519 completed 2nd year Vaccine group: 5,359 randomised; 5,263 completed 2nd year Control group: 5,349 randomised; 5,256 completed 2nd year **Inclusion:** healthy infants 6 - 12 weeks old in Hong Kong and Taiwan, or 11-17 weeks old in Singapore. **Exclusion**: chronic administration of immunosuppressants since birth, confirmed or suspected immunosuppressive or immunodeficient condition, history of allergic disease, any investigational drugs/vaccines from 30 days before Dose 1 or planned use during the study, received immunoglobulins and/or blood products since birth or planned administration during the study, any clinically significant history of chronic gastrointestinal disease including any malformation of gastrointestinal tract or other serious medical condition.
Intervention	1. Rotarix (RIX4414) vaccine contained 10 $^{6.0}$ PFU; 2 doses given 1-2 months apart 2. Placebo: same constituents as vaccine but without virus; 2 doses given 1-2 months apart Vaccination was postponed if temperature ≥ 37.5 (ax) or ≥ 38 (rectal) or GE within 7 days before planned vaccination. If oral polio vaccine is administered as part of routine schedule, a time interval of 2 weeks should be provided. 1st vaccine dose given at 6 - 11 weeks of age in Singapore and Hong Kong, 11 - 17 weeks in Taiwan. Except OPV other routine childhood vaccines could be administered concomitantly.
Outcomes	- all-cause diarrhoea: - severe all-cause diarrhoea (Vesikari-severity score ≥11) - RVGE with wild type RV - Severe rotavirus diarrhoea: see above (Vesikari-severity score ≥ 11) - Emergency department visits for capture GE episodes requiring hospitalisation - SAE; Intussusception and any other serious adverse events
Funding	GlaxoSmithKline Biologicals

Risk of bias	Assessment	Description
Adequate sequence generation	adequate	A randomisation list was generated at GSK Biologicals, Rixensart, using a standard SAS® program and was used to number the vaccines.
Allocation concealment	adequate	A randomisation blocking scheme was used to ensure that the balance between treatments was maintained. Treatment allocation at the investigator sites was performed using a central randomisation system on the internet.
Blinding	adequate	Study investigators, study personnel and parents/guardians of the infants were blinded throughout the study.
Missing output data	no	Missing data reported adequately.
Selective reporting	unclear	VE for total vaccinated cohort only presented for severe RVGE of 2-year period.
Other bias	unclear	No information.
Comments	Information about distribution and kind of included study centres missing (representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g., socio economic differences, siblings). Reasons for attendance of participants at study centres (hospitals) unknown (representativeness questionable). No placebo-intervention arm without irrigating ingredients (glucose). Virus concentration in vaccine different ($10^{6.0}$ vs. $10^{6.5}$) to that approved for use in Germany. Efficacy analysis was almost exclusively presented per protocol.	
References:	**Phua, K. B**., F. S. Lim, et al. (2009). "Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: Randomised, double-blind, controlled study." Vaccine 27(43): 5936-5941.	

Study	Kawamura-2011-RX [102]
Vaccine	**Rotarix**
Objectives	Aim of the study was to assess the efficacy, immunogenicity and safety of RIX4414 when administered to healthy Japanese infants 6-14 weeks of age.
Study period	June 2007 - November 2009
Study site	Japan (20 centers)
Methods	Randomized controlled trial (2:1); Length of follow-up: For efficacy: from 2 weeks post dose 2 until 2 years of age For safety: 8-day follow-up post vaccination for solicited symptoms; 31-day follow-up post-vaccination for unsolicited adverse events (AE), for serious AE (SAE) follow-up till the end of the study. Efficacy: ATP-analysis Safety. TVC-analysis
Participants	**Number**: 765 randomised; 748 (813) completed Vaccine group: 508 (540) randomised; 498 completed Control group: 257 (273) randomised; 250 completed **Inclusion:** healthy infants aged 6-14 weeks at the time of the first vaccination and born in time (36-42 week of gestation) **Exclusion:** received any investigational drug or vaccine 30 days preceding 1st dose, received other RV vaccine, were administered immunosuppressive drugs, had history of chronic gastrointestinal disease or gastrointestinal malformation, suspected immunosuppression or immunodeficiency, had GE 7 days preceding 1st dose.
Intervention	1. Rotarix (RIX4414) vaccine contained 10 $^{6.0}$ PFU; 2 doses given 1 month apart 2. Placebo: same constituents as vaccine but without virus; 2 doses given 1 month apart. 1st vaccine dose given at 6-14 weeks of age. Except OPV other routine childhood vaccines could be administered concomitantly.
Outcomes	**Efficacy:** Primary outcome: RVGE of any severity caused by wild-type RV leading to medical intervention, Secondary outcome: - severe RVGE caused by wild-type RV leading to medical intervention (Vesikari-severity score ≥11) - any RVGE caused by wild-type RV leading to medical intervention - hospitalisation due to RVGE caused by wild-type RV leading to medical intervention Vesikari-severity score used for assessment of severity **Safety:** solicited AEs (fever, diarrhoea, vomiting) were recorded from Day 0 to Day 7

	SAEs (Intussusception) were recorded throughout the study period	
Funding	GlaxoSmithKline Biologicals	
Risk of bias	**Assessment**	**Description**
Adequate sequence generation	adequate	SAS program was used to generate a randomization list (2:1 ratio) to number the vaccines and placebo packages.
Allocation concealment	adequate	Treatment allocation at each study site was performed using the central randomization system on the Internet (SBIR), randomization algorithm used a minimization procedure to account for each centre.
Blinding	adequate	Blinding was maintained throughout the study for study investigators, study personnel, parents.
Missing output data	yes	Number of withdrawals not adequately presented in trial profile (not include in enrolled participants).
Selective reporting	unclear	No data about all cause diarrhoea presented.
Other bias	unclear	No information.
Comments	Misleading trial profile with incorrect presented loss to follow-up numbers. Information about distribution and kind of included study centres missing (generalizability /representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g., socio economic differences, siblings). Reasons for attendance of participants at study centres (hospitals) unknown (representativeness questionable). No placebo-intervention arm without irrigating ingredients (glucose). Virus concentration in vaccine different ($10^{6.0}$ vs. $10^{6.5}$) to that approved for use in Germany. Evaluation of surveillance regarding gastroenteritis episodes not presented (e.g., number of not successful parent contacts, missing stool samples). Efficacy analysis was exclusively presented per protocol.	
References:	**Kawamura, N.,** Y. Tokoeda, et al. (2011). "Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life." Vaccine 29(37): 6335-6341.	

Study	Block-2007-RQ [105]	
Vaccine	**RotaTeq**	
Objectives	Evaluation of efficacy of RotaTeq at the end of shelf life in preventing RV-GE due to wild-type G1-G4, in regard to its safety and immunogenicity in healthy infants.	
Study period	September 2002 - June 2004	
Study site	27 study sites in the U.S. and 3 in Finland	
Methods	Randomized, double-blind, placebo-controlled (vaccine/placebo = 1:1). Length of follow up: 1 RV season. Active surveillance: parents contacted every 2 weeks in RV season. Efficacy: evaluation of VE against different clinical outcomes in ATP cohort (GE occurring 14 days after 3rd dose) and for one outcome in TVC (GE occurring after 1st dose) (= MITT analysis). Safety assessment in TVC. Immunogenicity in ATP-subgroup (n=150).	
Participants	**Number:** Sample size calculation: 1400; 1312 enrolled and randomised. Vaccine group: 650 TVC; 551 completed in ATP cohort Control group: 660 TVC; 564 completed in ATP cohort **Inclusion:** healthy infants between 6-12 weeks of age with informed consent from parents or guardian. Except OPV other licensed vaccines could be administered concomitantly. No restriction for feeding. **Exclusion**: if infant had received OPV 42 days before planned 1st dose vaccine/placebo or OPV would be administered during the study.	
Intervention	Vaccine: RotaTeq (WC3) containing 1.1 x 10^7 infectious units per dose. 1st dose given at 6-12 weeks of age, following 2 doses each with 4-10 weeks apart. Placebo: identical to vaccine but did not contain RV reassortant or trace trypsin; vaccination schedule see above.	
Outcomes	Primary outcome (ATP-cohort): RV-GE due to G1-G4-serotypes of any severity occurring 14 days or later after 3rd dose. Secondary outcomes: RV-GE due to G1-G4 with moderate-and-severe and exclusively severe disease (ATP); all GE with a positive RV-ELISA (ATP); RV-GE due to G1-G4 of any severity occurring in TVC (MITT). Safety (TVC): 7-day monitoring after any dose on vaccine reactions, 42-day monitoring on AE/SAE. Immunogenicity (n=150; ATP-subgroup): anti-RV IgA prior 1st dose and 42 d after 3rd dose.	
Funding	Merck & Co., Inc.	
Risk of bias	**Assessment**	**Description**
Adequate sequence generation	adequate	Enrolled infants were randomly assigned 1:1 by using computer-generated allocation schedules to receive either vaccine or placebo.
Allocation	adequate	Sequential identical containers; vaccine visibly

concealment		indistinguishable from placebo.
Blinding	adequate	Blinding was maintained throughout the study for study investigators, study personnel, parents.
Missing output data	no	Missing data reported adequately
Selective reporting	unclear	VE analysis is initially limited on efficacy against serotypes G1-G4: only VE against GE of any severity with positive RV-ELISA is reported but not against severe GE.
Other bias	unclear	No information
Comments	Information about distribution and kind of included study centres missing (generalizability /representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g., socio economic differences, siblings). No placebo-intervention arm without irrigating ingredients (glucose). Evaluation of surveillance regarding gastroenteritis episodes not presented (e.g., number of not successfully contacted parents, missing stool samples). Efficacy analysis was almost exclusively presented per protocol (ATP) and restricted on serotypes G1-G4.	
References:	**Block SL,** Vesikari T, Goveia MG et al: Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics 2007; 119: 11-18.	

Study	Vesikari-2006-RQ [101]
Vaccine	**RotaTeq**
Objectives	Evaluation of safety with regard to intussusception and other AE and of efficacy of RotaTeq in preventing RV-GE due to wild-type G1-G4 and associated use of health care resources.
Study period	January 2001 – May 2005
Study site	Study centres in 11 countries: Belgium (infants enrolled n=1791), Costa Rica (1641), Finland (23422), Germany (4650), Guatemala (350), Italy (48), Jamaica (1805), Mexico (1121), Puerto Rico (640), Sweden (624), Taiwan (189), United States (33556).
Methods	Randomized, double-blind, placebo-controlled trial (1:1 ratio). Length of follow up: at least 1 RV season up to 3 RV seasons (substudy: "Finnish Extension Study (FES)"). Active surveillance: parents were contacted on days 7, 14, 42 and every 6 weeks thereafter for at least 1 year. In "clinical efficacy substudy" they were contacted every 2 weeks for at least 1 RV season. In 3rd RV season (FES) parents were contacted every 12 weeks. Safety evaluation in TVC (68,038): primary safety hypothesis: no significantly higher risk of IS among vaccine than placebo recipients during 7-day or 42-day monitoring after each dose: based on RR and 95%CI: upper bound not >10. Detailed safety substudy (TVC subgroup, n=9605): detailed data on AE/SAE within 7-day (fever, vomiting etc.) and 42-day monitoring. Clinical efficacy substudy (ATP subgroup; n=5673): VE against RV-GE (G1-G4)14 d after dose 3 up to 2 RV seasons (only infants from Finland and the U.S.). MITT in TVC (66,178): VE against RV-GE G1-G4 of any severity and in respect to hospitalisation and ED visits. Healthcare analysis (ATP) (57,134): follow-up up to 2 RV seasons in respect to hospitalisation and ED visits. FES (20,732): VE in 3rd RV season in ATP and TVC. Immunogenicity in ATP-subgroup (350).
Participants	**Number:** Sample size calculation: 60,000; safety monitoring board decided to enrol additional 10,000 subjects. Totally enrolled 70,301; of them, 69,274 randomized; of them, 68,038 vaccinated. Vaccine group: 34,035 TVC; 28,646 completed in ATP cohort Control group: 34,003 TVC; 28,488 completed in ATP cohort **Inclusion:** healthy infants between 6-12 weeks of age with informed consent from parents or guardian. Except OPV other licensed vaccines could be administered concomitant. Breastfeeding was not restricted. **Exclusion:** if infant had received OPV 42 days before planned 1st dose vaccine/placebo or OPV would be administered during the study.
Intervention	Vaccine: RotaTeq (WC3) containing app. 6.7 x 10^7 to 12.4 x 10^7 infectious units per

	dose; 1st dose given at 6-12 weeks of age, following 2 doses each with 4-10 weeks apart. Placebo: visibly indistinguishable placebo (not more detailed reported); vaccination schedule see above.	
Outcomes	Safety (TVC): for SAE (including IS) for 42 days after each dose and for vaccine-related SAE till end of study (at least 1 RV season); "Detailed safety substudy" detailed data on AE/SAE within 7-day (fever, vomiting etc.) and 42-day monitoring. Clinical efficacy substudy (ATP): VE against RV-GE (G1-G4) of any severity 14 d after dose 3 for 1 year (primary efficacy). Secondary: VE against severe RV-GE G1-G4 and VE in 2nd season. Healthcare analysis (ATP): follow-up up to 2 RV seasons in respect to hosp and ED. FES: VE in 3rd RV season in respect to hosp and ED (ATP & TVC). MITT (TVC): VE against RV-GE G1-G4 of any severity and in respect to hosp/ED and medical attention. Immunogenicity: anti-RV IgA prior 1st dose and 14 d after 3rd dose.	
Funding	Merck & Co., Inc.	
Risk of bias	**Assessment**	**Description**
Adequate sequence generation	unclear	It can be assumed that it was a computer based randomisation, but no details are provided ("Infants were randomly assigned, in a 1.1 ratio, to receive three 2-ml oral doses of vaccine or visibly indistinguishable placebo").
Allocation concealment	unclear	Likely adequate, but not reported.
Blinding	adequate	Blinding was maintained throughout the study for study investigators, study personnel, parents.
Missing output data	no	Missing data reported adequately
Selective reporting	no	Data are provided for all RVGE outcomes but not for all cause GE.
Other bias	unclear	No information
Comments	Information about distribution and kind of included study centres missing (generalizability / representativeness); no information on method of enrolment, number of eligible infants missing (possible confounding: e.g., socio economic differences, siblings). No placebo-intervention arm without irrigating ingredients (glucose). Evaluation of surveillance regarding gastroenteritis episodes not presented (e.g., number of not successfully contacted parents, missing stool samples). Efficacy analysis was almost exclusively presented per protocol (ATP) and restricted on serotypes G1-G4.	
References:	**Vesikari T,** Matson DO, Dennehy P et al: Safety and efficacy of a pentavalent	

	human-bovine (WC3) reassortant rotavirus vaccine. NEJM 2006; 354: 23-33. Itzler R, Koch G, Matson DO et al: Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5). BMC Pediatrics 2010; 10: 42. Vesikari T, Karvonen A, Ferrante SA, Ciarlet M: Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. European Journal of Pediatrics 2010. 169: 1379-86. Vesikari T, Karvonen A, Ferrante SA et al: Sustained Efficacy of the Pentavalent Rotavirus Vaccine, RV5, up to 3.1 Years Following the Last Dose of Vaccine. PIDJ 2010. 29: 957-963.

MITT: Modified intention to treat analysis

TVC: Total vaccinated cohort

ATP: According to protocol cohort

SAE: Severe adverse events

PFU: Plaque forming unit

Appendix III: Observational studies

Table 1: Case-control studies

Ref	Study (year)	Country	Study design, data source and study period	Main outcome evaluated	Definition of cases (Number of cases)	Definition of controls (Number of controls)	VE % (95% CI)
Rotateq							
110	**Boom et al. (2010)**[*1]	USA	Matched case-control study; active surveillance at single hospital during RV-season 2008 and 2009 using clinical data, immunization records and parental interviews	VE of RQ against RVGE resulting in hospitalisation or ED visits	Children aged 15 days-25 (35)[*2] months of age with confirmed RVGE (n=98)	Two control-goups: (i) Children with ARI (n=225)† (ii) Children with AGE tested negative for RV (n=153)†	Adjusted VE for **3** doses for children age-eligible (≥ 6 months) to receive 3 doses of RQ: 86 (72-93), 83 (66-91) and 84 (70-92), using ARI, AGE and (ARI + AGE) as control-groups, respectively
112	**Cortese et al. (2010)**	USA	Case-control study; retrospective data collection at 5 hospitals during 3 RV-seasons (2007-2009) using admission notes and ICD-9 codes from discharge codes as well as vaccination data from ILSs	VE of RQ against RVGE resulting in hospitalisation or ED visits	Children born after 03/2006, age at evaluation ≥ 56 days with confirmed RVGE who had an ILS record (n=402; n=170 ≥ 8 months)	Two control-goups: (i) Children with AGE tested negative for RV who had an ILS record (n=825; n=341 ≥ 8 months)† (ii) Children from ILS matched 10:1 by birth day and zip code (n=2520 ≥ 8 months)	Adjusted VE for 3 doses for children ≥ 8 months: 89 (81-94) and 89 (83-93) using AGE and ILS as control-groups, respectively Adjusted VE for 2 doses for children ≥ 8 months: 90 (75-96) and 91 (79-96), respectively Adjusted VE for 1 doses for children aged 6 weeks-6 months: 71 (40-87) and 62 (20-82), respectively
114	**Guh et al. (2011)**	USA	Matched case-control study; retrospective data collection at 2 hospitals between 07/2006-12/2008 using hospital laboratory data and medical records; controls were identified using an immunization registry (CIRTS)	VE of RQ against RVGE resulting in hospitalisation	Children aged ≥2 months and <3 years with confirmed RVGE (n=54)	One control-group: Children from CIRTS matched 5:1 by birth date and town of residence (n=270)	Unadjusted VE for 3 doses: 92 (48-100) Unadjusted VE for ≥1 doses: 90.6 (59-97.9)
117	**Staat et al. (2011)**	USA	(Nested) case-control study; active, population-based surveillance at 3 hospitals in 3 US states during 3 RV-seasons (01/2006-06/2009) using medical records and parental interviews	VE of RQ against RVGE resulting in hospitalisation or ED visits	Children born after 03/2006, ageed 52 days-47 months with confirmed RVGE (n=184; n=159 matchable to controls)	Two control-groups: (i) Children with AGE tested negative for RV (n=613, n=329 could be matched to cases)† (ii) Children with ARI (n=2014, 675 matched)	Adjusted VE using AGE as control group: 74 (37-90), 88 (66-96) and 87 (71-94) for 1, 2 and 3 doses, respectively Adjusted VE using ARI as control group: 74 (37-90), 88 (66-96) and 87 (71-94) for 1, 2 and 3 doses, respectively

[*1] overall, four studies included [*2] Age of children eligible for participation: RV season 2008: 15 days-23 months; RV season 2009: 15 days-35 months † Controls were enrolled at study site

ARI: Acute respiratory infection **ILSs:** State electronic immunization information system **RQ:** Rotateq **VE:** Vaccine effectiveness

AGE: Acute gastroenteritis **RV:** Rotavirus **RVGE:** Laboratory confirmed rotavirus gastroenteritis

CIRTS: Connecticut Immunization Registry and Tracking System **RX:** Rotarix **RVV:** Rotavirus vaccine(s)

Table 1: Case-control studies (cont.)

Ref	Study (year)	Country	Study design, data source and study period	Main outcome evaluated	Definition of cases (Number of cases)	Definition of controls (Number of controls)	VE % (95% CI)
Rotarix and Rotateq							
111	**Castilla et al. (2011)**	Spain	Nested case-control study; surveilance at one tertiary and two small hospitals and 54 primary health care centers between 01/2008 and 07/2011 using electronic clinical reports of the Navarre Health Service	VE of RVV against confirmed RVGE and RVGE resulting in hospitalisation	Children aged 3-59 months with confirmed RVGE (n=756)	Children aged 3-59 months with AGE tested negative for RV (n=6036) †	Adjusted VE for fully vaccinated preventing RVGE: 78 (68-85) Adjusted VE for any dose in preventing RVGE: 78 (70-84) Adjusted VE for fully vaccinated preventing RVGE hospitalisation: 83 (65-93)
113	**Desai et al. (2010)**	USA	Matched case-control study; data collection at a single hospital during 2 RV-season (2006/2007 and 2008/2009) using clinical records, laboratory data and parental interviews; retrospective data collection in the first and prospective enrolment in the second season	VE of RVV against confirmed RVGE resulting in hospitalisation	Children aged 8 weeks-3 years with community acquired, laboratory confirmed RVGE (n=42)	Two control-goups: (i) Children admitted for reason other than RVGE (n=80) † (ii) Children who attended the same medical practice for their routine care but who were not hospitalised (n=73)	Adjusted VE for fully vaccinated in preventing RVGE: 94.3 (55.4-99.3) and 96.9 (59.4-99.8) using hospitalised and community controls, respectively
115	**Martinón-Torres et al. (2011)**	Spain	Case-control study; prospective data collection at primary, emergency and hospital care settings between 10/2008 and 06/2009 using a pediatric research network (ReGALIP)	VE of RVV against confirmed RVGE and RVGE resulting in hospitalisation	Children aged <2 years with confirmed RVGE (n=151)	One control-group: Children aged <2 years with AGE tested negativ for RV (n=316) †	Crude VE to prevent RVGE (any episode): 92.8 (84.7-96.6) and 91.5 (83.7-95.6) for fully and partially vaccinated, respectively VE to prevent RVGE hospitalisation: 98.3 (87.4-99.8) and 95.6 (85.6-98.6) for fully and partially vaccinated, respectively
116	**Muhsen et al. (2010)**	Israel	Case-control study; retrospective data collection at three hospitals between 11/2007 and 12/2009 using medical records and parental interviews	VE of RVV against RVGE resulting in hospitalisation	Children born after 07/2007 with confirmed RVGE (n=111)	One control-group: Children born after 07/2007 with AGE tested negativ for RV (n=216) †	Adjusted VE for ≥1 doses: 89.4 (51.9-97.6) Adjusted VE for 2-3 doses: 88.9 (6.8-98.6)

† Controls were enrolled at study site
ARI: Acute respiratory infection
AGE: Acute gastroenteritis
CIRTS: Connecticut Immunization Registry and Tracking System
ILSs: State electronic immunization information system
RQ: Rotateq
RV: Rotavirus
RVGE: Laboratory confirmed rotavirus gastroenteritis
RVV: Rotavirus vaccine(s)
RX: Rotarix
VE: Vaccine effectiveness

Table 2: Cohort studies

Ref	Study (year)	Country	Study design, data source and study period	Main outcome evaluated	Cases in vaccinated children (definition / number)	Cases in not vaccinated children (definition / number)	VE % (95% CI)
Rotateq							
118	**Field et al. (2010)**	Australia, Queensland	Retrospective cohort study; ICD-10 codes for AGE and RVGE from a national hospital admission system (QHAPDC) and vaccination data from a vaccination information system (VIVAS); 2007-2008	VE (screening method)[*1] against AGE- and RVGE-hospitalisation, respectively, for the first annual birth cohort in Queensland eligible for RVV	Children born between 05/2007 and 05/2008 with confirmed RVGE leading to hosp. (n=12 cases of 45048 fully vaccinated infants)	Children in the same age range with RVGE hosp. without RV vaccination (n=16 cases of 6424 not vaccinated infants)	Crude VE (fully vaccinated) against RVGE-hospitalisation: 89.3 (75.9-95.4) Crude VE (fully vaccinated) against AGE-hospitalisation: 62.2 (51.8-70.3)
119	**Gagneur et al. (2011)**	France	Cohort study; prospective enrolment at single hospital during two RV-seasons (2007-2009) using hospitalisation data	VE against RVGE-hospitalisation	Children born between 02/2007 and 12/2008 aged <2 years with confirmed RVGE (n=124; for VE analysis n=48)	Children in the same age range without hospitalisation due to RVGE (n=3949)	Crude VE (fully vaccinated) against RVGE-hospitalisation: 98 (83-100)
120	**Wang et al. (2010)**	USA	Cohort study; retrospective analysis of 2 cohorts of infants using ICD-9 diagnosis codes from a national, health insurance claim database during two RV-seasons (2007 and 2008)	VE against AGE- and RVGE-hospitalisation, emergency department and physican office visits	Children who were enrolled in the health plan within 1 week after birth and had received 3 doses of RQ (n=33140)	Children who were enrolled in the health plan within 1 week after birth and had received 3 doses of DTaP (but not RQ) (n=26167)	Crude VE (fully vaccinated) against AGE-hospitalisation/ ED-visit and outpatient, respectively: 59 (46-69); 27 (22-33) Crude VE (fully vaccinated) against RVGE-hospitalisation/ ED-visit and outpatient, respectively: 100 (87-100); 96 (76-100)
Rotarix (and Rotateq)							
116	**Musen et al. (2010)**	Israel	Cohort study, retospective analysis of children insured in the second-largest Healthcare Service using ICD-9 (for AGE) diagnosis codes (2004 and 2009)	Vaccine effectiveness of RX against AGE requiring physician visit	Vaccinated children <12 months with AGE ICD-9 code (n=1758)	Non- vaccinated children <12 months with AGE ICD-9 code	Crude VE (fully vaccinated) against AGE: 50 (47-52) Crude VE (one dose) against AGE: 46 (36-53)

***1** Screening method: Comparing the proportion of cases vaccinated with the proportion of the population vaccinated

AGE: Acute gastroenteritis **RV:** Rotavirus **VE**: Vaccine effectiveness

DTaP: Combined vaccine against diphtheria, tetanus, and pertussis **RVGE**: Laboratory confirmed rotavirus gastroenteritis

Table 3: Impact studies, Europe

Ref	Study (year)	Vaccine; year of availability	Country/ estimated vaccine coverage (VC)	Data source, study period	Herd immunity	Genotype distribution	Nosocomial infections	Main results
122	**Braeckman et al. (2010)**	RX + RQ 10/2006	Belgium; VC: 30% (2007) - 90% (2010)	National network of sentinel laboratories and epidemiological data from hospitals; no age restriction, majority <2 years; 1999-2010	NA	NA	NA	(i) Sustained decrease of lab-confirmed RVGE: about 50% compared to mininimum of previous seasons
123	**Hanquet et al. (2011)**	RX + RQ 10/2006	Belgium; VC: 30% (2007) - 90% (2009)	National network of sentinel laboratories (see above)	Not observed	NA	NA	(i) Decrease of lab-confirmed RVGE: 61% in 2nd year after RVV introduction (about 20% decline in performed tests) (ii) Increase in the mean age of cases
125	**Paulke-Korinek et al. (2010)**	RX + RQ 2006 (1/2007)	Austria; VC: 72% (2008)	Austrian surveillance (11 hospitals; clinical records) of RVGE of hospitalized children <15 years; 2001-2008	Not observed	NA	Significant decrease of nosocomial infections	(i) Decrease of RVGE-hospitalisations: 42% and 74% for children aged <90 days and 90 days to 20 months, respectively (ii) Increase of age of hospitalised children
124	**Trimis et al. (2011)**	RX + RQ 01/2007	Greece; VC: <30% (2010)	Prospective observational study, single hospital, clinical records, children <5 years; 09/2006-09/2010	Not observed	Variation of circulating genotypes reported, not significant	NA	(i) Decrease of RVGE-hospitalisations in children ≤11 months by 39% (ii) Increase in the mean age of cases
78	**Zeller et al. (2010)**	RX + RQ (mainly RX); 10/2006	Belgium; VC: 88% (2007-2010)	Prospective observational study, single hospital, laboratory data, children <5 years; 1999-2009	Observed in one (out of 3) seasons	Significant increase of G2-genotype after RVV introduction	NA	(i) Decrease of lab-confirmed RVGE-hospitalisations by 35%, 49% and 66% in the 3 years following vaccine introduction (ii) Increase of G2-genotype in 3 seasons after RVV introduction of about 30%

NA: Not available
RQ: Rotateq
RVGE: Laboratory confirmed rotavirus gastroenteritis
RVV: Rotavirus vaccine(s)
RX: Rotarix
VC: Vaccine coverage
VE: Vaccine effectiveness

Table 4: Impact studies, Australia

Ref	Study (year)	Vaccine; year of availability	State/ estimated vaccine coverage (VC)	Data source, study period	Herd immunity	Genotype distribution	Nosocomial infections	Main results
126	**Belshaw et al. (2009)**	RX; 07/2007	New South Wales; VC: NA	Laboratory data (6 hospitals) and AGE diagnosis codes of EDs (43 hospitals); children < 5 years; 2001-2008	Effect possible	NA	NA	(i) Decrease of lab-confirmed RVGE in children < 5 years (~ 35% compared to minimum of previous 7 years) (ii) Lower rates of AGE EDs visits in both, vaccinated and unvaccinated age-groups
127	**Buttery et al. (2011)**	RX + RQ; 07/2007	New South Wales, Queensland, Victoria VC (national data): 84% and 87% for one dose and full vaccine course, respectively; (12/2008)	Admission (ICD-9) and laboratory data; children < 5 years (Queensland: < 21 years); 2001-2009	(i) Reduction in RV-hospitalisations in all age groups (ii) Reduction in AGE-hospitalisations in children < 5 years	NA	87% decrease of nosocomial infections	(i) Decline in proportion of tests positive for RV about 50% (ii) Decrease in RVGE-hospitalisations in all age groups: (e.g. 68% and 53% for children aged 0-24 and 25-36 months, respectively) (iii) Decrease in AGE-short-stay admissions in children <5 years by about 60%
128	**Clarke et al. (2010)**	RX + RQ; 07/2007	South Australia; VC: NA	Admission data (ICD-10 for RVGE and AGE) from all SA hospitals; children <6 years; 2005-2007 vs. 2008-2010	Reduction in RV- and AGE-hospitalisation in children 3-6 years	NA	NA	(i) Decline in hospitalisation in all age-groups (0-6 years): AGE: 2142 vs 4153 admissions (- ~48%) RVGE: 165 vs. 955 admissions (- ~83%)
118	**Field et al. (2010)**	RX + RQ; 07/2007	Queensland; VC: 73% (3 doses), 13% (2 doses), 4% (1 dose), 10% not vaccinated	Admission data (ICD-10 for RVGE and AGE) from all hospitals in Queensland; children and adults (age specific data reported); 2000-2006 vs. 2007/08	Reduction of RVGE in children > 5 -19 years; reduction of AGE in children < 5 years	NA	NA	(i) Reduction in RVGE-hospitalisations in persons < 20 years (ii) Reduction in AGE-hospitalisations in children < 5 years (iii) Increase of RVGE- and AGE-hospitalisations in older age groups but only minor changes in the absolute numbers
129	**Lambert et al. (2009)**	RQ; 07/2007	Queensland; VC: NA	Laboratory data (2000-2008) and RV-notifications (2006-2008) in all age-groups (0- >64 years)	Reduction of RV-notifications in non-vaccinated age groups	NA	NA	(i) Decline in annual RV-notifications: >50% overall; up to 65% in children <2 years (ii) Decline in proportion of tests positive for RV: 43-45% (iii) Absolute increase in RV-testing due to an increase in tests in older age groups

ED: Emergency department
NA: Not available
RQ: Rotateq
RVGE: Laboratory confirmed rotavirus gastroenteritis
RVV: Rotavirus vaccine(s)
RX: Rotarix
VC: Vaccine coverage
VE: Vaccine effectiveness

Table 5: Impact studies, USA

Ref	Study (year)	Vaccine; year of availability	State/county; estimated vaccine coverage (VC)	Data source, study period	Herd immunity	Genotype distribution	Nosocomial infections	Main results
131	**Anderson et al. (2011)**	RQ; 02/2006	Chicago VC: children <2 years: 56% (2007/08)	Prospective surveillance, single hospital using clinical and laboratory data, 2003-2008; all children age-groups	Decline of RVGE-hospitalisation higher than portion of vaccinated children	NA	Sustained decrease of nosocomial infections (>50%)	(i) Decline of community aquired RVGE per 1000 admissions by 82%
121	**Bégue and Perrin (2010)**	RQ; 02/2006	New Orleans area; VC in age-eligible in 2008/ 2009: 46% (at least 1 dose)	Retrospective data collection on AGE in children <5 years in 38 pediatric practices and 1 hospital using ICD-9 codes, medical records and laboratory data; 2004-2009	(i) Decline of RV- and AGE-hospitalisation/ED-visits higher than portion of vaccinated children (ii) Decrease in RV-visits in children ≥ 2 years (strong trend)	NA	NA	(i) Decline in detected AGE-episodes by 20%-28% (ii) Decline in AGE-hospitalisations by 50% (iii) Decline in RVGE-hospitalisations 50%-85%
132	**CDC (2008)**	RQ; 02/2006	3 US counties; VC: 34% (fully vaccinated); 2008	Network of US laboratories (NREVSS) and population-based vaccine surveillance network (NVSN) using epidemiological (epi), clinical and laboratory (lab) data; children < 3 years; 1991-2008 (lab data) and 2006-2008 (epi data)	Decline of RVGE higher than portion of vaccinated children	NA	NA	Overall, RV activity diminished in magnitude bei > 50% (i) Decline in proportion of tests positive for RV (NREVSS data) (ii) Decline of specimen tested positive for RV (inpatient, outpatient and Eds) (NVSN data)
133	**Chang et al. (2010)**	RQ; 02/2006	New York state VC: NA	Collection of discharge and laboratory data of hospitalised children in 10 sentinel hospitals and data of a statewide discharge register (ICD-9)	Decline of AGE- and RVGE-hospitalisations in unvaccinated age groups (see *main results*)	NA	NA	(i) Decline in AGE- and RVGE-hospitalisations 1-23 months: 40% and 85%, respectively 2-5 years: 36-37% and 76-88%, respectively 5-18 years: 9% and 70%, respectively (ii) Decline in proportion of tests positive for RV 89%
134	**Clark et al. (2009)**	RQ; 02/2006	Philadelphia VC: NA	Prospective, active RV-surveillance in 1 hospital, 1991-2008, children of all ages	Decrease of cases (≥ 3 years) by around 76% after RV introduction	Increase of genotype G3 observed	Decline not observed	(i) Decrease of RVGE-hospitalisation by up to 87%

ED: Emergency department
NA: Not available
RQ: Rotateq
RVGE: Laboratory confirmed rotavirus gastroenteritis
RVV: Rotavirus vaccine(s)
RX: Rotarix
VC: Vaccine coverage
VE: Vaccine effectiveness

Table 5: Impact studies, USA (cont.)

Ref	Study (year)	Vaccine; year of availability	State/county; estimated vaccine coverage (VC)	Data source, study period	Herd immunity	Genotype distribution	Nosocomial infections	Main results
141	**Cortes et al (2010); ICID abstract**	RQ; 02/2006	8 locations in the USA VC: 60-70% (at least 1 dose); 03/2009	Sentinel immunization information system (8 locations) and national network of 70 laboratories; 2000-2009	NA	NA	NA	(i) Rotavirus activity declined by 64% (2007/08) and 60% (2008/09), respectively
135	**Payne et al (2011)**	RQ; 02/2006	Cincinnati, Nashville, Rochester VC in ARI cases: 2007:10%; 2009: 67%	New Vaccine Surveillance Network (NVSN); Prospective active surveillance for RV in children <3 years in 3 hospitals; 2006-2009	Decline of RVGE-hospitalisation by 92% (2008) but increase by 89% (2009) in children 24-35 months	Changes in genotypes reported	NA	(i) Decline in RVGE- hospitalisations in children < 3 years by 89% (2008) and 55% (2009), respectively (ii) Increase of median age of RV cases
136	**Tate et al. (2011)**	RQ; 02/2006	Nationwide VC: NA	Nationwide laboratory network (NREVSS); 2000-2010	NA	NA	NA	(i) Decrease in proportion of tests positive for RV: 65% reduction (2008), 58% (2009) and 86% (2010) (ii) RV activity onset delayed
137	**Yen et al. (2010)**	RQ; 02/2006	Nationwide VC: NA	National network of pediatric hospitals; hospital discharge data in children <5 years; 2003-2009	Reduction of AGE-hospitalisations by 17% (2007/08) and 48% (2008/09) in children aged 2-4 years	NA	NA	(i) Decline in AGE-hospitalisations in children < 5 years by 50% in 2007/08 and by 29% in 2008/09, respectively (ii) Decline in RVGE-hospitalisations in children < 5 years by 83% in 2007/08 and by 66% % in 2008/09, respectively

ED: Emergency department **RQ:** Rotateq **RVV:** Rotavirus vaccine(s) **VC:** Vaccine coverage
NA: Not available **RVGE:** Laboratory confirmed rotavirus gastroenteritis **RX:** Rotarix **VE:** Vaccine effectiveness

Table 6: Impact studies, Mexico

Ref	Study (year)	Vaccine; year of availability	Country/ estimated vaccine coverage (VC)	Data source, study period	Herd immunity	Genotype distribution	Nosocomial infections	Main results
138	**Quintanar-S et al. (2011)**	RX; 02/2006 (05/2007)	Mexico; VC: 74% one doses, 51% full course; 2008	National System of Health information (ICD-10 discharge data from all Mexican hospitals; children <5 years)	No significant effect observed in children >24 months	NA	NA	(i) Decline in AGE-hospitalisations in children < 5 years: 11% in 2008 to 40% in 2009
139	**Richardson et al. (2010)**	RX; 02/2006	Mexico; VC: see above	National System of Health information (ICD-10 discharge data from all Mexican hospitals; children <5 years); 2003-2009	No significant effect observed	NA	NA	(i) Decline in diarrhea-related mortality: Relative Reduction of 35% in children < 5 years
140	**Richardson et al. (2011)**	RX; 02/2006	Mexico; VC: see above	National System of Health information (ICD-10 discharge data from all Mexican hospitals); 2003-2010	NA	NA	NA	(i) Sustained decline in diarrhea-related mortality: 56% in children < 5 years

ED: Emergency department
NA: Not available
RQ: Rotateq
RVGE: Laboratory confirmed rotavirus gastroenteritis
RVV: Rotavirus vaccine(s)
RX: Rotarix
VC: Vaccine coverage
VE: Vaccine effectiveness

Table 7: Intussusception

Ref	Study (year)	Setting/ Country	Study design/ data source	Study period	Observed time period (after RVV)	Cases observed	Controls observed or expected	Point estimator (95% CI)
Rotateq								
149	**Belongia et al. (2007)**	**USA**	Passive national surveillance system (VAERS)	02/2006-02/2007	1-21 days after any dose 1-7 days after any dose 1-21 days after first dose	17 cases 11 cases 9 cases	expected: 52 expected: 17 expected: NA	RR: 0.3 (0.2-0.6) RR: 0.6 (0.3-1.2) NA
150	**Belongia et al. (2011)**	**USA**	Prospective cohort study; active national surveillance system (VSD)	11/2006-05/2008	1-30 days after any doses	5 cases among 207.000 doses administered	expected: 6.75	RR: 0.7 (ns, CI: NA)
					1-30 days after first dose	2 cases among 87.000 doses administered	expected: 1.41	RR: 1.4 (ns, CI: NA)
151	**Haber et al. (2008)**	**USA**	Observed vs. expected analysis; passive national surveillance system (VAERS)	02/2006-09/2007	1-21 days after any dose 1-7 days after any dose	47 cases 27 cases	expected: 151 expected: 50	RR: 0.5 (0.4-0.8) RR: 0.9 (0.6-1.4)
			Prospective cohort study; active national surveillance system (VSD)	02/2006-09/2007	1-30 days after any dose	3 among 111.521 doses administered	9 among 186.722 controls	RR: 0.8 (0.1-3.9)
152	**Loughlin et al. (2012)**	**USA**	Prospective cohort study; health insurance claims database	01/2006-12/2007	1-30 days after any dose	6 among 17.433 person- years	5 among 12.339 person-years	RR: 0.8 (CI 0.2-3.5)
			Prospective cohort study; health insurance claims database		1-30 days after first dose	4/ 7.049 person- years	3 among 5186 person-years	RR:1.0 (CI 0.2-6.7)
153	**Shui et al. (2012)**	**USA**	Comparative cohort study; concurrent comparison group; active national surveillance system (VSD)	2006-2010	1-30 days after any doses	14 among 786.725 doses administered	8 among 389.026 doses administered	RR: 0.95 (0.4-2.6)
					1-7 days after any doses	3 among 786.725 doses administered	2 among 389.026 doses administered	RR: 0.9 (0.1- 11.1)
					1-30 days after first dose	4 among 309.844 doses administered	0 among 102.523 doses administered	RR: undefined (0.2-∞)
					1-7 days after first dose	1 among 309.844 doses administered	0 among 102.523 doses administered	RR: undefined (0.01-∞)
			Comparative cohort study, historical comparison group; active national surveillance system (VSD)	2006-2010	1-30 days after first dose	7 among 309.844 doses administered	expected: 5.7	RR: 0.9 (0.1- 11.1)
					1-7 days after first dose	1 among 309.844 doses administered	expected: 0.8	RR: 1.2 (0.03-6.8)

CI: 95% confidence interval **OR**: Odds ratio **RR:** Risk ratio **VAERS:** Vaccine Adverse Event Reporting System, USA
IS: Intussusception **RI:** Relative incidence **RVV:** Rotavirus vaccination **VSD:** Vaccine Safety Datalink, USA

Table 7: Intussusception (cont.)

Ref	Study (year)	Setting/ Country	Study design/ data source	Study period	Observed time period (after RVV)	Cases observed	Controls observed or expected	Point estimator (95% CI)
Rotarix								
191	**Escolano et al. (2011)**	**Worldwide**	Case series analysis (data source: NA)	01/2005-02/2010	3-7 days after first dose	63 cases after dose 1	11 cases after dose 2 (comparison group)	Ratio of IR: 5.0 (1,7-14,3)
156	**Patel et al. (2011)**	**Brazil**	Case-series analysis; active surveillance at 53 hospitals	08/2008-08/2010	1-7 days after second dose	21/300	50/1169	IR: 2.6 (1.3-5.2)
			Case-control study; active surveillance at 53 hospitals		1-7 days after first dose	4/321	13/1271	Adjusted OR: 1.4 (0.4-4.8)
			Case-control study; active surveillance at 53 hospitals		1-7 days after second dose	21/300	50/1169	Adjusted OR: 1.9 (1.1-3.4)
		Mexico	Case-series analysis; active surveillance at 16 hospitals	08/2008-08/2010	1-7 days after first dose	24/274	17/701	IR: 5.3 (3.0-9.3)
			Case-control study; active surveillance at 16 hospitals		1-7 days after first dose	24/274	17/701	Adjusted OR: 5.8 (2.6-13.0)
Rotarix and Rotateq								
154	**Buttery et al. (2011)**	**Australia**	Two active national surveillance systems	07/2007-12/2008	1-21 days after any dose	**RX:** 13 cases among 302.455 doses administered	expected: 9.5	RR: 1.4 (0.7-2.3)
						RQ: 10 cases among 296.023 doses administerd	expected: 13.1	RR: 0.8 (0.4-1.4)
					1-7 days after any dose	**RX:** 5 cases among 302.455 doses administered	expected: 3.2	RR: 1.6 (0.5-3.7)
						RQ: 5 cases among 296.023 doses administerd	expected: 4.4	RR: 1.2 (0.4-2.7)
					1-7 days after first dose, infants 1 to <3 month	**RX:** 3 cases among 154.289 doses administered	expected: 0.9	RR: 3.5 (0.7-10.1)
						RQ: 3 cases among 111.553 doses administerd	expected: 0.6	RR: 5.3 (1.1-15.4)
155	**Carlin et al. (2011)**	**Australia**	Self-controlled case series analysis; active surveillance in 3 states	07/2007-12/2009	1-7 days after first dose	**RX:** 5 cases	Overall 274 IS cases in observed, 47 within 21 days	RI: 3.9 (1.5-9-9)
					1-7 days after first dose	**RQ:** 3 cases		RI: 4.1 (1.3-13.5)

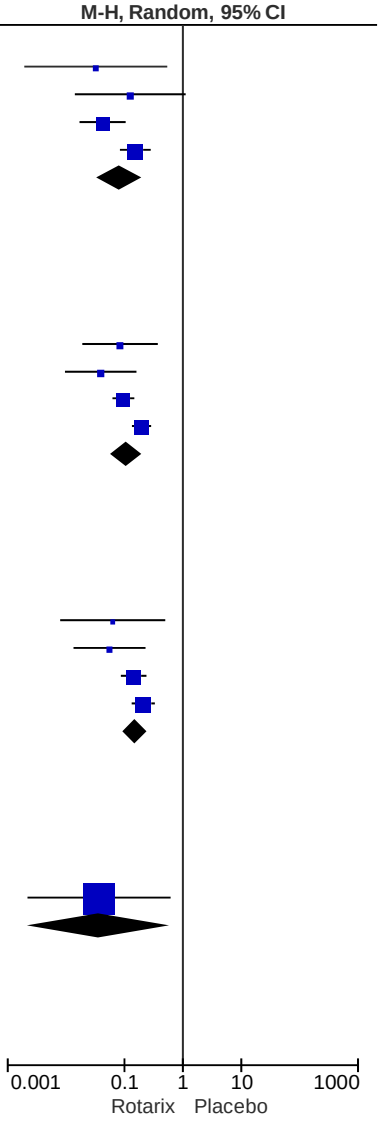
CI: 95% confidence interval **IS:** Intussusception **OR**: Odds ratio **RR:** Risk ratio
IR: Incidence ratio **NA:** Not applicable **RI:** Relative incidence **RVV:** Rotavirus vaccination

Appendix IV: Data and Analyses: Vaccine efficacy, Safety, Reactogenicity, Vaccine effectiveness

1: Comparison Rotarix vs placebo

1.1 Outcome RVGE, severe

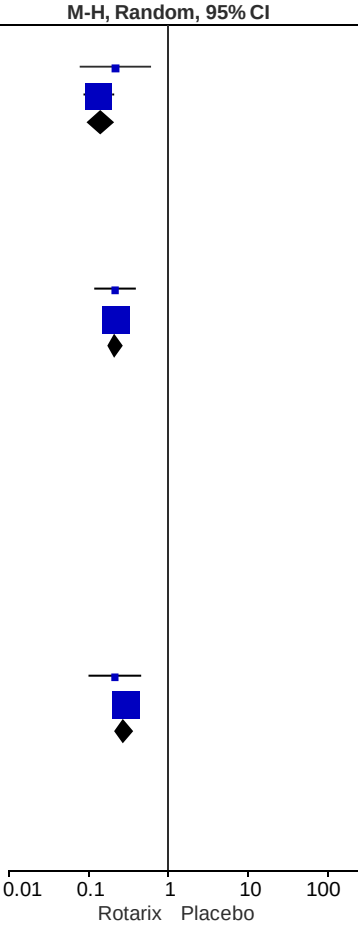
Study or Subgroup	Rotarix Events	Rotarix Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 1st year Phua-						
2009-RX Kawamura-	0	5263	15	5256	8.5%	0.03 [0.00, 0.54]
2011-RX	1	498	4	250	12.8%	0.13 [0.01, 1.12]
Vesikari-2007-RX	5	2572	60	1302	35.0%	0.04 [0.02, 0.10]
Ruiz-Palacios-2006-RX	12	9009	77	8858	43.8%	0.15 [0.08, 0.28]
Subtotal (95% CI)		**17342**		**15666**	**100.0%**	**0.08 [0.03, 0.20]**
Total events	18		156			
Heterogeneity: Tau² = 0.38; Chi² = 6.13, df = 3 (P = 0.11); I² = 51%						
Test for overall effect: Z = 5.46 (P < 0.00001)						
1.1.2 1st + 2nd year						
Kawamura-2011-RX	2	498	12	250	12.5%	0.08 [0.02, 0.37]
Phua-2009-RX	2	5263	51	5256	13.4%	0.04 [0.01, 0.16]
Vesikari-2007-RX	24	2572	127	1302	36.3%	0.10 [0.06, 0.15]
Ruiz-Palacios-2006-RX	32	7205	161	7081	37.8%	0.20 [0.13, 0.29]
Subtotal (95% CI)		**15538**		**13889**	**100.0%**	**0.11 [0.06, 0.20]**
Total events	60		351			
Heterogeneity: Tau² = 0.23; Chi² = 9.55, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 6.98 (P < 0.00001)						
1.1.4 2nd year						
Kawamura-2011-RX	1	498	8	250	4.8%	0.06 [0.01, 0.50]
Phua-2009-RX	2	5221	36	5194	9.6%	0.06 [0.01, 0.23]
Vesikari-2007-RX	19	2554	67	1294	41.0%	0.14 [0.09, 0.24]
Ruiz-Palacios-2006-RX	22	7175	103	7062	44.6%	0.21 [0.13, 0.33]
Subtotal (95% CI)		**15448**		**13800**	**100.0%**	**0.15 [0.09, 0.24]**
Total events	44		214			
Heterogeneity: Tau² = 0.07; Chi² = 4.51, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 7.93 (P < 0.00001)						
1.1.5 3rd year						
Phua-2009-RX	0	4222	13	4185	100.0%	0.04 [0.00, 0.62]
Subtotal (95% CI)		**4222**		**4185**	**100.0%**	**0.04 [0.00, 0.62]**
Total events	0		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.29 (P = 0.02)						



Test for subgroup differences: Chi² = 2.23, df = 3 (P = 0.53), I² = 0%

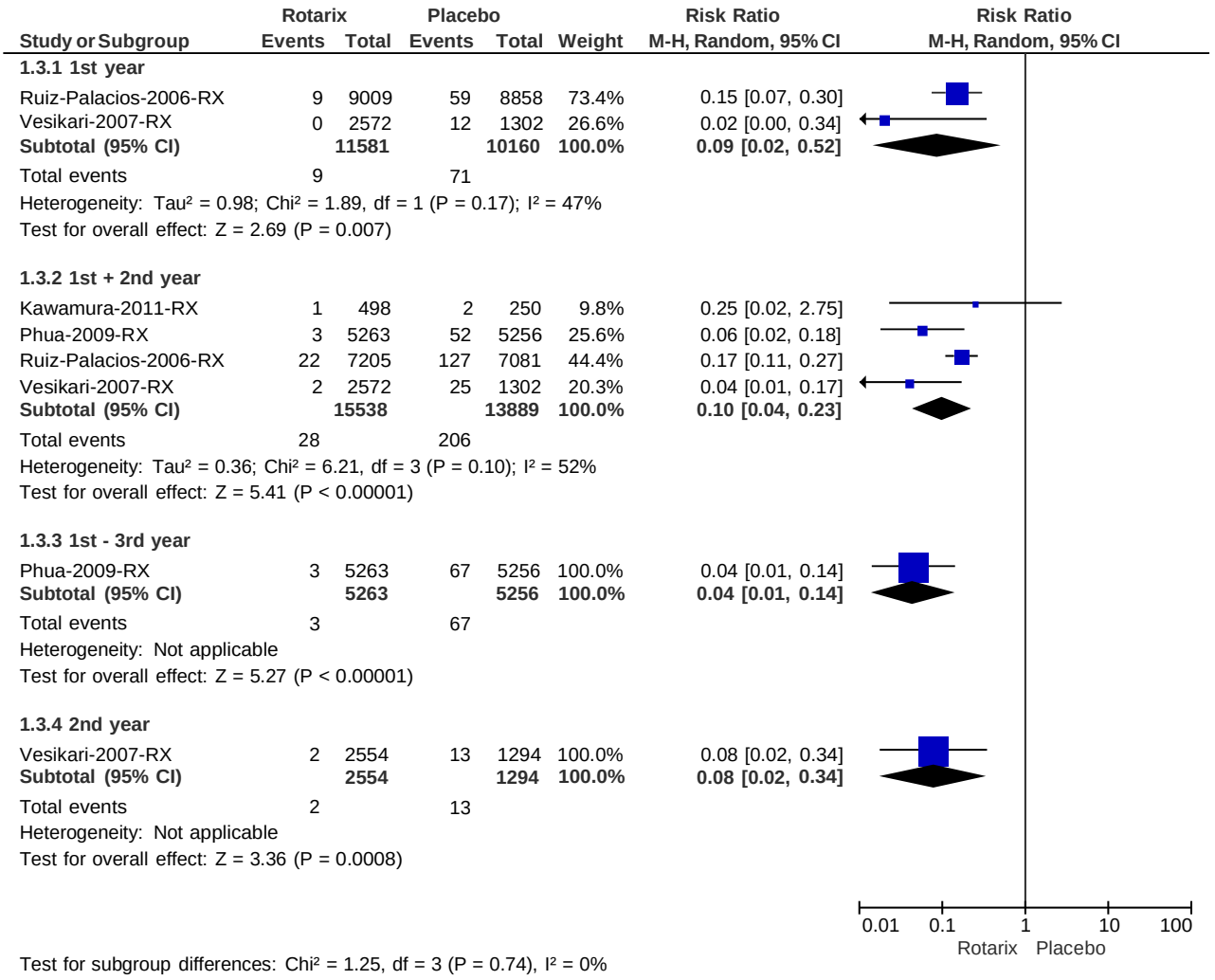
1.2 Outcome RVGE, any severity

Study or Subgroup	Rotarix Events	Rotarix Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 1st year						
Kawamura-2011-RX	5	498	12	250	15.6%	0.21 [0.07, 0.59]
Vesikari-2007-RX	24	2572	94	1302	84.4%	0.13 [0.08, 0.20]
Subtotal (95% CI)		**3070**		**1552**	**100.0%**	**0.14 [0.09, 0.21]**
Total events	29		106			
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 9.49 (P < 0.00001)						
1.2.2 1st + 2nd year						
Kawamura-2011-RX	14	498	34	250	14.1%	0.21 [0.11, 0.38]
Vesikari-2007-RX	85	2572	204	1302	85.9%	0.21 [0.17, 0.27]
Subtotal (95% CI)		**3070**		**1552**	**100.0%**	**0.21 [0.17, 0.26]**
Total events	99		238			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 13.50 (P < 0.00001)						
1.2.3 1st - 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.4 2nd year						
Kawamura-2011-RX	9	498	22	250	13.9%	0.21 [0.10, 0.44]
Vesikari-2007-RX	61	2554	110	1294	86.1%	0.28 [0.21, 0.38]
Subtotal (95% CI)		**3052**		**1544**	**100.0%**	**0.27 [0.20, 0.36]**
Total events	70		132			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 9.07 (P < 0.00001)						



Test for subgroup differences: Chi² = 6.79, df = 2 (P = 0.03), I² = 70.5%

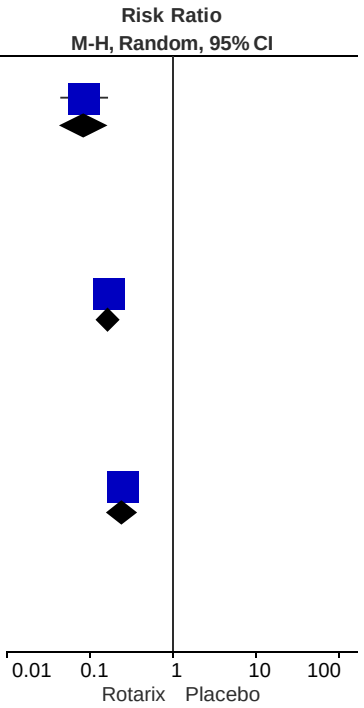
1.3 Outcome RVGE, hospitalization



Test for subgroup differences: Chi² = 1.25, df = 3 (P = 0.74), I² = 0%

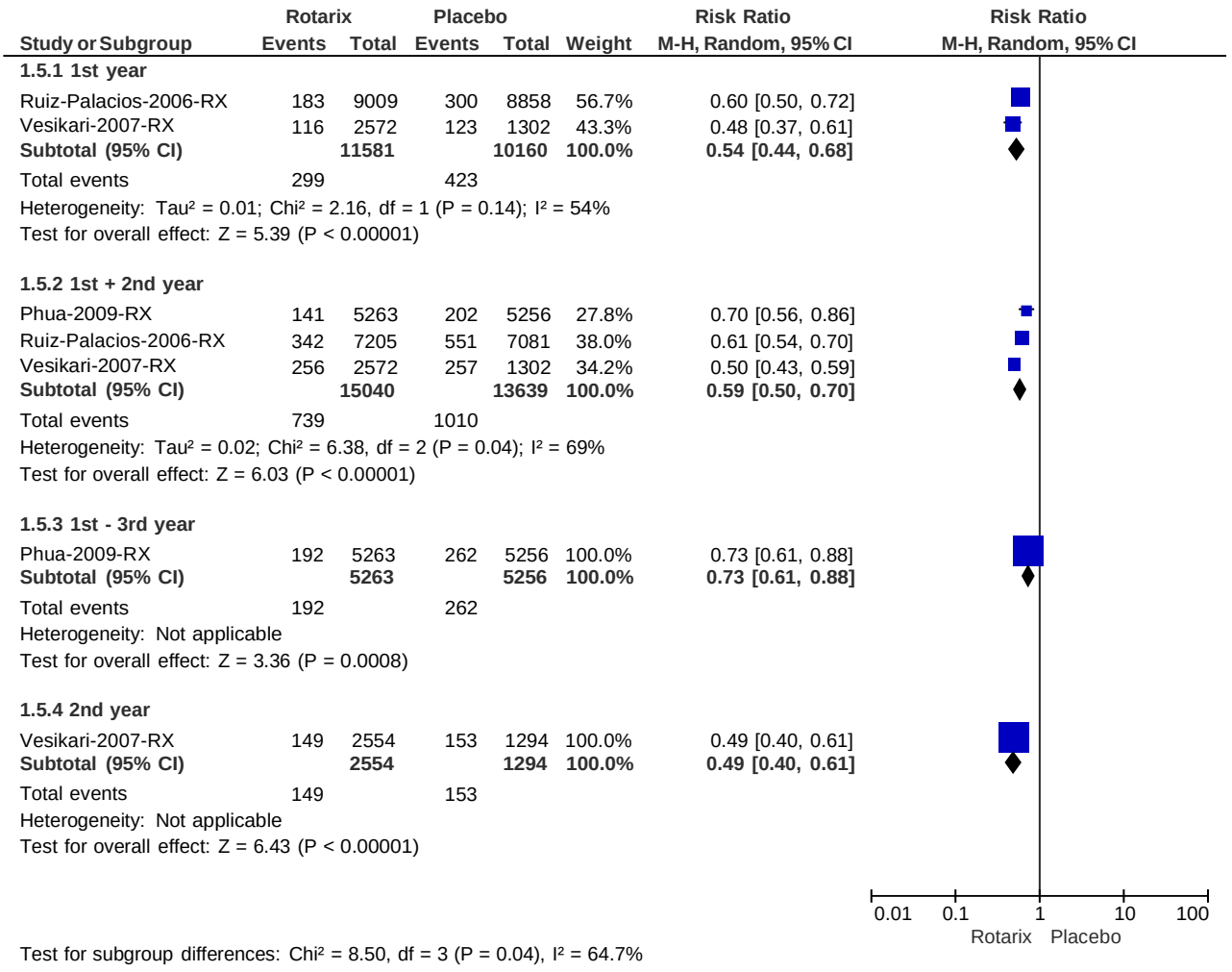
1.4 Outcome RVGE, medical attention

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 1st year						
Vesikari-2007-RX	10	2572	62	1302	100.0%	0.08 [0.04, 0.16]
Subtotal (95% CI)		**2572**		**1302**	**100.0%**	**0.08 [0.04, 0.16]**
Total events	10		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.39 (P < 0.00001)						
1.4.2 1st + 2nd year						
Vesikari-2007-RX	41	2572	128	1302	100.0%	0.16 [0.11, 0.23]
Subtotal (95% CI)		**2572**		**1302**	**100.0%**	**0.16 [0.11, 0.23]**
Total events	41		128			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.32 (P < 0.00001)						
1.4.4 2nd year						
Vesikari-2007-RX	31	2554	66	1294	100.0%	0.24 [0.16, 0.36]
Subtotal (95% CI)		**2554**		**1294**	**100.0%**	**0.24 [0.16, 0.36]**
Total events	31		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.68 (P < 0.00001)						



Test for subgroup differences: $Chi^2 = 7.19$, df = 2 (P = 0.03), $I^2 = 72.2\%$

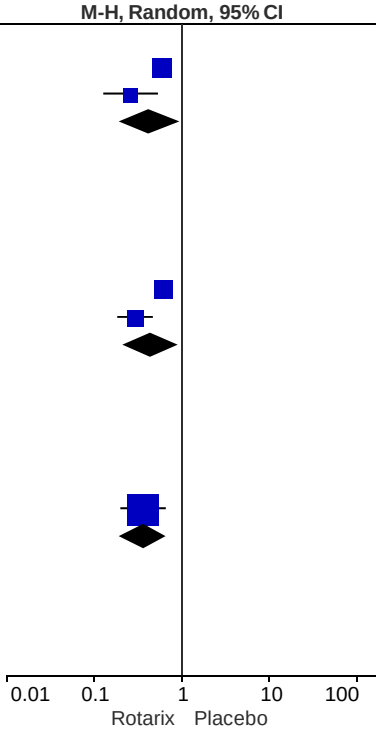
1.5 Outcome all cause GE, severe



Test for subgroup differences: Chi² = 8.50, df = 3 (P = 0.04), I² = 64.7%

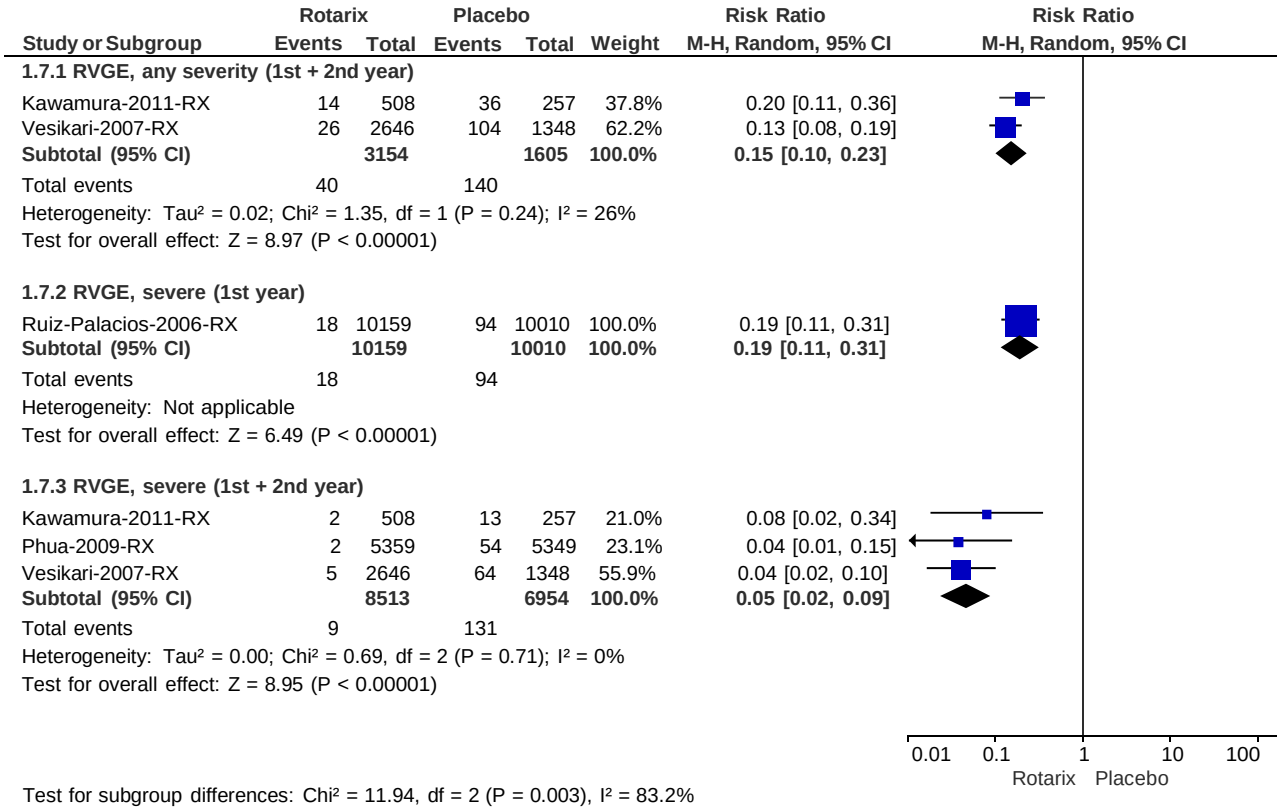
1.6 Outcome all cause GE, hospitalization

Study or Subgroup	Rotarix Events	Rotarix Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 1st year						
Ruiz-Palacios-2006-RX	145	9009	246	8858	59.1%	0.58 [0.47, 0.71]
Vesikari-2007-RX	11	2572	22	1302	40.9%	0.25 [0.12, 0.52]
Subtotal (95% CI)		**11581**		**10160**	**100.0%**	**0.41 [0.19, 0.92]**
Total events	156		268			
Heterogeneity: Tau² = 0.27; Chi² = 4.70, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 2.17 (P = 0.03)						
1.6.2 1st + 2nd year						
Ruiz-Palacios-2006-RX	265	7205	429	7081	54.4%	0.61 [0.52, 0.71]
Vesikari-2007-RX	27	2572	48	1302	45.6%	0.28 [0.18, 0.45]
Subtotal (95% CI)		**9777**		**8383**	**100.0%**	**0.43 [0.21, 0.90]**
Total events	292		477			
Heterogeneity: Tau² = 0.26; Chi² = 9.16, df = 1 (P = 0.002); I² = 89%						
Test for overall effect: Z = 2.24 (P = 0.03)						
1.6.4 2nd year						
Vesikari-2007-RX	18	2554	26	1294	100.0%	0.35 [0.19, 0.64]
Subtotal (95% CI)		**2554**		**1294**	**100.0%**	**0.35 [0.19, 0.64]**
Total events	18		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.44 (P = 0.0006)						



Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%

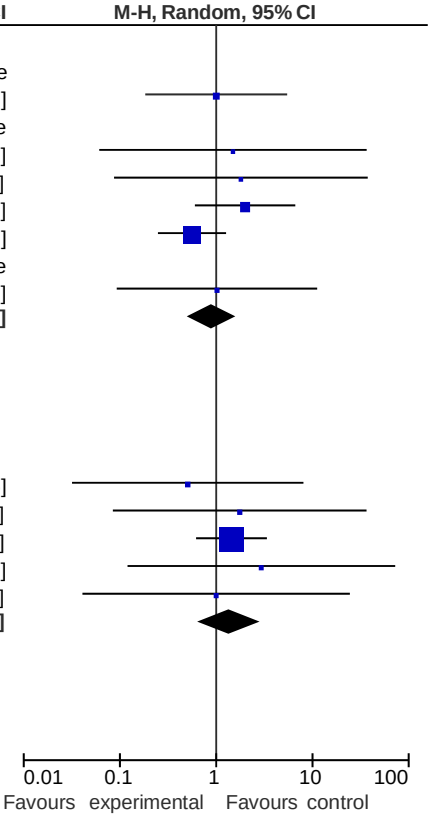
1.7 MITT-analysis



Test for subgroup differences: Chi² = 11.94, df = 2 (P = 0.003), I² = 83.2%

1.8 Outcome Serious adverse events

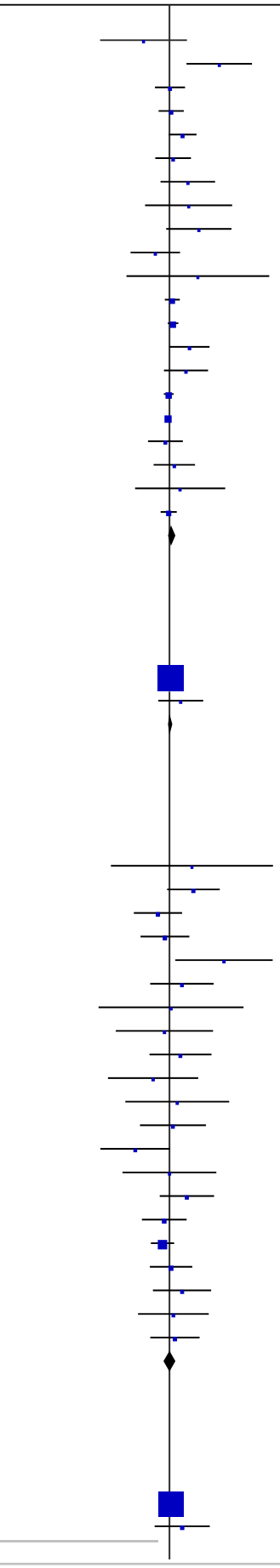
Study or Subgroup	Rotarix Events	Rotarix Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Intussusception						
Dennehy-2005-RX	0	421	0	108		Not estimable
GSK[024]-2008-RX	4	4376	2	2192	11.9%	1.00 [0.18, 5.47]
Kawamura-2011-RX	0	508	0	257		Not estimable
Madhi-2010-RX	1	3298	0	1641	3.3%	1.49 [0.06, 36.63]
Phua-2005-RX	2	1811	0	653	3.7%	1.80 [0.09, 37.54]
Phua-2009-RX	8	5359	4	5349	23.8%	2.00 [0.60, 6.63]
Ruiz-Palacios-2006-RX	9	31673	16	31552	51.3%	0.56 [0.25, 1.27]
Vesikari-2004-RX	0	270	0	135		Not estimable
Vesikari-2007-RX	2	2646	1	1348	5.9%	1.02 [0.09, 11.23]
Subtotal (95% CI)		**50362**		**43235**	**100.0%**	**0.91 [0.51, 1.63]**
Total events	26		23			
Heterogeneity: Tau² = 0.00; Chi² = 3.31, df = 5 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.8.2 Kawasaki						
Kawamura-2011-RX	1	508	1	257	7.2%	0.51 [0.03, 8.06]
Phua-2005-RX	2	1811	0	635	6.0%	1.75 [0.08, 36.51]
Phua-2009-RX	13	5359	9	5349	76.2%	1.44 [0.62, 3.37]
Ruiz-Palacios-2006-RX	1	7636	0	7493	5.4%	2.94 [0.12, 72.25]
Salinas-2005-RX	1	1618	0	537	5.4%	1.00 [0.04, 24.44]
Subtotal (95% CI)		**16932**		**14271**	**100.0%**	**1.38 [0.66, 2.89]**
Total events	18		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.40)						

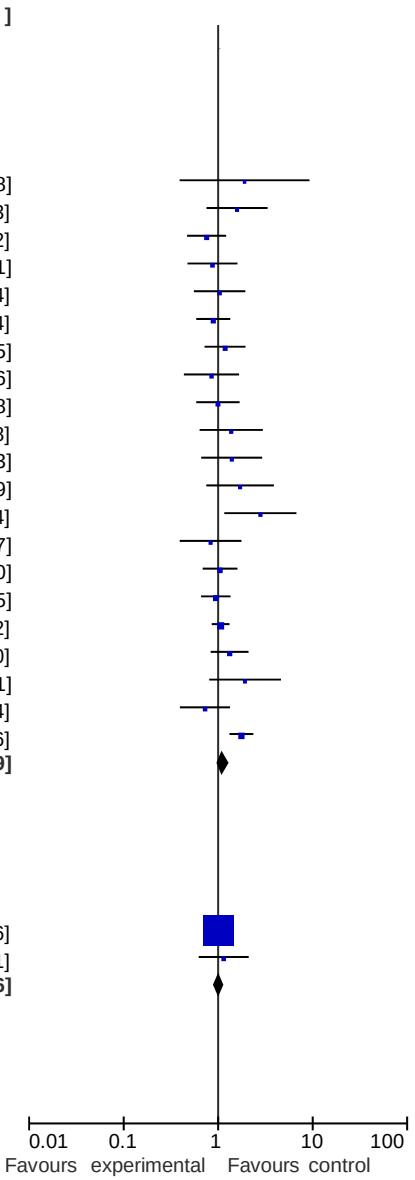


Test for subgroup differences: Chi² = 0.75, df = 1 (P = 0.39), I² = 0%

1.9 Outcome Reactogenicity

Study or Subgroup	Rotarix Events	Rotarix Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Fever after 1st dose						
Bernstein-1998-RX	3	21	6	20	0.6%	0.48 [0.14, 1.65]
Bernstein-1999-RX	21	108	5	107	1.0%	4.16 [1.63, 10.63]
Dennehy-2005-RX	83	421	21	108	4.1%	1.01 [0.66, 1.56]
GSK [013]-2007-RX	62	189	30	96	5.4%	1.05 [0.73, 1.50]
GSK [021]-2007-RX	91	177	18	51	4.6%	1.46 [0.98, 2.17]
GSK[033]-2007-RX	98	730	15	124	3.1%	1.11 [0.67, 1.85]
GSK[039]-2007-RX	68	348	6	52	1.4%	1.69 [0.77, 3.70]
GSK[041]-2007-RX	10	100	3	52	0.6%	1.73 [0.50, 6.03]
GSK[044]-2007-RX	14	182	6	181	1.0%	2.32 [0.91, 5.90]
GSK[045]-2007-RX	16	196	12	98	1.7%	0.67 [0.33, 1.35]
GSK[048]-2007-RX	9	200	1	50	0.2%	2.25 [0.29, 17.35]
GSK[051]-2008-RX	182	297	44	78	10.2%	1.09 [0.88, 1.35]
GSK[063]-2008-RX	239	300	54	75	13.6%	1.11 [0.95, 1.29]
GSK[101555]-2008-RX	39	100	11	50	2.5%	1.77 [1.00, 3.16]
Kawamura-2011-RX	38	508	12	257	2.1%	1.60 [0.85, 3.01]
Phua-2005-RX	497	1811	183	653	14.0%	0.98 [0.85, 1.13]
Salinas-2005-RX	1002	1618	346	537	18.2%	0.96 [0.89, 1.03]
Steele-2008-RX	37	297	21	150	3.2%	0.89 [0.54, 1.46]
Vesikari-2004-RX	32	265	14	133	2.4%	1.15 [0.63, 2.07]
Vesikari-2004a-RX	8	122	3	62	0.6%	1.36 [0.37, 4.93]
Vesikari-2007-RX	166	914	91	490	9.5%	0.98 [0.78, 1.23]
Subtotal (95% CI)		**8904**		**3424**	**100.0%**	**1.09 [0.99, 1.20]**
Total events	2715		902			
Heterogeneity: Tau² = 0.01; Chi² = 31.73, df = 20 (P = 0.05); I² = 37%						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.9.2 Fever after 2nd dose						
Cochrane Review-2010	2563	8188	895	2968	99.0%	1.04 [0.97, 1.11]
Kawamura-2011-RX	33	499	12	250	1.0%	1.38 [0.72, 2.62]
Subtotal (95% CI)		**8687**		**3218**	**100.0%**	**1.04 [0.98, 1.11]**
Total events	2596		907			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
1.9.3 Diarrhoea after 1st dose						
Bernstein-1998-RX	2	21	1	20	0.5%	1.90 [0.19, 19.40]
Bernstein-1999-RX	18	108	9	107	5.2%	1.98 [0.93, 4.21]
Dennehy-2005-RX	28	421	10	108	6.2%	0.72 [0.36, 1.43]
GSK [013]-2007-RX	19	189	11	96	6.0%	0.88 [0.44, 1.77]
GSK [021]-2007-RX	33	177	2	51	1.5%	4.75 [1.18, 19.14]
GSK[033]-2007-RX	42	730	5	124	3.6%	1.43 [0.58, 3.54]
GSK[039]-2007-RX	7	348	1	52	0.7%	1.05 [0.13, 8.33]
GSK[041]-2007-RX	5	100	3	52	1.5%	0.87 [0.22, 3.49]
GSK[044]-2007-RX	11	182	8	181	3.8%	1.37 [0.56, 3.32]
GSK[045]-2007-RX	5	196	4	98	1.8%	0.63 [0.17, 2.28]
GSK[048]-2007-RX	10	200	2	50	1.3%	1.25 [0.28, 5.53]
GSK[051]-2008-RX	21	297	5	78	3.3%	1.10 [0.43, 2.83]
GSK[063]-2008-RX	9	300	6	75	2.9%	0.38 [0.14, 1.02]
GSK[101555]-2008-RX	6	100	3	50	1.6%	1.00 [0.26, 3.83]
Kawamura-2011-RX	26	508	8	257	4.9%	1.64 [0.76, 3.58]
Phua-2005-RX	31	1811	13	653	7.2%	0.86 [0.45, 1.63]
Salinas-2005-RX	111	1618	45	537	26.8%	0.82 [0.59, 1.14]
Steele-2008-RX	29	297	14	150	8.0%	1.05 [0.57, 1.92]
Vesikari-2004-RX	20	265	7	133	4.2%	1.43 [0.62, 3.31]
Vesikari-2004a-RX	11	122	5	62	2.9%	1.12 [0.41, 3.08]
Vesikari-2007-RX	24	914	11	490	5.9%	1.17 [0.58, 2.37]
Subtotal (95% CI)		**8904**		**3424**	**100.0%**	**1.02 [0.86, 1.21]**
Total events	468		173			
Heterogeneity: Tau² = 0.00; Chi² = 19.06, df = 20 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.9.4 Diarrhoea after 2nd dose						
Cochrane Review-2010	358	8188	125	2968	94.0%	1.04 [0.85, 1.27]
Kawamura-2011-RX	23	499	8	250	6.0%	1.44 [0.65, 3.17]
Subtotal (95% CI)		**8687**		**3218**	**100.0%**	**1.06 [0.87, 1.28]**

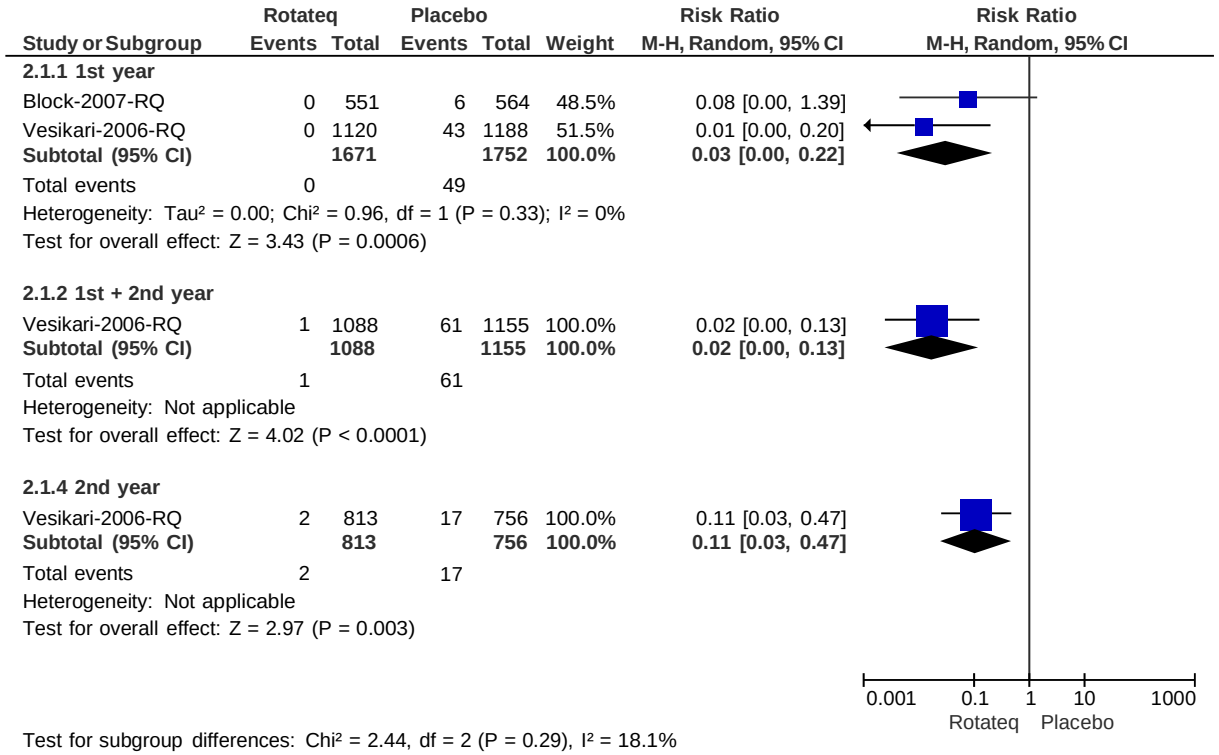




Total events	381		133			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.9.5 Vomiting after 1st dose						
Bernstein-1998-RX	4	21	2	20	0.7%	1.90 [0.39, 9.28]
Bernstein-1999-RX	16	108	10	107	2.8%	1.59 [0.75, 3.33]
Dennehy-2005-RX	56	421	19	108	5.7%	0.76 [0.47, 1.22]
GSK [013]-2007-RX	24	189	14	96	3.9%	0.87 [0.47, 1.61]
GSK [021]-2007-RX	36	177	10	51	3.7%	1.04 [0.55, 1.94]
GSK[033]-2007-RX	115	730	22	124	6.9%	0.89 [0.59, 1.34]
GSK[039]-2007-RX	103	348	13	52	5.3%	1.18 [0.72, 1.95]
GSK[041]-2007-RX	18	100	11	52	3.4%	0.85 [0.43, 1.66]
GSK[044]-2007-RX	24	182	24	181	4.9%	0.99 [0.59, 1.68]
GSK[045]-2007-RX	22	196	8	98	2.7%	1.38 [0.64, 2.98]
GSK[048]-2007-RX	39	200	7	50	2.8%	1.39 [0.66, 2.93]
GSK[051]-2008-RX	39	297	6	78	2.4%	1.71 [0.75, 3.89]
GSK[063]-2008-RX	56	300	5	75	2.1%	2.80 [1.16, 6.74]
GSK[101555]-2008-RX	15	100	9	50	2.8%	0.83 [0.39, 1.77]
Kawamura-2011-RX	58	508	28	257	6.6%	1.05 [0.68, 1.60]
Phua-2005-RX	102	1811	39	653	8.2%	0.94 [0.66, 1.35]
Salinas-2005-RX	285	1618	89	537	12.9%	1.06 [0.86, 1.32]
Steele-2008-RX	55	297	21	150	5.9%	1.32 [0.83, 2.10]
Vesikari-2004-RX	23	265	6	133	2.1%	1.92 [0.80, 4.61]
Vesikari-2004a-RX	20	122	14	62	3.9%	0.73 [0.39, 1.34]
Vesikari-2007-RX	171	914	52	490	10.2%	1.76 [1.32, 2.36]
Subtotal (95% CI)		**8904**		**3424**	**100.0%**	**1.13 [0.99, 1.29]**
Total events	1281		409			
Heterogeneity: Tau² = 0.02; Chi² = 27.76, df = 20 (P = 0.12); I² = 28%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.9.6 Vomiting after 2nd dose						
Cochrane Review-2010	820	8188	292	2968	95.9%	1.02 [0.90, 1.16]
Kawamura-2011-RX	32	499	14	250	4.1%	1.15 [0.62, 2.11]
Subtotal (95% CI)		**8687**		**3218**	**100.0%**	**1.02 [0.90, 1.16]**
Total events	852		306			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 1.93, df = 5 (P = 0.86), I² = 0%						

2: Comparison Rotateq vs placebo

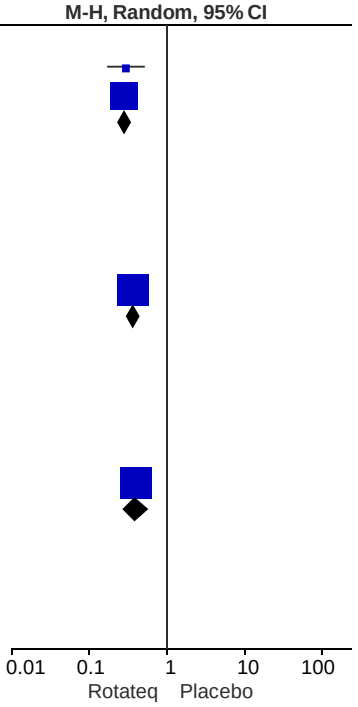
2. Outcome 1 RVGE, severe



Test for subgroup differences: Chi² = 2.44, df = 2 (P = 0.29), I² = 18.1%

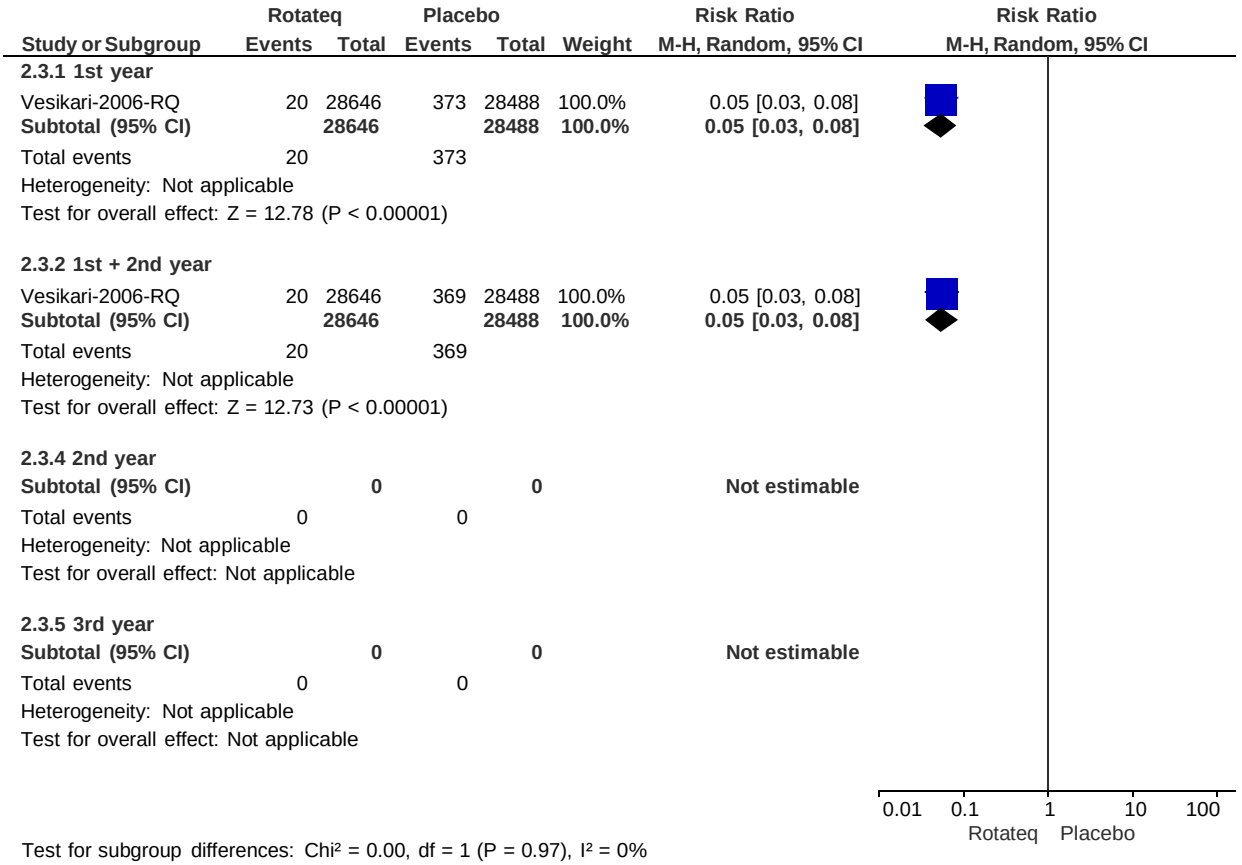
2.2 Outcome RVGE, any severity

Study or Subgroup	Rotateq Events	Rotateq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 1st year						
Block-2007-RQ	15	551	54	564	15.1%	0.28 [0.16, 0.50]
Vesikari-2006-RQ	82	2207	315	2305	84.9%	0.27 [0.21, 0.34]
Subtotal (95% CI)		**2758**		**2869**	**100.0%**	**0.27 [0.22, 0.34]**
Total events	97		369			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 11.68 (P < 0.00001)						
2.2.2 1st + 2nd year						
Vesikari-2006-RQ	112	1100	338	1173	100.0%	0.35 [0.29, 0.43]
Subtotal (95% CI)		**1100**		**1173**	**100.0%**	**0.35 [0.29, 0.43]**
Total events	112		338			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.34 (P < 0.00001)						
2.2.4 2nd year						
Vesikari-2006-RQ	36	813	88	756	100.0%	0.38 [0.26, 0.55]
Subtotal (95% CI)		**813**		**756**	**100.0%**	**0.38 [0.26, 0.55]**
Total events	36		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.05 (P < 0.00001)						



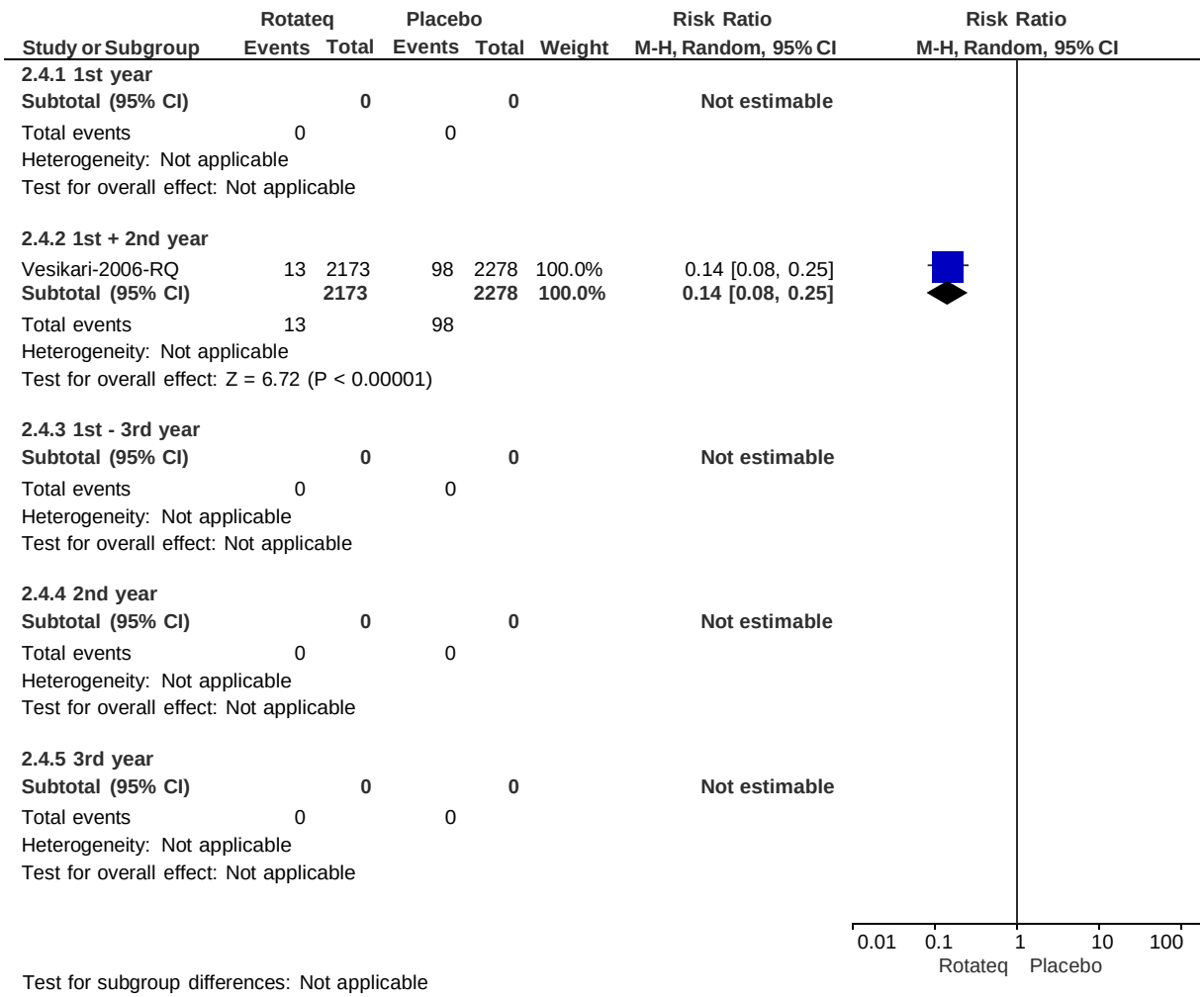
Test for subgroup differences: Chi² = 3.76, df = 2 (P = 0.15), I² = 46.8%

2.3 Outcome RVGE, hospitalization



Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$

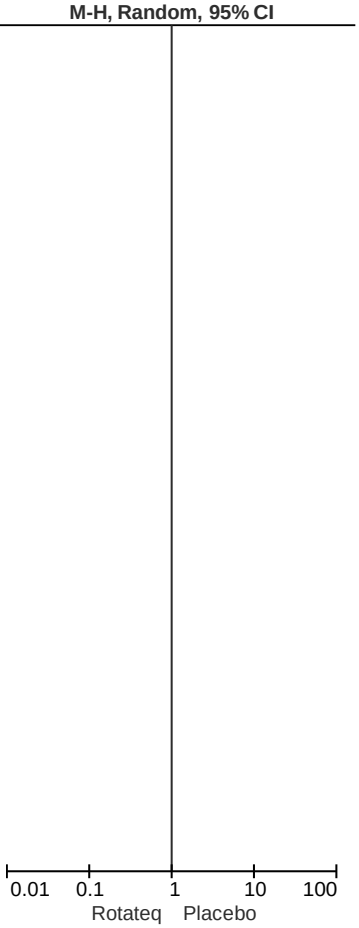
2.4 Outcome RVGE, medical attention



Test for subgroup differences: Not applicable

2.5 Outcome all cause GE, severe

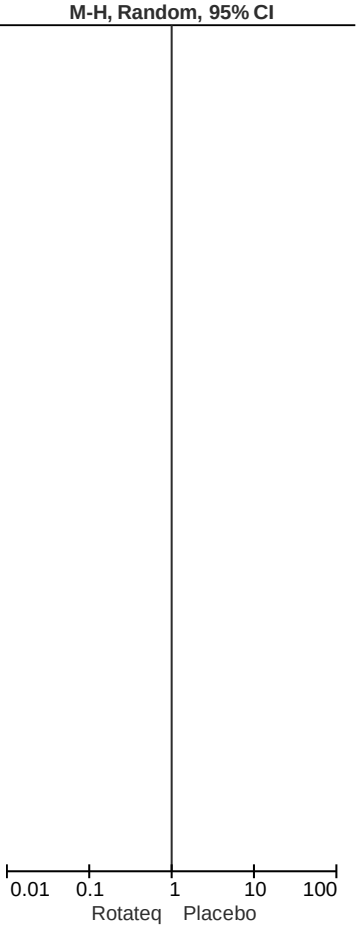
Study or Subgroup	Rotateq Events	Rotateq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 1st year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.2 1st + 2nd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.3 1st - 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.4 2nd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.5 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

2.6 Outcome all cause GE, hospitalization

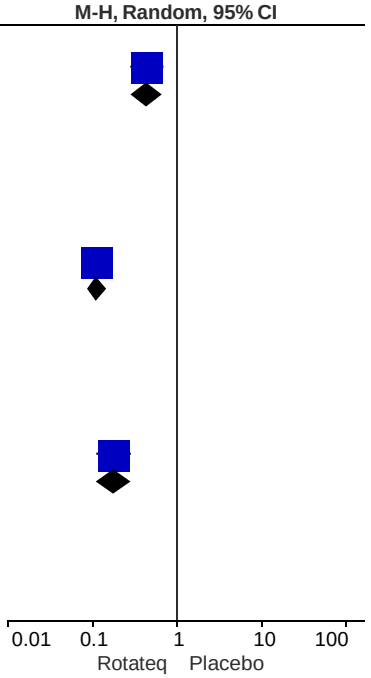
Study or Subgroup	Rotateq Events	Rotateq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 1st year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.2 1st + 2nd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.3 1st - 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.4 2nd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.5 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

2.7 MITT-analysis

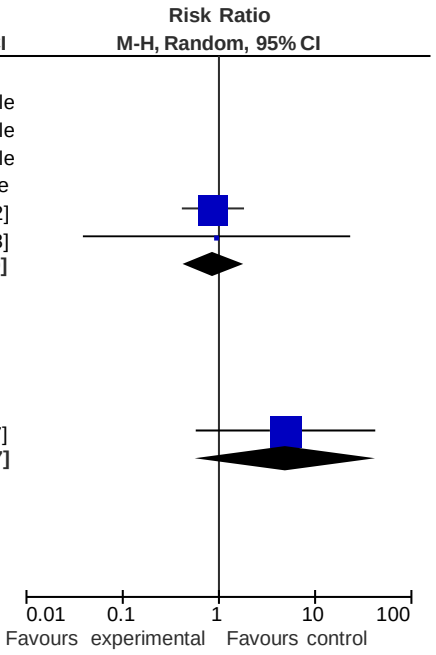
Study or Subgroup	Rotateq Events	Rotateq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 RVGE, any severity 1st year						
Block-2007-RQ	27	650	64	660	100.0%	0.43 [0.28, 0.66]
Subtotal (95% CI)		**650**		**660**	**100.0%**	**0.43 [0.28, 0.66]**
Total events	27		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.81 (P = 0.0001)						
2.7.2 RVGE, hospitalization 1st + 2nd year						
Vesikari-2006-RQ	58	33163	522	33015	100.0%	0.11 [0.08, 0.15]
Subtotal (95% CI)		**33163**		**33015**	**100.0%**	**0.11 [0.08, 0.15]**
Total events	58		522			
Heterogeneity: Not applicable						
Test for overall effect: Z = 15.93 (P < 0.00001)						
2.7.3 RVGE, medical attention (1st + 2nd year)						
Vesikari-2006-RQ	21	2403	123	2432	100.0%	0.17 [0.11, 0.27]
Subtotal (95% CI)		**2403**		**2432**	**100.0%**	**0.17 [0.11, 0.27]**
Total events	21		123			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.49 (P < 0.00001)						



Test for subgroup differences: Chi² = 26.75, df = 2 (P < 0.00001), I² = 92.5%

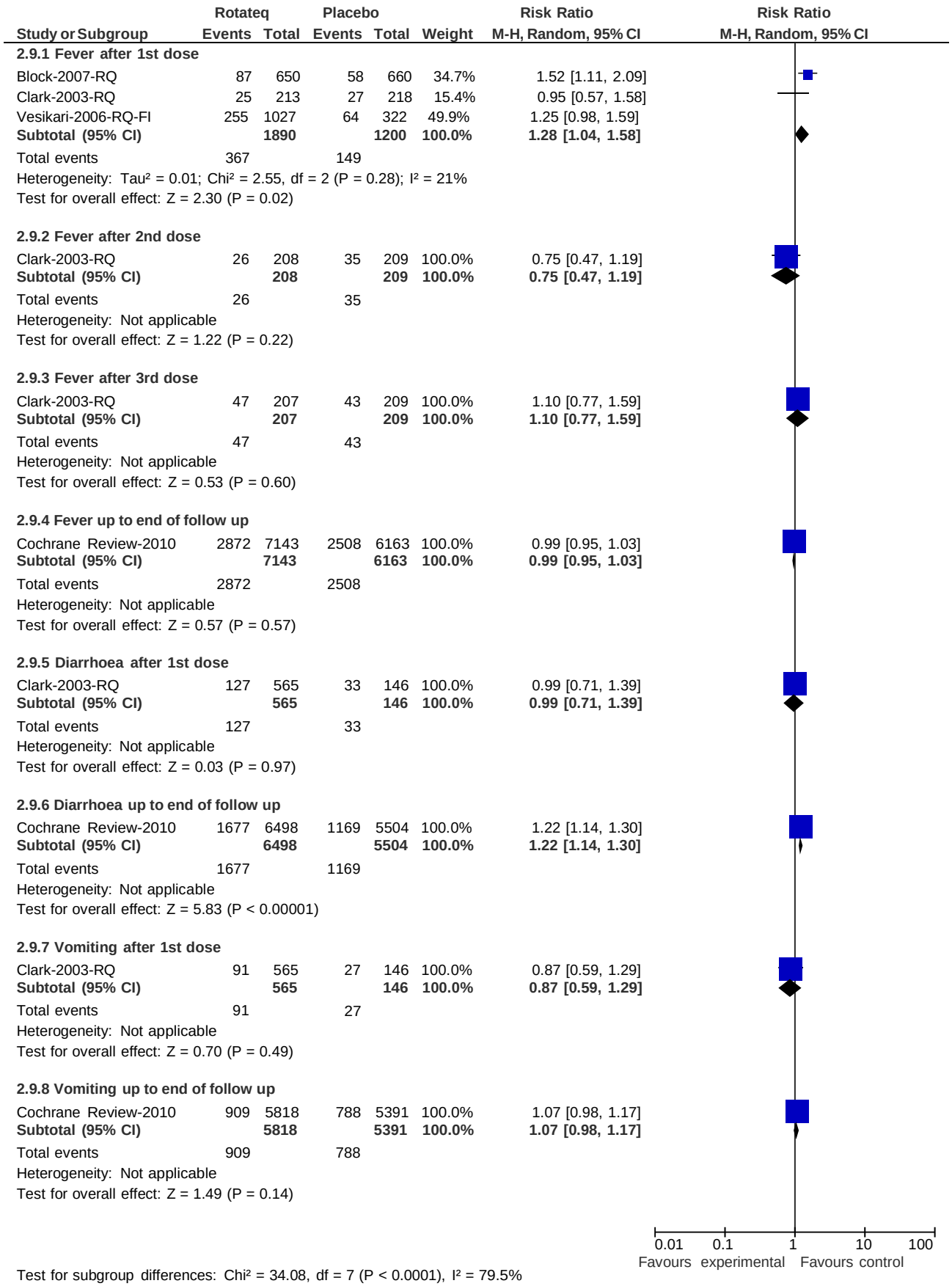
2.8 Outcome Serious adverse events

Study or Subgroup	Rotateq Events	Rotateq Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Intussusception						
Block-2007-RQ	0	650	0	660		Not estimable
Ciarlet-2009-RQ	0	201	0	202		Not estimable
Clark-2003-RQ	0	573	0	148		Not estimable
Kim-2008-RQ	0	115	0	63		Not estimable
Vesikari-2006-RQ	13	34002	15	33969	94.9%	0.87 [0.41, 1.82]
Vesikari-2006-RQ-FI	1	1027	0	322	5.1%	0.94 [0.04, 23.08]
Subtotal (95% CI)		**36568**		**35364**	**100.0%**	**0.87 [0.42, 1.79]**
Total events	14		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
2.8.2 Kawasaki						
Vesikari-2006-RQ	5	36150	1	35536	100.0%	4.92 [0.57, 42.07]
Subtotal (95% CI)		**36150**		**35536**	**100.0%**	**4.92 [0.57, 42.07]**
Total events	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						



Test for subgroup differences: Chi² = 2.25, df = 1 (P = 0.13), I² = 55.5%

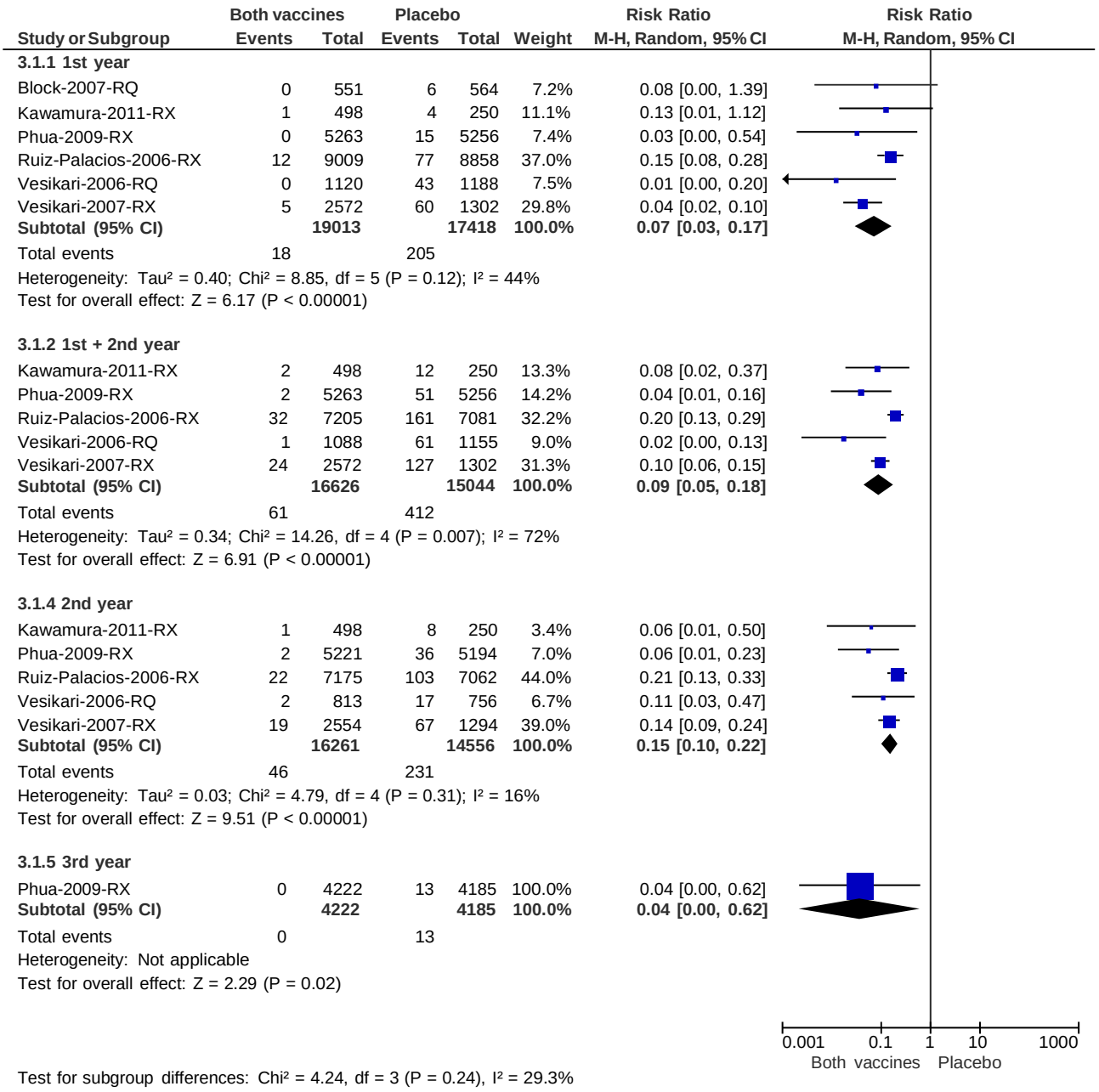
2.9 Outcome Reactogenicity



Test for subgroup differences: Chi² = 34.08, df = 7 (P < 0.0001), I² = 79.5%

3: Comparison both vaccines vs placebo

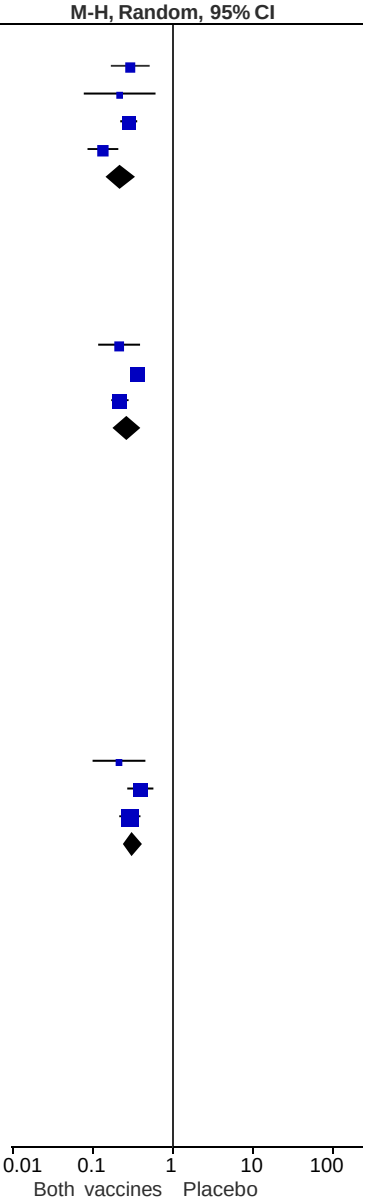
3.1 Outcome RVGE, severe



Test for subgroup differences: Chi² = 4.24, df = 3 (P = 0.24), I² = 29.3%

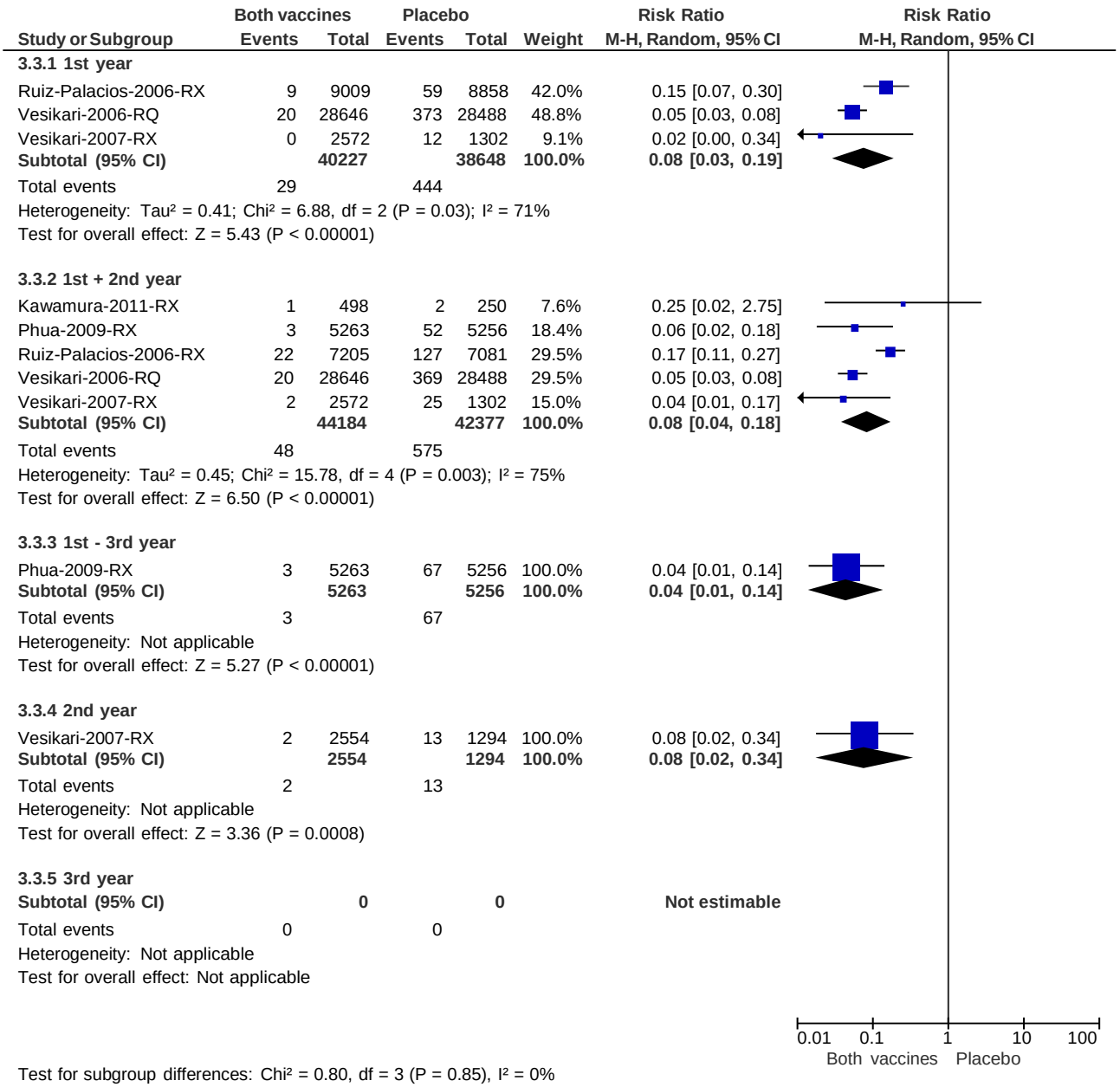
3.2 Outcome RVGE, any severity

Study or Subgroup	Both vaccines Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 1st year						
Block-2007-RQ	15	551	54	564	23.7%	0.28 [0.16, 0.50]
Kawamura-2011-RX	5	498	12	250	11.8%	0.21 [0.07, 0.59]
Vesikari-2006-RQ	82	2207	315	2305	36.4%	0.27 [0.21, 0.34]
Vesikari-2007-RX	24	2572	94	1302	28.2%	0.13 [0.08, 0.20]
Subtotal (95% CI)		**5828**		**4421**	**100.0%**	**0.22 [0.14, 0.33]**
Total events	126		475			
Heterogeneity: Tau² = 0.11; Chi² = 8.95, df = 3 (P = 0.03); I² = 66%						
Test for overall effect: Z = 7.17 (P < 0.00001)						
3.2.2 1st + 2nd year						
Kawamura-2011-RX	14	498	34	250	22.6%	0.21 [0.11, 0.38]
Vesikari-2006-RQ	112	1100	338	1173	39.6%	0.35 [0.29, 0.43]
Vesikari-2007-RX	85	2572	204	1302	37.8%	0.21 [0.17, 0.27]
Subtotal (95% CI)		**4170**		**2725**	**100.0%**	**0.26 [0.17, 0.39]**
Total events	211		576			
Heterogeneity: Tau² = 0.10; Chi² = 11.48, df = 2 (P = 0.003); I² = 83%						
Test for overall effect: Z = 6.44 (P < 0.00001)						
3.2.3 1st - 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.4 2nd year						
Kawamura-2011-RX	9	498	22	250	12.0%	0.21 [0.10, 0.44]
Vesikari-2006-RQ	36	813	88	756	38.1%	0.38 [0.26, 0.55]
Vesikari-2007-RX	61	2554	110	1294	49.9%	0.28 [0.21, 0.38]
Subtotal (95% CI)		**3865**		**2300**	**100.0%**	**0.30 [0.23, 0.40]**
Total events	106		220			
Heterogeneity: Tau² = 0.02; Chi² = 2.65, df = 2 (P = 0.27); I² = 25%						
Test for overall effect: Z = 8.45 (P < 0.00001)						
3.2.5 3rd year						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



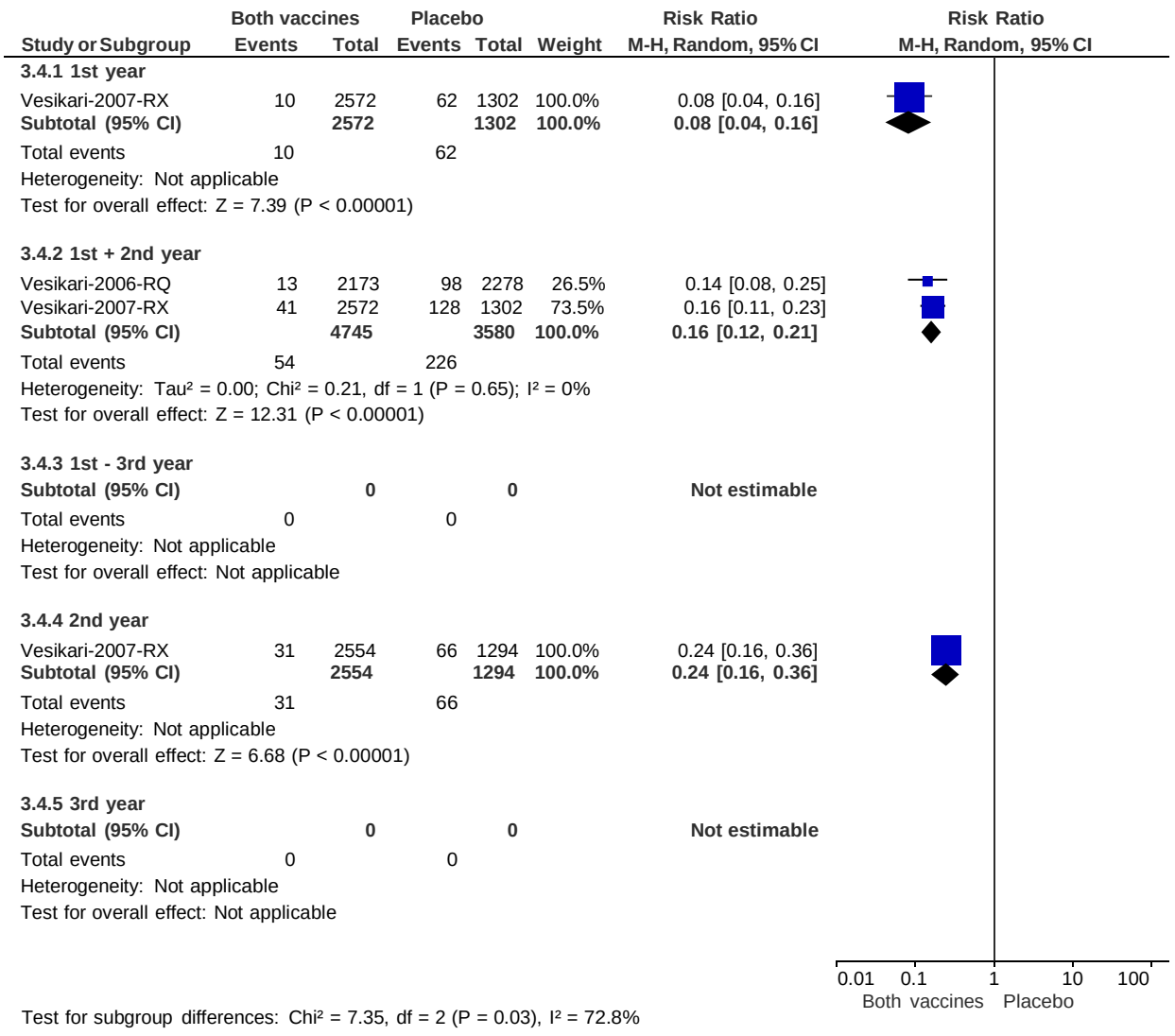
Test for subgroup differences: Chi² = 1.84, df = 2 (P = 0.40), I² = 0%

3.3 Outcome RVGE, hospitalization



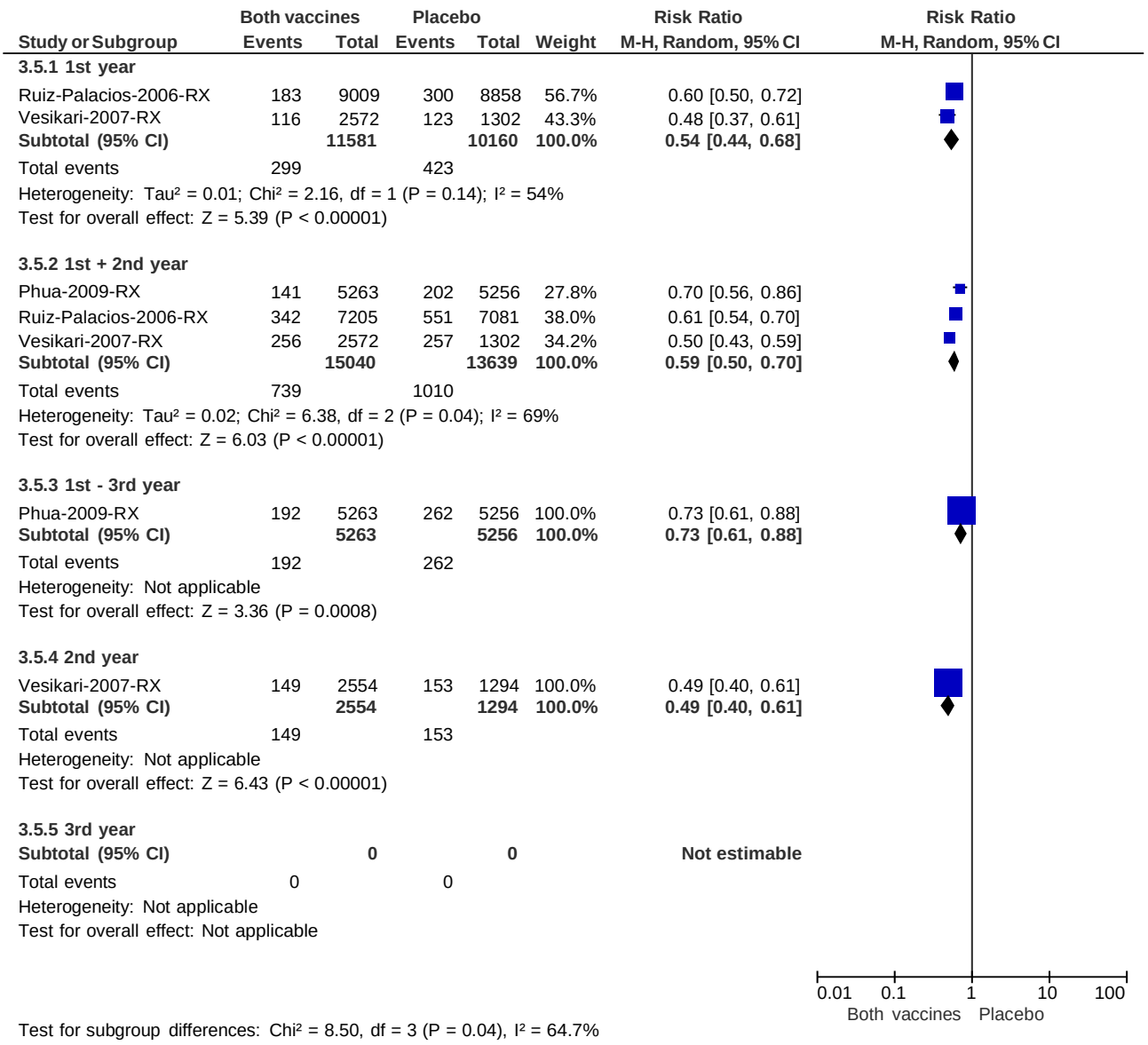
Test for subgroup differences: Chi² = 0.80, df = 3 (P = 0.85), I² = 0%

3.4 Outcome RVGE, medical attention



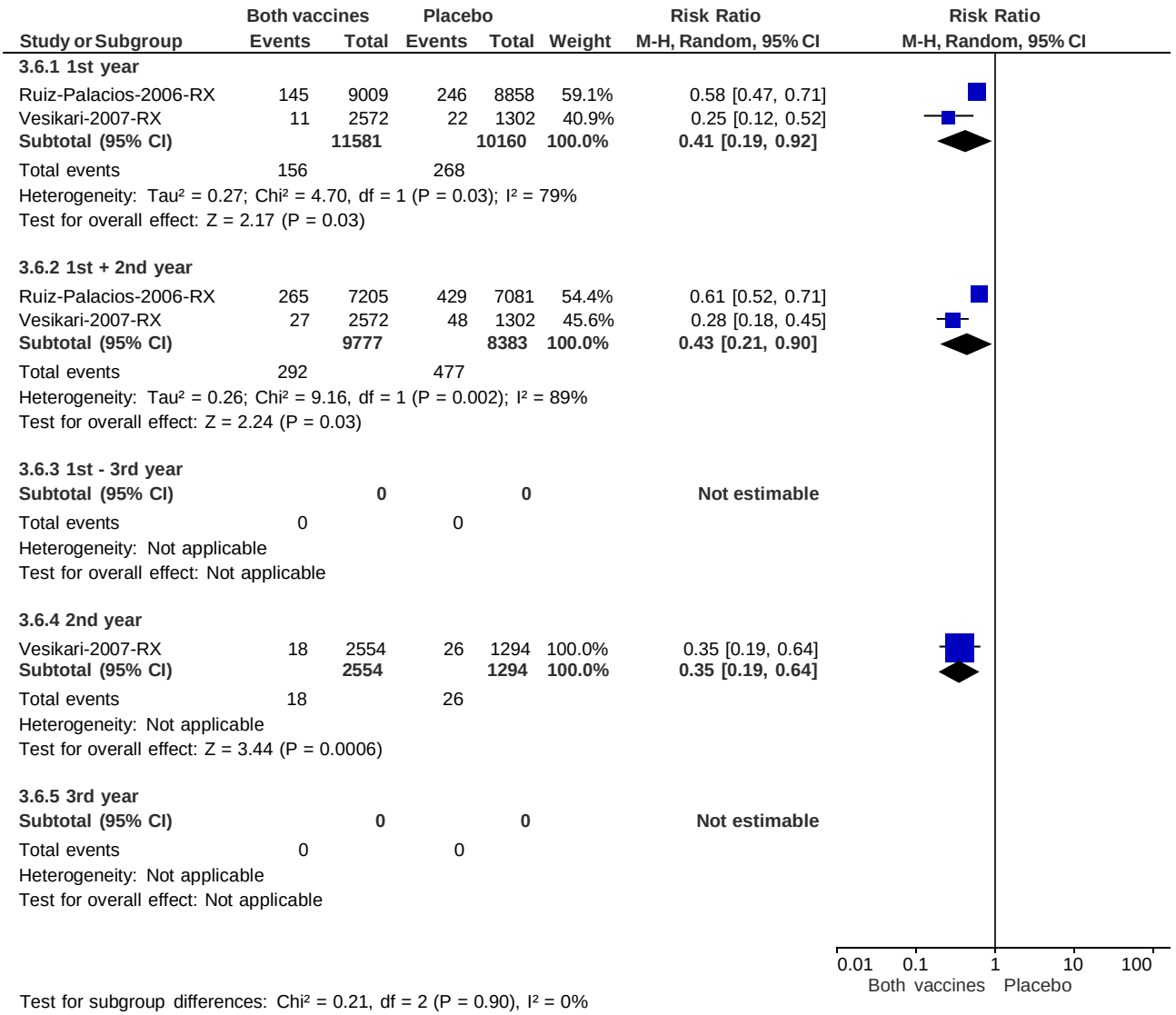
Test for subgroup differences: Chi² = 7.35, df = 2 (P = 0.03), I² = 72.8%

3.5 Outcome all cause GE, severe



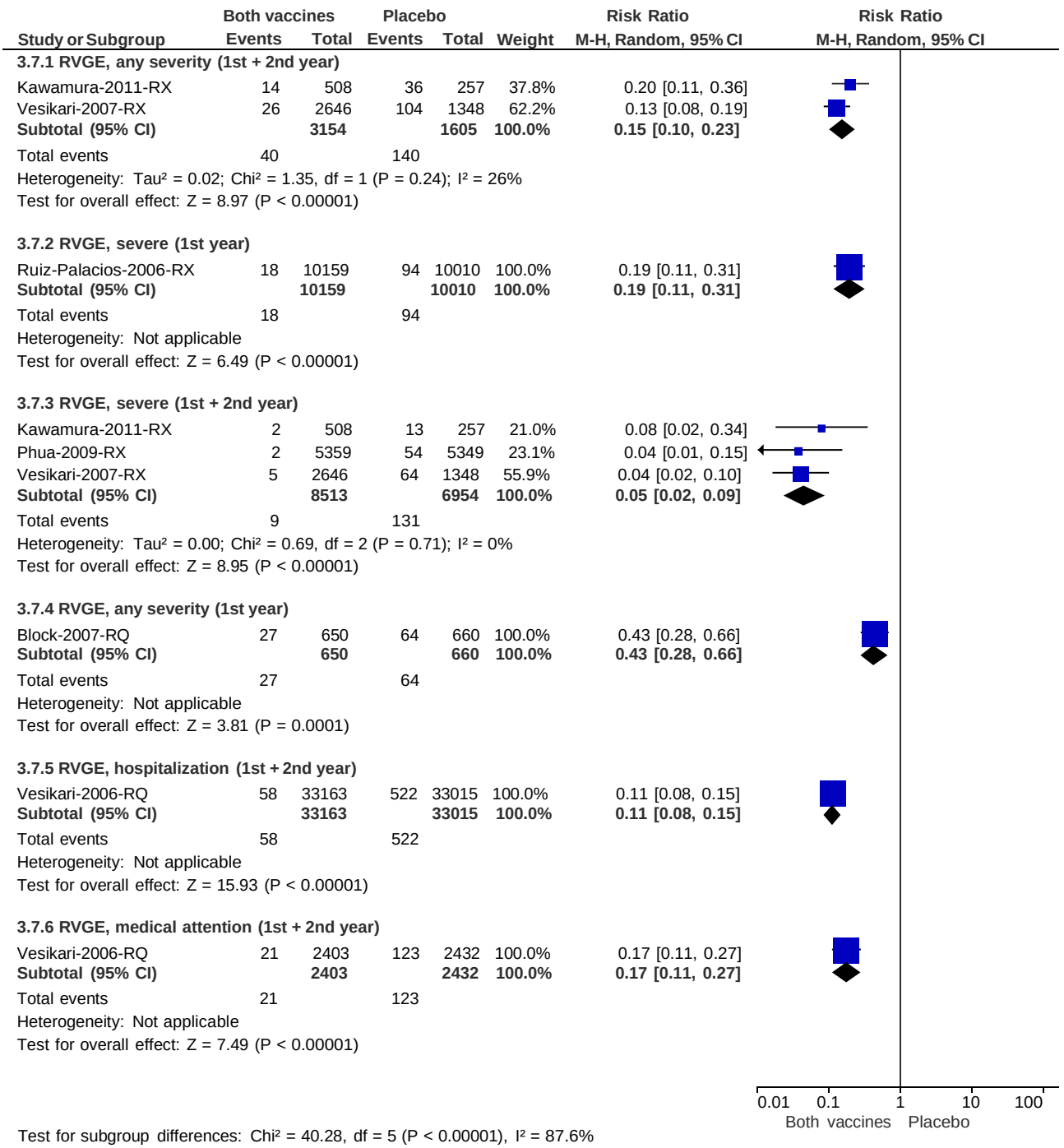
Test for subgroup differences: Chi² = 8.50, df = 3 (P = 0.04), I² = 64.7%

3.6 Outcome all cause GE, hospitalization



Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%

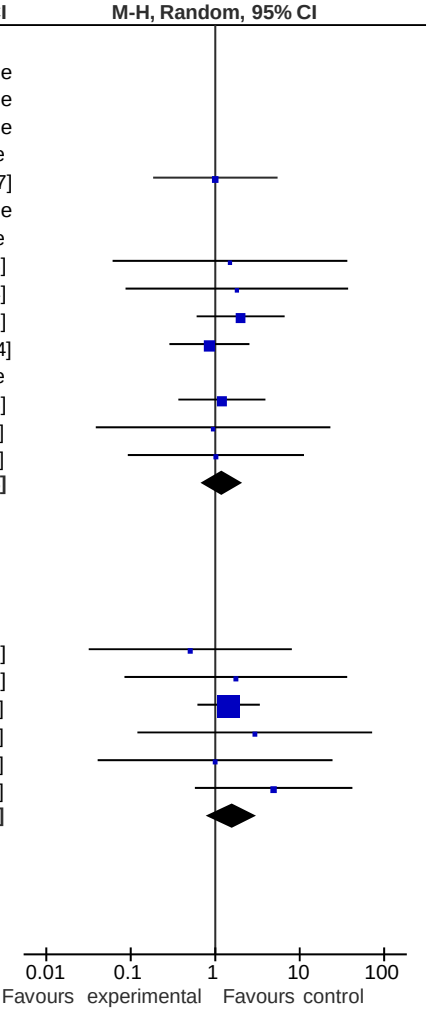
3.7 MITT-analysis



Test for subgroup differences: Chi² = 40.28, df = 5 (P < 0.00001), I² = 87.6%

3.8 Outcome Serious adverse events

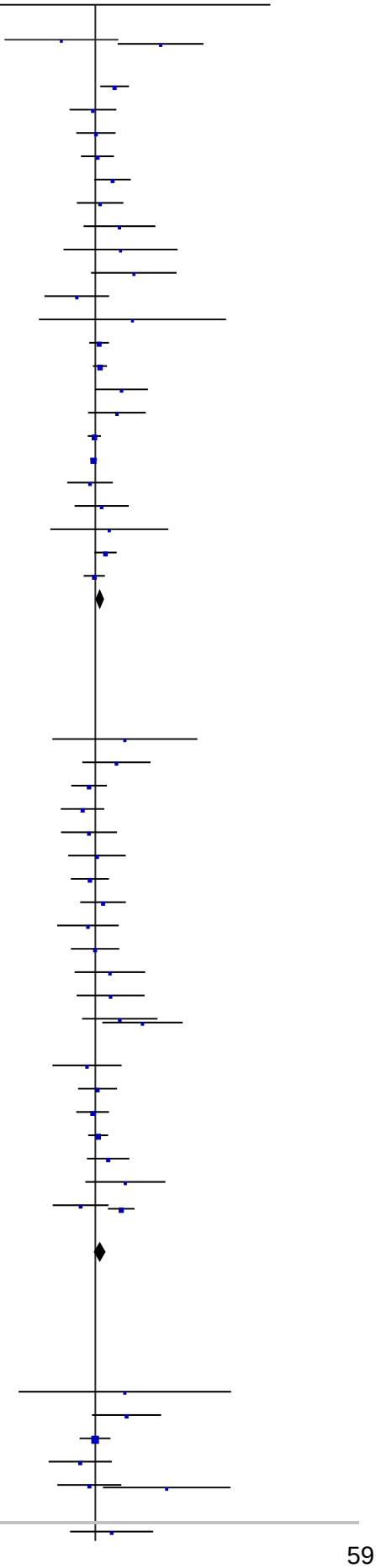
Study or Subgroup	Both vaccines Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Intussusception						
Block-2007-RQ	0	650	0	660		Not estimable
Ciarlet-2009-RQ	0	201	0	202		Not estimable
Clark-2003-RQ	0	573	0	148		Not estimable
Dennehy-2005-RX	0	421	0	108		Not estimable
GSK[024]-2008-RX	4	4376	2	2192	11.3%	1.00 [0.18, 5.47]
Kawamura-2011-RX	0	508	0	257		Not estimable
Kim-2008-RQ	0	115	0	63		Not estimable
Madhi-2010-RX	1	3298	0	1641	3.2%	1.49 [0.06, 36.63]
Phua-2005-RX	2	1811	0	653	3.5%	1.80 [0.09, 37.54]
Phua-2009-RX	8	5359	4	5349	22.6%	2.00 [0.60, 6.63]
Ruiz-Palacios-2006-RX	6	31673	7	31552	27.4%	0.85 [0.29, 2.54]
Vesikari-2004-RX	0	270	0	135		Not estimable
Vesikari-2006-RQ	6	34837	5	34788	23.1%	1.20 [0.37, 3.93]
Vesikari-2006-RQ-FI	1	1027	0	322	3.2%	0.94 [0.04, 23.08]
Vesikari-2007-RX	2	2646	1	1348	5.7%	1.02 [0.09, 11.23]
Subtotal (95% CI)		**87765**		**79418**	**100.0%**	**1.21 [0.68, 2.14]**
Total events	30		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 7 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
3.8.5 Kawasaki						
Kawamura-2011-RX	1	508	1	257	6.4%	0.51 [0.03, 8.06]
Phua-2005-RX	2	1811	0	635	5.3%	1.75 [0.08, 36.51]
Phua-2009-RX	13	5359	9	5349	68.0%	1.44 [0.62, 3.37]
Ruiz-Palacios-2006-RX	1	7636	0	7493	4.8%	2.94 [0.12, 72.25]
Salinas-2005-RX	1	1618	0	537	4.8%	1.00 [0.04, 24.44]
Vesikari-2006-RQ	5	36150	1	35536	10.6%	4.92 [0.57, 42.07]
Subtotal (95% CI)		**53082**		**49807**	**100.0%**	**1.58 [0.78, 3.18]**
Total events	23		11			
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						



Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%

3.9 Outcome Reactogenicity

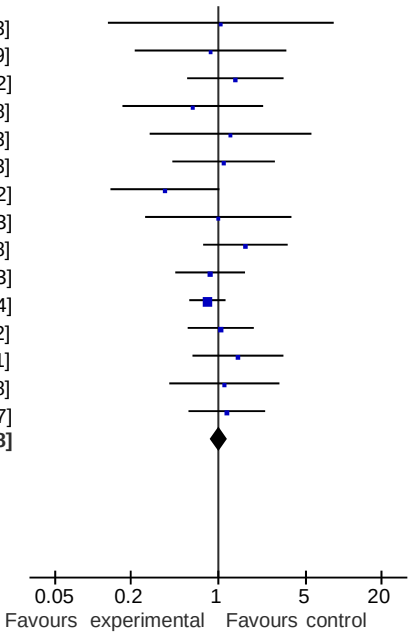
Study or Subgroup	Rotarix Events	Rotarix Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Fever after 1st dose						
Bernstein-1998-RX	3	21	6	20	0.6%	0.48 [0.14, 1.65]
Bernstein-1999-RX	21	108	5	107	1.0%	4.16 [1.63, 10.63]
Block-2007-RQ	87	650	58	660	5.7%	1.52 [1.11, 2.09]
Clark-2003-RQ	25	213	27	218	2.9%	0.95 [0.57, 1.58]
Dennehy-2005-RX	83	421	21	108	3.7%	1.01 [0.66, 1.56]
GSK [013]-2007-RX	62	189	30	96	4.8%	1.05 [0.73, 1.50]
GSK [021]-2007-RX	91	177	18	51	4.2%	1.46 [0.98, 2.17]
GSK[033]-2007-RX	98	730	15	124	2.9%	1.11 [0.67, 1.85]
GSK[039]-2007-RX	68	348	6	52	1.4%	1.69 [0.77, 3.70]
GSK[041]-2007-RX	10	100	3	52	0.6%	1.73 [0.50, 6.03]
GSK[044]-2007-RX	14	182	6	181	1.0%	2.32 [0.91, 5.90]
GSK[045]-2007-RX	16	196	12	98	1.6%	0.67 [0.33, 1.35]
GSK[048]-2007-RX	9	200	1	50	0.2%	2.25 [0.29, 17.35]
GSK[051]-2008-RX	182	297	44	78	8.5%	1.09 [0.88, 1.35]
GSK[063]-2008-RX	239	300	54	75	10.7%	1.11 [0.95, 1.29]
GSK[101555]-2008-RX	39	100	11	50	2.3%	1.77 [1.00, 3.16]
Kawamura-2011-RX	38	508	12	257	2.0%	1.60 [0.85, 3.01]
Phua-2005-RX	497	1811	183	653	11.1%	0.98 [0.85, 1.13]
Salinas-2005-RX	1002	1618	346	537	13.5%	0.96 [0.89, 1.03]
Steele-2008-RX	37	297	21	150	3.0%	0.89 [0.54, 1.46]
Vesikari-2004-RX	32	265	14	133	2.2%	1.15 [0.63, 2.07]
Vesikari-2004a-RX	8	122	3	62	0.5%	1.36 [0.37, 4.93]
Vesikari-2006-RQ-FI	255	1027	64	322	7.6%	1.25 [0.98, 1.59]
Vesikari-2007-RX	166	914	91	490	8.0%	0.98 [0.78, 1.23]
Subtotal (95% CI)		**10794**		**4624**	**100.0%**	**1.12 [1.02, 1.24]**
Total events	3082		1051			
Heterogeneity: Tau² = 0.02; Chi² = 41.24, df = 23 (P = 0.01); I² = 44%						
Test for overall effect: Z = 2.38 (P = 0.02)						
3.9.2 Vomiting after 1st dose						
Bernstein-1998-RX	4	21	2	20	0.7%	1.90 [0.39, 9.28]
Bernstein-1999-RX	16	108	10	107	2.6%	1.59 [0.75, 3.33]
Clark-2003-RQ	91	565	27	146	6.9%	0.87 [0.59, 1.29]
Dennehy-2005-RX	56	421	19	108	5.3%	0.76 [0.47, 1.22]
GSK [013]-2007-RX	24	189	14	96	3.6%	0.87 [0.47, 1.61]
GSK [021]-2007-RX	36	177	10	51	3.5%	1.04 [0.55, 1.94]
GSK[033]-2007-RX	115	730	22	124	6.4%	0.89 [0.59, 1.34]
GSK[039]-2007-RX	103	348	13	52	5.0%	1.18 [0.72, 1.95]
GSK[041]-2007-RX	18	100	11	52	3.1%	0.85 [0.43, 1.66]
GSK[044]-2007-RX	24	182	24	181	4.6%	0.99 [0.59, 1.68]
GSK[045]-2007-RX	22	196	8	98	2.5%	1.38 [0.64, 2.98]
GSK[048]-2007-RX	39	200	7	50	2.6%	1.39 [0.66, 2.93]
GSK[051]-2008-RX	39	297	6	78	2.2%	1.71 [0.75, 3.89]
GSK[063]-2008-RX	56	300	5	75	2.0%	2.80 [1.16, 6.74]
GSK[101555]-2008-RX	15	100	9	50	2.6%	0.83 [0.39, 1.77]
Kawamura-2011-RX	58	508	28	257	6.2%	1.05 [0.68, 1.60]
Phua-2005-RX	102	1811	39	653	7.6%	0.94 [0.66, 1.35]
Salinas-2005-RX	285	1618	89	537	12.0%	1.06 [0.86, 1.32]
Steele-2008-RX	55	297	21	150	5.5%	1.32 [0.83, 2.10]
Vesikari-2004-RX	23	265	6	133	2.0%	1.92 [0.80, 4.61]
Vesikari-2004a-RX	20	122	14	62	3.6%	0.73 [0.39, 1.34]
Vesikari-2007-RX	171	914	52	490	9.5%	1.76 [1.32, 2.36]
Subtotal (95% CI)		**9469**		**3570**	**100.0%**	**1.11 [0.97, 1.26]**
Total events	1372		436			
Heterogeneity: Tau² = 0.02; Chi² = 29.41, df = 21 (P = 0.10); I² = 29%						
Test for overall effect: Z = 1.56 (P = 0.12)						
3.9.3 Diarrhoea after 1st dose						
Bernstein-1998-RX	2	21	1	20	0.4%	1.90 [0.19, 19.40]
Bernstein-1999-RX	18	108	9	107	4.1%	1.98 [0.93, 4.21]
Clark-2003-RQ	127	565	33	146	20.7%	0.99 [0.71, 1.39]
Dennehy-2005-RX	28	421	10	108	4.9%	0.72 [0.36, 1.43]
GSK [013]-2007-RX	19	189	11	96	4.8%	0.88 [0.44, 1.77]
GSK [021]-2007-RX	33	177	2	51	1.2%	4.75 [1.18, 19.14]
GSK[033]-2007-RX	42	730	5	124	2.8%	1.43 [0.58, 3.54]



	42			124		[0.58,
GSK[039]-2007-RX	7	348	1	52	0.5%	1.05 [0.13, 8.33]
GSK[041]-2007-RX	5	100	3	52	1.2%	0.87 [0.22, 3.49]
GSK[044]-2007-RX	11	182	8	181	3.0%	1.37 [0.56, 3.32]
GSK[045]-2007-RX	5	196	4	98	1.4%	0.63 [0.17, 2.28]
GSK[048]-2007-RX	10	200	2	50	1.1%	1.25 [0.28, 5.53]
GSK[051]-2008-RX	21	297	5	78	2.6%	1.10 [0.43, 2.83]
GSK[063]-2008-RX	9	300	6	75	2.3%	0.38 [0.14, 1.02]
GSK[101555]-2008-RX	6	100	3	50	1.3%	1.00 [0.26, 3.83]
Kawamura-2011-RX	26	508	8	257	3.9%	1.64 [0.76, 3.58]
Phua-2005-RX	31	1811	13	653	5.7%	0.86 [0.45, 1.63]
Salinas-2005-RX	111	1618	45	537	21.2%	0.82 [0.59, 1.14]
Steele-2008-RX	29	297	14	150	6.4%	1.05 [0.57, 1.92]
Vesikari-2004-RX	20	265	7	133	3.4%	1.43 [0.62, 3.31]
Vesikari-2004a-RX	11	122	5	62	2.3%	1.12 [0.41, 3.08]
Vesikari-2007-RX	24	914	11	490	4.7%	1.17 [0.58, 2.37]
Subtotal (95% CI)		**9469**		**3570**	**100.0%**	**1.01 [0.87, 1.18]**
Total events	595		206			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 19.05$, df = 21 (P = 0.58); $I^2 = 0\%$

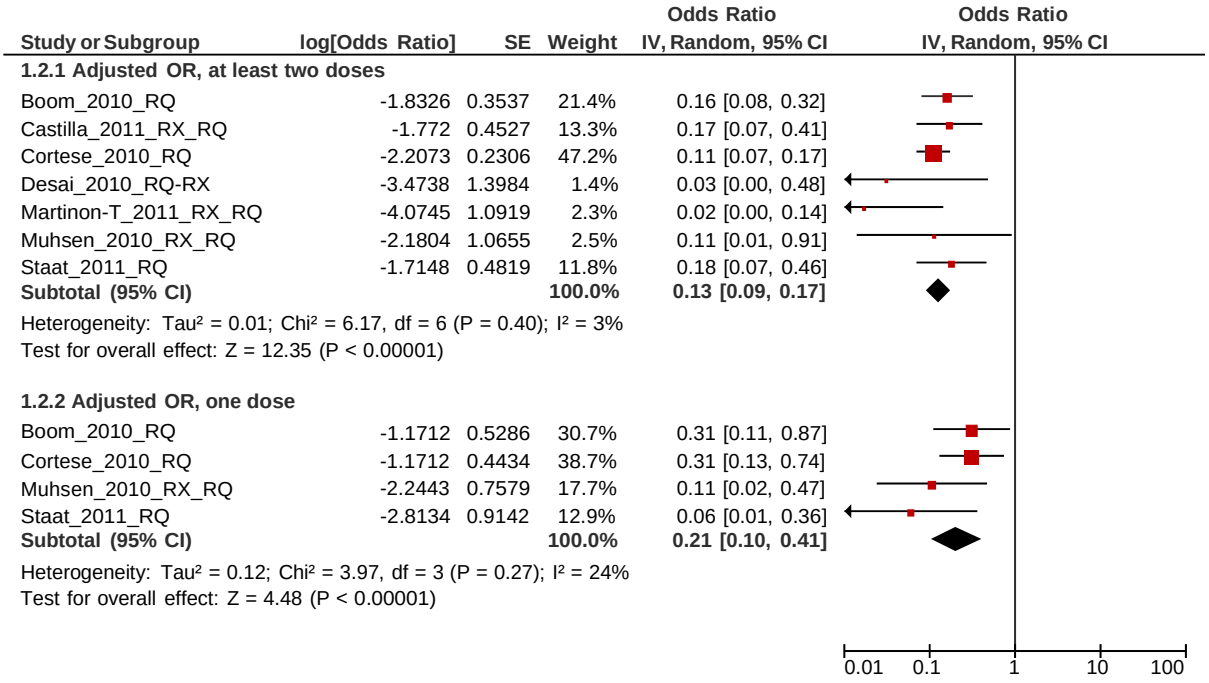
Test for overall effect: Z = 0.16 (P = 0.87)



Test for subgroup differences: $Chi^2 = 1.32$, df = 2 (P = 0.52), $I^2 = 0\%$

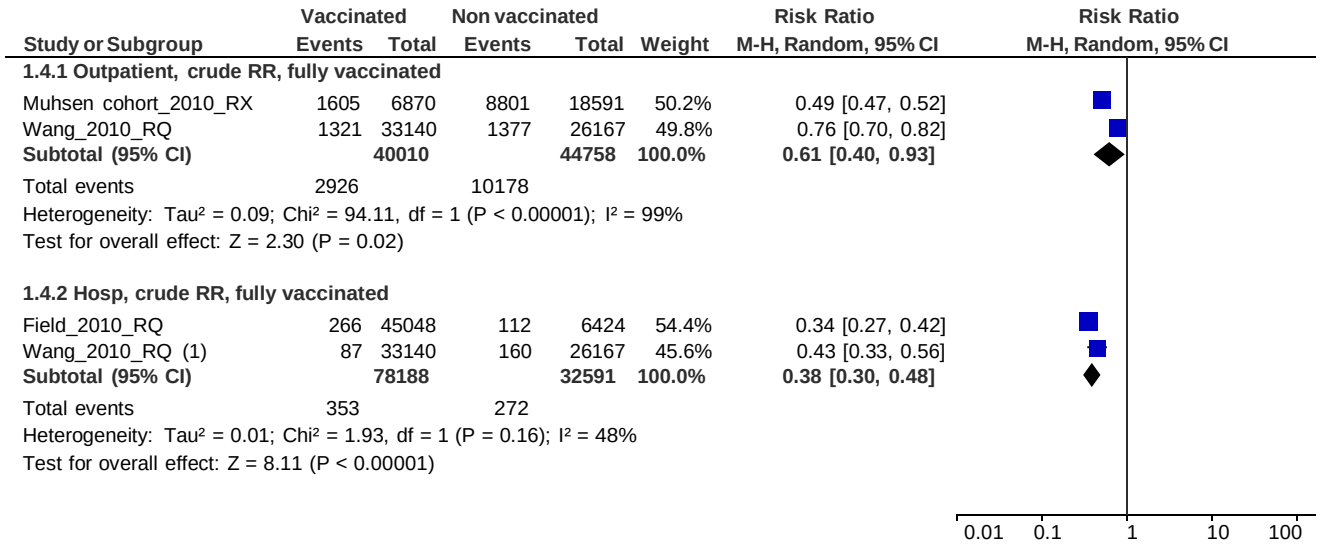
4: Vaccine effectiveness of rotavirus vaccines

4.2 Outcome RVGE hospitalization (adjusted), case-control



Test for subgroup differences: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.3%

4.4 Outcome all cause GE (crude), cohort



Test for subgroup differences: Chi² = 3.84, df = 1 (P = 0.05), I² = 74.0%

(1) Wang: cases (events) hosp or ED

Appendix V: Test for Publication Bias (Funnel plots)

Figure 1: RVGE, hospitalisation; 1st + 2nd year

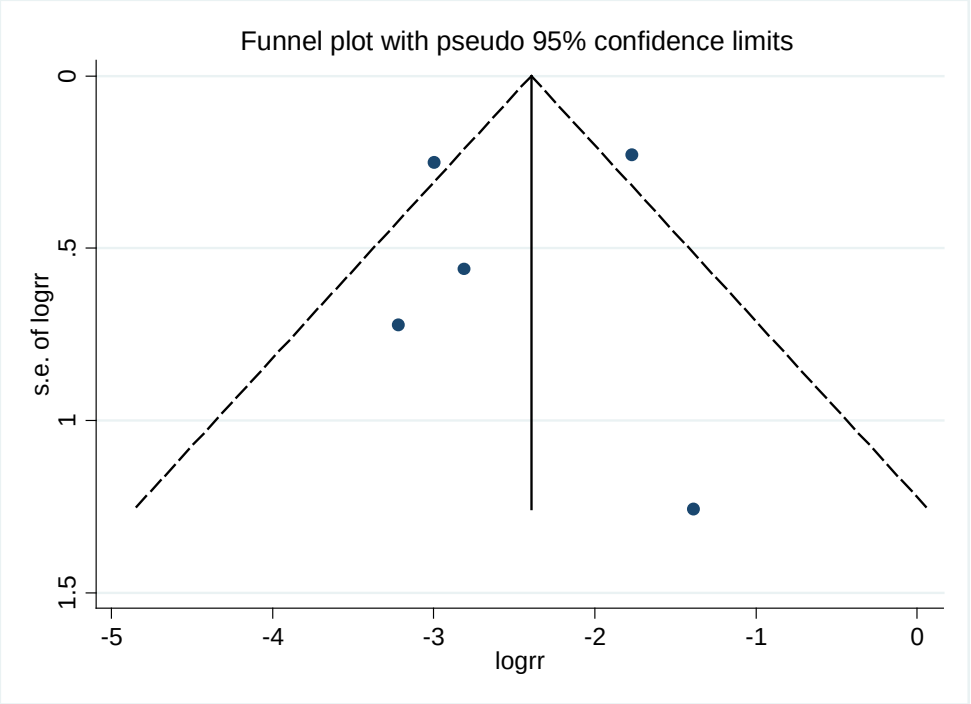


Figure 2: RVGE, severe; 1st + 2nd year

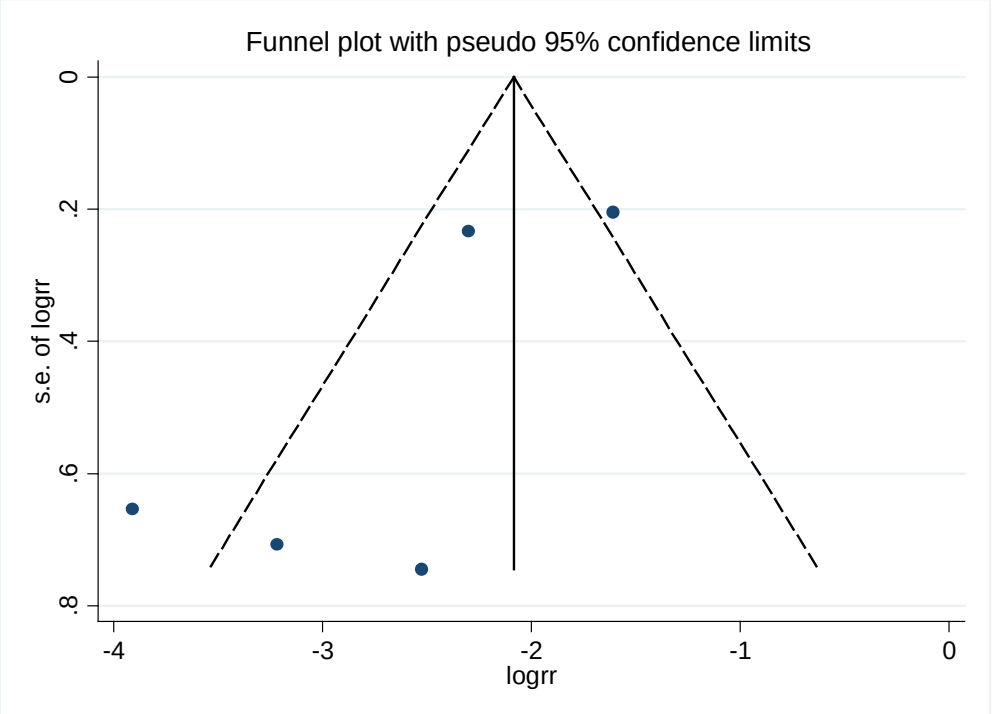


Figure 3: RVGE, any severity; 1st + 2nd year

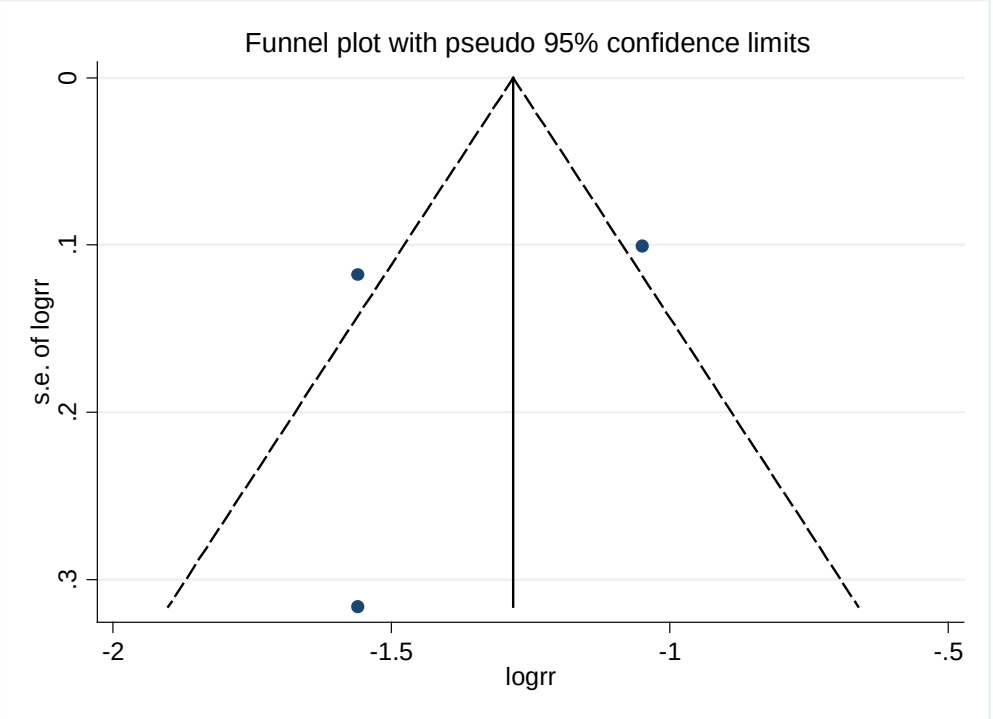


Figure 4: all cause GE, severe; 1st + 2nd year

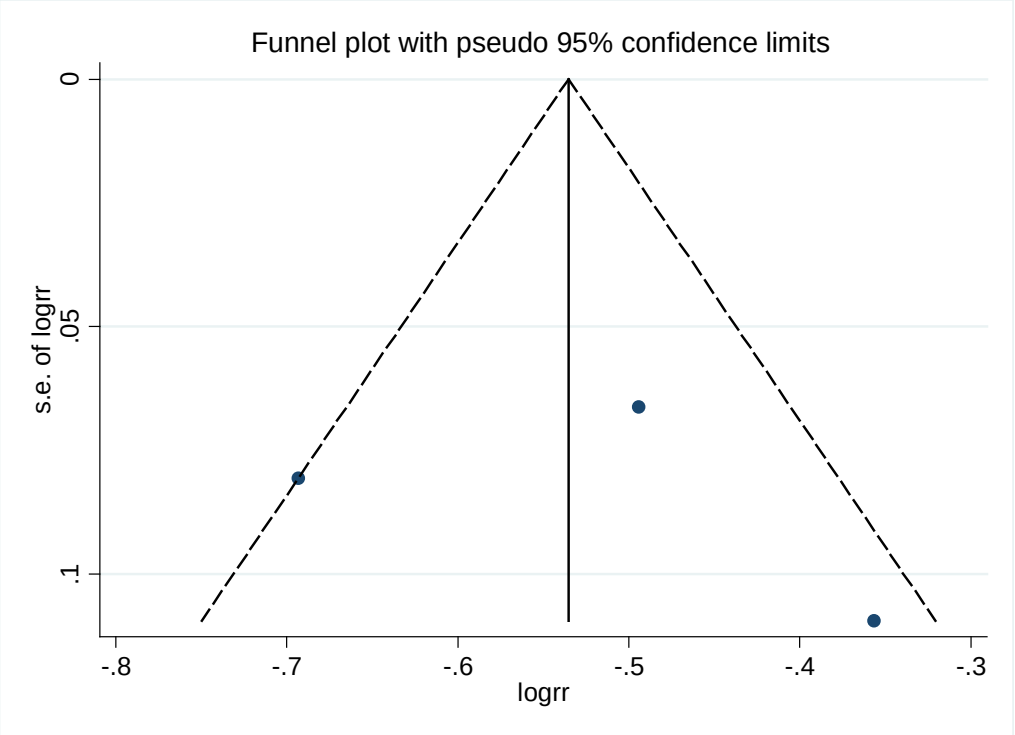


Figure 5: Intussusception

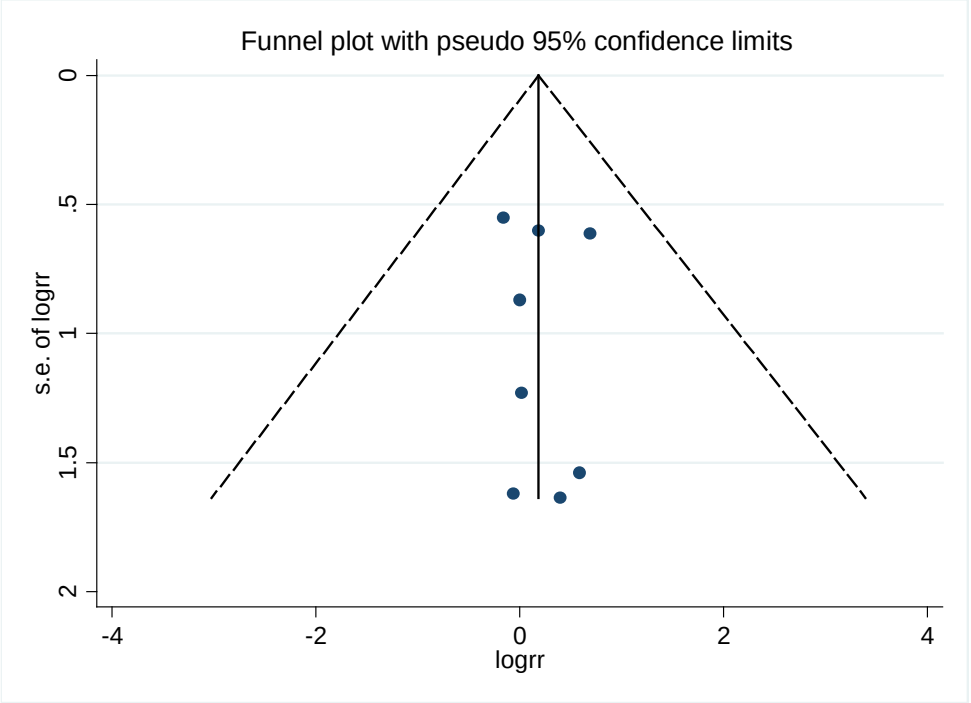
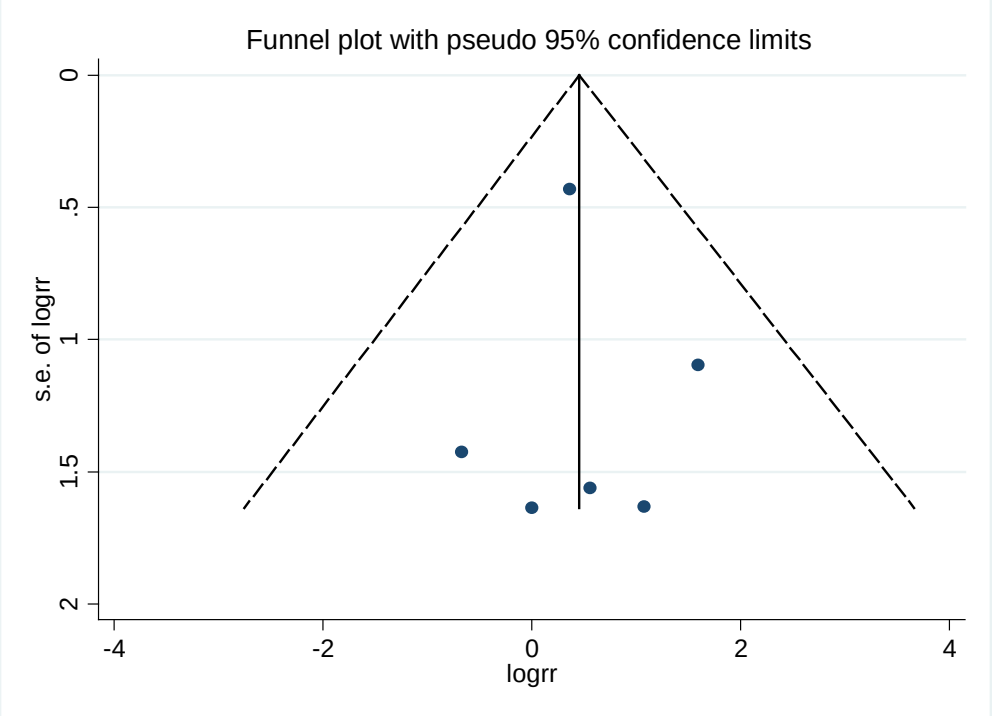


Figure 6: Kawasaki disease



References:

78. Zeller M, Rahman M, Heylen E, et al. (2010) Rotavirus incidence and genotype distribution before and after national rotavirus vaccine introduction in Belgium. Vaccine 28:7507-7513

100. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. (2006) Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis. N Engl J Med 354:11-22

101. Vesikari T, Matson DO, Dennehy P, et al. (2006) Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 354:23-33

102. Kawamura N, Tokoeda Y, Oshima M, et al. (2011) Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. Vaccine 29:6335-6341

103. Phua KB, Lim FS, Lau YL, et al. (2009) Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. Vaccine 27:5936-5941

104. Vesikari T, Karvonen A, Prymula R, et al. (2007) Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 370:1757-1763

105. Block SL, Vesikari T, Goveia MG, et al. (2007) Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatr 119:11-18

107. Linhares AC, Velazquez FR, Perez-Schael I, et al. (2008) Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet 371:1181-1189

110. Boom JA, Tate JE, Sahni LC, et al. (2010) Sustained protection from pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. Pediatr Infect Dis J 29:1133-1135

111. Castilla J, Beristain X, Martinez-Artola V, et al. (2012) Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. Vaccine 30:539-543

112. Cortese MM, LeBlanc J, White KE, et al. (2011) Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. Pediatr 128:1474-1481

113. Desai SN, Esposito DB, Shapiro ED, Dennehy PH, Vázquez M (2010) Effectiveness of rotavirus vaccine in preventing hospitalization due to rotavirus gastroenteritis in young children in Connecticut, USA. Vaccine 28:7501-7506

114. Guh AY, Hadler JL (2011) Use of the state immunization information system to

assess rotavirus vaccine effectiveness in Connecticut, 2006-2008. Vaccine 29:6155-6158

115. Martinón-Torres F, Bouzón Alejandro M, Redondo Collazo L, et al. (2011) Effectiveness of rotavirus vaccination in Spain. Human Vaccines 7:757-761

116. Muhsen K, Shulman L, Kasem E, et al. (2010) Effectiveness of rotavirus vaccines for prevention of rotavirus gastroenteritis-associated hospitalizations in Israel: a case-control study. Human Vaccines 6:450-454

117. Staat MA, Payne DC, Donauer S, et al. (2011) Effectiveness of pentavalent rotavirus vaccine against severe disease. Pediatr 128:267-275

118. Field EJ, Vally H, Grimwood K, Lambert SB (2010) Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. Pediatr 126:506-512

119. Gagneur A, Nowak E, Lemaitre T, et al. (2011) Impact of rotavirus vaccination on hospitalizations for rotavirus diarrhea: The IVANHOE study. Vaccine 29:3753-3759

120. Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD (2010) Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. Pediatr 125:208-213

121. Begue RE, Perrin K (2010) Reduction in gastroenteritis with the use of pentavalent rotavirus vaccine in a primary practice. Pediatr 126:e40-45

122. Braeckman T, Van Herck K, Raes M, Vergison A, Sabbe M, Van Damme P (2011) Rotavirus vaccines in Belgium: policy and impact. Pediatr Infect Dis J 30:21-24

123. Hanquet G, Ducoffre G, Vergison A, et al. (2011) Impact of rotavirus vaccination on laboratory confirmed cases in Belgium. Vaccine 29:4698-4703

124. Trimis G, Koutsoumbari I, Kottaridi C, et al. (2011) Hospital-based surveillance of rotavirus gastroenteritis in the era of limited vaccine uptake through the private sector. Vaccine 29:7292-7295

126. Belshaw DA, Muscatello DJ, Ferson MJ, Nurkic A (2009) Rotavirus vaccination one year on. Communicable diseases intelligence 33:337-340

127. Buttery JP, Lambert SB, Grimwood K, et al. (2011) Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J 30:S25-29

128. Clarke MF, Davidson GP, Gold MS, Marshall HS (2011) Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations in South Australian children following the introduction of rotavirus vaccination. Vaccine 29:4663-4667

129. Lambert SB, Faux CE, Hall L, et al. (2009) Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland. The Medical Journal of Australia 191:157-160

131. Anderson EJ, Rupp A, Shulman ST, Wang D, Zheng X, Noskin GA (2011) Impact of rotavirus vaccination on hospital-acquired rotavirus gastroenteritis in children. Pediatr

127:264-270

132. Centers for Disease C, Prevention (2008) Delayed onset and diminished magnitude of rotavirus activity--United States, November 2007-May 2008. MMWR Morbidity and mortality weekly report 57:697-700

133. Chang HG, Smith PF, Tserenpuntsag B, Markey K, Parashar U, Morse DL (2010) Reduction in hospitalizations for diarrhea and rotavirus infections in New York state following introduction of rotavirus vaccine. Vaccine 28:754-758

134. Clark HF, Lawley D, Mallette LA, DiNubile MJ, Hodinka RL (2009) Decline in cases of rotavirus gastroenteritis presenting to The Children's Hospital of Philadelphia after introduction of a pentavalent rotavirus vaccine. Clinical and Vaccine Immunology 16:382-386

135. Payne DC, Staat MA, Edwards KM, et al. (2011) Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US Counties, 2006-2009. Clin Infec Dis 53:245-253

136. Tate JE, Mutuc JD, Panozzo CA, et al. (2011) Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. Pediatr Infect Dis J 30:30-34

137. Yen C, Tate JE, Wenk JD, Harris Ii JM, Parashar UD (2011) Diarrhea-associated hospitalizations among US Children over 2 rotavirus seasons after vaccine introduction. Pediatr 127:9-15

138. Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM (2011) Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. Pediatr Infect Dis J 30:11-15

139. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, et al. (2010) Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med 362:299-305

140. Richardson V, Parashar U, Patel M (2011) Childhood diarrhea deaths after rotavirus vaccination in Mexico. N Engl J Med 365:772-773

149. Belongia E, Izurieta H, Braun MM, et al. (2007) Postmarketing monitoring of intussusception after RotaTeq (TM) vaccination - United States, February 1, 2006-February 15, 2007. MMWR report 56:218-222

150. Belongia EA, Irving SA, Shui IM, et al. (2010) Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. Pediatr Infect Dis J 29:1-5

151. Haber P, Patel M, Izurieta HS, et al. (2008) Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. Pediatr 121:1206-1212

152. Loughlin J, Mast C, Doherty M, Wang FT, Wong J, Seeger JD (2012) Post Marketing Evaluation of the Short-term Safety of the Pentavalent Rotavirus Vaccine. Pediatr Infect Dis J 31:292-296

153. Shui IM, Baggs J, Patel M, et al. (2012) Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants. JAMA: The Journal of the American Medical Association 307:598-604

154. Buttery JP, Danchin MH, Lee KJ, et al. (2011) Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 29:3061-3066

155. Carlin JLK (2011) Rotavirus vaccination and risk of intussusception. Australian Government; Department of Health and Ageing; Therapeutic Goods Administration. http://www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm

156. Patel MM, López-Collada VR, Bulhões MM, et al. (2011) Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med 364:2283-2292

191. Escolano S, Farrington CP, Hill C, Tubert-Bitter P (2011) Intussusception after rotavirus vaccination--spontaneous reports. 365:2139