Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
OTHER Armah 2013	RCT of withdrawn RV vaccine RRV-TV
OTHER Bines 2015	Neonatal RV vaccine RV3-BB in development
OTHER Bines 2018	RCT of unlicensed neonatal RV3-BB rotavirus vaccine (ACTRN12612001282875)
OTHER Bucardo 2018	Prospective cohort study
OTHER Bucher 2012	Diagnostic test accuracy study
OTHER Chatterjee 2012	RCT, not rotavirus vaccine
OTHER Cowley 2017	RCT of unlicensed neonatal RV3-BB rotavirus vaccine
OTHER CTRI/2009/091/000821	RCT of Rotasiil versus placebo
OTHER Dang 2012	RCT evaluating safety and immunogenicity of vaccine licensed in Vietnam (NCT01377571); vaccine not prequalified by the WHO
OTHER de Palma 2010	Case-control study
OTHER Dickson 2017	Brief narrative report
OTHER Diness 2010	Study of vitamin A supplementation with Bacille Calmette-Guerin vaccine for rotavirus diarrhoea outcomes
OTHER Dutta 2011	RCT, not rotavirus vaccine
OTHER Ella 2018	All infants received rotavirus vaccine, and were randomized to Rotavac (116E) with or without buffering agent. (CTRI/2014/04/004548)
OTHER Friedrich 2017	Editorial on Rotasiil rotavirus vaccine
OTHER Gagneur 2011	Observational study (IVANHOE)
OTHER Groome 2017	RCT in infants of RV vaccine in development: parenteral P2-VP8-P[8] subunit RV vaccine (NCT02109484)
OTHER Hiramatsu 2018	Prospective cohort study
OTHER Isanaka 2017-NER	Reporting on an RCT (NCT02145000) that evaluates safety and efficacy in a vaccine licensed in India but not prequalified by the WHO
OTHER Kempe 2007	Survey of paediatricians about rotavirus disease and rotavirus vaccines

(*Continued*)

OTHER Kulkarni 2017	Reporting on an RCT (NCT02133690) that evaluates safety and efficacy in a vaccine licensed in India but not prequalified by the WHO
OTHER Muhsen 2010	Case-control study
OTHER NCT00981669	RCT included adults aged 18 - 40 years
OTHER NCT01195844	Observational study, prematurely terminated for poor recruitment
OTHER NCT01236066	Ongoing observational study
OTHER NCT01375907	Ongoing study with adult participants
OTHER NCT01571505	RCT in infants comparing RV vaccine administered with IPV or OPV
OTHER Rivera 2011	RCT, no placebo comparison
OTHER Thyagarajan 2011	Procedural codes for rotavirus vaccination in the USA
OTHER Yin 2017	Oral RV vaccine (not specified, could be both RV1 and RV5) was administered before versus after other injected vaccines to compare injection site pain of the other vaccines
OTHER Zade 2014a-IND	Reporting on an RCT that evaluates safety in a vaccine licensed in India but not prequalified by the WHO
OTHER Zade 2014b-IND	Reporting on an RCT (CTRI/2010/091/003064) that evaluates safety in a vaccine licensed in India but not prequalified by the WHO
RV1 / RV5 Libster	RCT of RV1 and RV5 combined in different sequences
RV1 Ali 2014	Comparing different age schedules of RV1
RV1 Armah 2016	Comparing alternative dosing schedules
RV1 Buyse 2014	Integrated analysis
RV1 Correia 2010	Case-control study
RV1 CTRI/2012/02/002454	Ongoing RCT with no placebo group
RV1 Dennehy 2008	RCT of RV1 vaccine, but no placebo group reported
RV1 Emperador 2016	No placebo group: RV1 on a staggered versus concomitant schedule with other vaccines
RV1 GSK[107077-057] 2008	RCT of RV1 vaccine, but no placebo group reported
RV1 GSK[107876-061] 2008	RCT of RV1 vaccine, but no placebo group reported

(*Continued*)

RV1 GSK[444563-020] 2007	RCT, but excluded because report mentioned that "4 groups received an investigational vaccination regimen", but no details are provided about this vaccine (may be related to GlaxoSmithKline's RV1 vaccine)
RV1 Herrera 2013	Not an RCT
RV1 Kazi 2017	1 arm of an RCT (RV1 Ali 2014) was included in this sub-study analysing histo-blood group antigens
RV1 Kompithra 2014	No placebo group: immunogenicity for 3 versus 5 doses RV1
RV1 Lazarus 2017	All received RV vaccine with or without zinc and/or probiotic supplements
RV1 Lu 2013	Not an RCT
RV1 NCT00353366	Ongoing non-randomized study
RV1 NCT00382772 2008	RCT comparing RV1 liquid formulation to lyophilized formulation, no placebo
RV1 NCT00653198	Ongoing case-control study
RV1 NCT00655187	Ongoing case-control study
RV1 NCT01162590	Ongoing study with adult participants
RV1 NCT01177826	Ongoing observational study
RV1 NCT01273077	Ongoing observational study
RV1 NCT01339221	Ongoing observational study
RV1 Plosker 2011	Economic analysis
RV1 Ramani 2016	No placebo group: RV1 co-administered with IPV or with OPV was compared
RV1 Rojas 2007	Viral conversion on the same population of RV1 Ruiz-Palac 06-LA/EU (included trial)
RV1 Rongsen-Chandola 2014	Infants were breastfed versus not breastfed 30 mins prior and post RV1 administration. No placebo group
RV1 Suryakiran 2011	Not RCT, integrated safety summary
RV1 Taddio 2015	To assess pain at injection site of other vaccines, participants were randomised to 1. oral RV1 then other injected vaccines then oral sucrose, or to 2. oral sucrose then other injected vaccines then oral RV1
RV1 Zaman 2016	Study investigated co-administration of Measles-rubella vaccines with RV vaccine

(*Continued*)

RV5 / BRV-TV Saluja 2017	RCT of BRV-TV versus RV5
RV5 ACTRN12611000559910	Ongoing observational study
RV5 Ciarlet 2008	RCT of RV5 vaccine, but no placebo group reported
RV5 El Khoury 2011	Mathematical model in Brazil
RV5 El Khoury 2011a	Mathematical model in six Asian countries
RV5 Martinon-Torres 2017	RCT comparing standard versus alternative formulation of RV5
RV5 McGrath 2014	Not an RCT
RV5 NCT00130832 2010	Not RCT; open-label study investigating different schedules of rotavirus and polio vaccine combinations without placebo
RV5 NCT00496054	Ongoing non-randomized study
RV5 NCT01926015	Staggered versus concomitant administration of DTP-IPV with RV5
RV5 Saleh 2018	Standard versus alternative schedule RV5 (NCT01960725)
RV5 Tugcu 2009	RCT of RV5 vaccine, no placebo group reported
RV5 Uprety 2017	Sub-study of RV5 Levin 2017-AF, this sub-study only included participants in the vaccine arm and compared HIV-positive to HIV-exposed but uninfected infants
RV5 Vesikari 2011	RCT of RV5 and MenCC vaccines - concomitant or sequential administration, no placebo group reported
RV5 Weinberg 2017	Sub-study of selected participants from RV5 Levin 2017-AF, reporting only irrelevant outcomes for this review.

Characteristics of ongoing studies *[ordered by study ID]*

OTHER ACTRN12610000525088

Trial name or title	"A Phase 1 double-blind, randomized study to compare the safety, tolerability and immunogenicity of oral RV3-BB rotavirus vaccine and placebo in infants, children and male adults"
Methods	"Randomized controlled trial, parallel assignment"
Participants	**Number:** 60 (target) **Description:** cohort 3: infants (male and female) aged 6 to 8 weeks inclusive, in good health

OTHER ACTRN12610000525088 (*Continued*)

Interventions	1 mL oral dose administered once 1. live attenuated human rotavirus vaccine RV3-BB 2. Placebo
Outcomes	1. Adverse events 2. Serologic markers of rotavirus immunity (immunoglobulin G (IgG) and immunoglobulin A (IgA), neutralizing antibodies (NAs)) 3. Presence of RV3-BB rotavirus vaccine in faecal extracts
Starting date	27 January 2010 **Completion:** not stated
Contact information	Dr Carl Kirkwood, Murdoch Childrens Research Institute 4th Floor, Front Entry Building Royal Children's Hospital Flemington Road Parkville, Victoria 3052, Australia carl.kirkwood@mcri.edu.au
Notes	**Location:** Australia **Registration number:** ACTRN12610000525088 (Australian New Zealand Clinical Trials Registry) **Source of funding:** Murdoch Childrens Research Institute

OTHER CTRI/2015/07/006034

Trial name or title	"Clinical trial on Rotavirus vaccine to check consistency of different lots of vaccines manufactured and to check vaccine interference with other childhood vaccines given under universal immunization program in India"
Methods	Randomized, parallel-group, multiple arm trial
Participants	**Number:** 1500 **Description:** Healthy infants, age 6-8 weeks
Interventions	1.3 doses Rotasiil/BRV-PV 2. 3 doses RV1 2 mL orally with routine vaccinations at 6, 4 and 10 weeks of age
Outcomes	1. Rotavirus Immunogenicity 2. Immunogenicity of other vaccines 3. Immediate adverse events
Starting date	November 2015 **Completion:** not stated
Contact information	Dr Prasad Kulkarni; drpsk@seruminstitute.com
Notes	**Location:** India **Registration number:** CTRI/2015/07/006034 **Source of funding:** Serum Institute of India Pvt Ltd.

OTHER CTRI/2015/12/006428

Trial name or title	"Randomized open label study to compare immunogenicity and safety of ROTAVAC® and ROTARIX® rotavirus vaccine"
Methods	Randomized, parallel-group, active controlled trial
Participants	**Number:** 464 **Description:** Healthy infants, age 6 - 8 weeks
Interventions	1. 3 doses ROTAVAC®: 0.5 mL single dose containing NLT 105.0 FFU of live rotavirus116E 2. 2 doses RV1: Each 1-mL dose contains a suspension of at least 106.0 median Cell Culture Infective Dose (CCID50) **Schedule:** 4-week interval between doses
Outcomes	1. Immunogenicity (GMTs) 2. Safety solicited for 7 days 3. SAEs throughout the study period
Starting date	December 2015 **Completion:** not stated
Contact information	Dr Binod Sah, binod3161@bharatbiotech.com
Notes	**Location:** India **Registration number:** CTRI/2015/12/006428 **Source of funding:** Bharat Biotech

OTHER NCT01061658

Trial name or title	"Phase I/II, Randomized, Double-blind, Placebo-controlled, Dosage Selection (10e5.5 or 10e6.25 FFU of Each Constituent Serotype Per 0.5 mL) Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 3-dose Series of Live Attenuated Tetravalent (G1-G4) Bovine-Human Reassortant Rotavirus Vaccine [BRV-TV] Administered to Healthy Indian Infants"
Methods	"Randomized, Placebo Control, Safety Study, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator)"
Participants	**Number:** 90 (target) **Description:** healthy infants of either sex, 6 to 8 weeks of age at time of enrolment
Interventions	1. Live attenuated tetravalent (G1 - G4) bovine-human reassortant rotavirus vaccine 2. Placebo
Outcomes	1. Reactogenicity 2. Adverse events 3. Shedding of vaccine rotavirus in stool samples 4. Seroconversion rate 5. Sero-response rate 6. GMT of serum IgA antibody against rotavirus

OTHER NCT01061658 (*Continued*)

Starting date	1 July 2010 **Completion:** not stated
Contact information	Gagandeep Kang, MD PhD, gkang@cmcvellore.ac.in
Notes	**Location:** India **Registration number:** NCT01061658 **Source of funding:** Shantha Biotechnics Limited

OTHER NCT02153866

Trial name or title	"The Safety and Immunogenicity Study of Rotavirus Vaccine Simultaneously Vaccinated With MR or MMR Vaccine"
Methods	Randomized, open label
Participants	**Number:** 2800 (target) **Description:** 8 ~ 9 months healthy child
Interventions	1. RV vaccine 2. measles-rubella vaccine 3. measles-mumps-rubella vaccine 4. RV + measles-rubella vaccine 5. RV + measles-mumps-rubella vaccine
Outcomes	1. General reactions 2. Severe adverse events 3. Antibody geometric mean titres
Starting date	December 2013 **Completion:** August 2014
Contact information	Rui Ao, Sichuan Center for Disease Control and Prevention
Notes	**Location:** China **Registration number:** NCT02153866 **Source of funding:** Sichuan Center for Disease Control and Prevention

OTHER NCT02193061

Trial name or title	"Randomized, Controlled Single-blind Clinical Study to Assess Vaccine Interchangeability Between RV5 and RV1 Using Seven Combined Anti-rotavirus Prevention Programs"
Methods	Randomized, controlled, single-blind

OTHER NCT02193061 (*Continued*)

Participants	**Number:** 1498 (target) **Description:** healthy infants 6 - 10 weeks old
Interventions	1. 1 dose RV1 2. 1 dose RV5 3. 1 dose RV1 + 2 doses RV5 4. 1 dose RV5 + 2 doses RV1 5. 2 doses RV5 + 1 dose RV1 6. 1 dose RV5 + 1 dose RV1 + 1 dose RV5 7. 1 dose RV1 + 1 dose RV5 + 1 dose RV1
Outcomes	1. Temperature 2. Evacuations
Starting date	November 2013 **Completion:** November 2017
Contact information	Mercedes Macias Parra, MSc, National Institute of Pediatrics, Mexico
Notes	**Location:** Mexico **Registration number:** NCT02193061 **Source of funding:** National Institute of Pediatrics, Mexico; Centro Nacional para la Salud de la Infancia y la Adolescencia; Merck Sharp & Dohme Corp

OTHER NCT02542462

Trial name or title	"Potential Mechanisms for Intussusception After Rotavirus Vaccine-Pilot Study"
Methods	Prospective randomized clinical trial , phase 4
Participants	**Number:** 101 **Description:** Healthy infants aged 6 - 13 weeks
Interventions	1. RV1, single oral dose of licensed rotavirus vaccine, given alone 2. RV1, with other routine vaccines 3. RV5, single oral dose of licensed rotavirus vaccine given alone 4. RV5, with other routine vaccines
Outcomes	1. The effects of RV1 and RV5 with or without other routine immunizations on gastrointestinal anatomy 2. The feasibility of conducting a larger-scale study as determined by study recruitment rates and percentage of completed study visits
Starting date	November 2015 **Completion:** May 2017 (actual primary completion date), May 2018 (estimated study completion date)
Contact information	Mary A. Staat, MD, MPH Children's Hospital Medical Center, Cincinnati Ohio, United States, 45219

OTHER NCT02542462 (*Continued*)

Notes	**Location:** USA **Registration number:** NCT02542462 **Source of funding:** Children's Hospital Medical Center, Cincinnati, USA

OTHER NCT02646891

Trial name or title	"Safety and Immunogenicity Study of Trivalent P2-VP8 Subunit Rotavirus Vaccine in Adults, Toddlers and Infants"
Methods	Phase I/II double-blind, randomized, placebo-controlled trial
Participants	**Number:** 609 **Description:** Healthy adults (≥ 18 and ≤ 45 years), toddlers (≥ 2 and ≤ 3 years), and infants (≥ 6 and ≤ 8 weeks)
Interventions	1. Trivalent P2VP8 (15 mcg) 2. Trivalent P2VP8 (30 mcg) 3. Trivalent P2VP8 (90 mcg) 4. Placebo
Outcomes	1. Serious adverse events 2. Adverse events 3. Participants with vaccine-related reactogenicity events 4. Proportion of infants with anti-P2VP8 IgG sero-responses 5. Proportion of infants with anti-P2VP8 IgA sero-responses 6. Proportion of infants with neutralizing antibody responses
Starting date	February 2016 **Completion:** January 2018
Contact information	Michelle Groom, MBBCh Chris Hani Baragwanath Hospital
Notes	**Location:** South Africa **Registration number:** NCT02646891 **Source of funding:** PATH

OTHER NCT02847026

Trial name or title	"Fractional Inactivated Poliovirus Vaccine Booster and Rotavirus Study (fIPV)"
Methods	Open-label phase IV, randomized controlled trial
Participants	**Number:** 1144 **Description:** Infants 6 weeks of age (range: 42 - 48 days)

OTHER NCT02847026 (*Continued*)

Interventions	1. RV1 at 6 and 10 weeks of age 1.1 RV1 + full dose of IPV at 14 and 22 weeks of age 1.2 RV1 + full dose of IPV at 14 weeks of age and a fractional dose IPV at 22 weeks of age 1.3 RV1 + full dose of IPV at 6 weeks of age and a fractional dose IPV at 22 weeks of age 1.4 RV1 + fractional doses of IPV at 6, 14, and 22 weeks of age 2. RV5 at 6, 10, and 14 weeks of age 2.1 RV5 + full dose of IPV at 14 and 22 weeks of age 2.2 RV5 + full dose of IPV at 14 weeks of age and a fractional dose IPV at 22 weeks of age 2.3 RV5 + full dose of IPV at 6 weeks of age and a fractional dose IPV at 22 weeks of age 2.4 RV5 + fractional doses of IPV at 6, 14, and 22 weeks of age
Outcomes	1. Seroconversion 4. Rotavirus IgA geometric mean titres 5. Rotavirus IgA seroconversion and geometric mean titres by secretor status, Lewis and salivary ABO blood group phenotype
Starting date	September 2016 **Completion:** December 2017
Contact information	Centers for Disease Control and Prevention
Notes	**Location:** Bangladesh **Registration number:** NCT02847026 **Source of funding:** Centers for Disease Control and Prevention

OTHER NCT03462108

Trial name or title	"Safety and Immunogenicity of Rotavirus (Bio Farma) Vaccine in Adults, Children & Neonates"
Methods	Phase 1, mixed methods study; double-blind, randomized study (neonates); open-label study (adults and children)
Participants	**Number:** 100 **Description:** Adults, children and neonates
Interventions	1. Rotavirus (Bio Farma) Vaccine 2. Placebo
Outcomes	1. Solicited symptoms 2. Adverse events 3. Serious adverse events 4. Number of infants who have abnormality value of routine haematology and biochemical evaluation that probably related to the vaccination 5. Excretion of rotavirus in stools in neonates group 6. Number of infants with ≥ 3 times increasing antibody from baseline to post-investigational product dosing 7. Serum anti-rotavirus immunoglobulin (Ig)A 8. Serum neutralizing antibody 9. Geometric mean titre

OTHER NCT03462108 (*Continued*)

Starting date	April 2018 **Completion:** December 2018 (estimated)
Contact information	Novilia Sjafri Bachtiar; novilia@biofarma.co.id
Notes	**Location:** Indonesia **Registration number:** NCT03462108 **Source of funding:** PT Bio Farma

OTHER NCT03483116

Trial name or title	"A Phase II Randomized, Double Blind, Parallel Group Dose-ranging Study of Oral RV3-BB Rotavirus Vaccine"
Methods	Phase II randomized, controlled trial. Double-blind
Participants	**Number:** 688 **Description:** up to 18 weeks (Child)
Interventions	1. RV3-BB 2. Placebo
Outcomes	1.Cumulative anti-rotavirus serum IgA response 2. Cumulative vaccine take and components of vaccine take (serum anti rotavirus IgA response or shedding of RV3-BB) 3. Adverse events 4. Serious adverse events 5. Diarrhoea
Starting date	April 2018 **Completion:** May 2019 (primary completion date estimated), August 2019 (Estimated study completion date)
Contact information	Julie Bines, MD, +61393454107, julie.bines@mcri.edu.au
Notes	**Location:** Malawi **Registration number:** NCT03483116 **Source of funding:** Murdoch Childrens Research Institute

RV1 ISRCTN86632774

Trial name or title	"A phase II, double blind randomized, placebo controlled study to assess the safety reactogenicity and immunogenicity of three doses of GSK Biologicals (South Africa)"
Methods	"randomized, controlled study with three parallel groups with balanced allocation (1:1:1)"

RV1 ISRCTN86632774 (*Continued*)

Participants	Target number: 271 **Description:** participants' parents/guardians who could comply with the protocol requirements (e.g. completion of diary cards, return for follow-up visits); male or female aged 6 to 10 weeks of age at the time of first vaccination; written informed consent from parents/guardians; born after a gestation period of 36 to 42 weeks
Interventions	1. RIX4414 (RV1): 2 doses vaccine at $10^{6.5}$ CCID50 viral concentration plus 1 dose of placebo 2. Placebo: 3 doses
Outcomes	1. Seroprotection for each polio serotype (primary) 2. Vaccine take 3. Viral shedding 4. Presence of rotavirus in diarrhoeal stools 5. Anti-poliovirus antibody titres 6. Serum anti-rotavirus immunoglobulin A (IgA) antibody titres 7. Solicited symptoms 8. Unsolicited adverse events 9. Serious adverse events
Starting date	1 January 2001 **Anticipated end date:** 1 January 2003, completed
Contact information	Dr Duncan Steele (steeled@who.int), WHO
Notes	**Location:** South Africa **Registration number:** ISRCTN86632774 **Source of funding:** RAPID trials (USA); WHO (Switzerland)

RV1 NCT02941107

Trial name or title	"Optimising Rotavirus Vaccine in Aboriginal Children"
Methods	Phase 4, double-blind, randomized controlled trial
Participants	**Number:** 1000 **Description:** infants aged ≥ 6 months and < 12 months
Interventions	1. RV1 2. Placebo
Outcomes	1.Time to medical attendance (hospitalization, emergency department or medical clinic presentation) for which primary reason for presentation is presumed or confirmed acute gastroenteritis or acute diarrhoea illness before age 36 months 2. Anti-rotavirus IgA seroconversion 3.Time to hospitalization for which the primary coded reason for admission is presumed or confirmed acute gastroenteritis or acute diarrhoea illness before age 36 months 4. Time to hospitalization for which rotavirus confirmed diarrhoea illness occurs before age 36 months 5. Rotavirus infection meeting the jurisdictional case definition

RV1 NCT02941107 (*Continued*)

	6. Change in anti-rotavirus IgA log titre between administration of intervention (RV1/placebo) and 28 to 55 days post-dose 7. The occurrence of intussusception fulfilling Brighton criteria 8. Serious adverse events
Starting date	March 2018 **Completion:** December 2020 (estimated)
Contact information	Tom Snelling, tom.snelling@telethonkids.org.au Carly McCallum, carly.foulis@telethonkids.org.au
Notes	**Location:** Australia **Registration number:** NCT02941107 **Source of funding:** Telethon Kids Institute

RV1 Tatochenko 2008

Trial name or title	Co-administration of a human rotavirus vaccine Rix4414 with DTPw-HBv vaccines: immunogenicity and reactogenicity in healthy infants
Methods	Randomized controlled trial
Participants	**Number:** 308 **Description:** healthy infants 11 to 17 weeks of age
Interventions	1. RIX4414 vaccine 2. Placebo
Outcomes	1. Immunogenicity 2. Safety
Starting date	Not reported
Contact information	GlaxoSmithKline
Notes	**Location:** not reported **Registration number:** not reported **Source of funding:** GlaxoSmithKline

RV5 NCT02728869

Trial name or title	"Safety, Reactogenicity and Immunogenicity of Heat-stable Rotavirus Vaccine (HSRV) in Adults and Infants"
Methods	Phase I/II, randomized, single-blind trial
Participants	**Number:** 100 **Description:** Healthy infants of either sex, 6 - 8 weeks of age; healthy adults

RV5 NCT02728869 (*Continued*)

Interventions	1. Hilleman Labs heat stable pentavalent vaccine 2. RV5 **Schedule: 3 doses at 4-week intervals**
Outcomes	3. Any adverse event 4. Serious adverse events 5. Anti-Rotavirus IgA sero-response rate 7. Viral shedding
Starting date	June 2016 **Completion:** April 2017
Contact information	K Zaman, MBBS, PhD; International Center for Diarrheal Disease Research, Bangladesh
Notes	**Location:** Bangladesh **Registration number:** NCT02728869 **Source of funding:** MSD Wellcome Trust Hilleman Laboratories Pvt. Ltd.

BRV: bovine-human reassortant vaccine; GMT: geometric mean titre; SAE: serious adverse event

DATA AND ANALYSES

Comparison 1. RV1 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	11	49893	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.14, 0.34]
1.1 Low-mortality countries (WHO strata A & B)	7	43779	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.09, 0.26]
1.2 High-mortality countries (WHO strata D & E)	4	6114	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.60]
2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	12		Risk Ratio (Fixed, 95% CI)	0.34 [0.29, 0.41]
2.1 Low-mortality countries (WHO strata A & B)	9		Risk Ratio (Fixed, 95% CI)	0.18 [0.14, 0.23]
2.2 High-mortality countries (WHO strata D & E)	3		Risk Ratio (Fixed, 95% CI)	0.65 [0.51, 0.83]
3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	6	33690	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.54, 0.80]
3.1 Low-mortality countries (WHO strata A & B)	3	28051	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.47, 0.74]
3.2 High-mortality countries (WHO strata D & E)	3	5639	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.56, 0.95]
4 All-cause diarrhoea: severe cases (up to 2 years follow-up)	5	12181	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.92]
4.1 Low-mortality countries (WHO strata A & B)	3	9417	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.02]
4.2 High-mortality countries (WHO strata D & E)	2	2764	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.96]
5 All-cause diarrhoea: severe episodes (up to 1 year follow-up)	1		Rate Ratio (Fixed, 95% CI)	Totals not selected
5.1 Low-mortality countries (WHO strata A & B)	1		Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 All-cause diarrhoea: severe episodes (up to 2 years follow-up)	2		Rate Ratio (Fixed, 95% CI)	Subtotals only
6.1 Low-mortality countries (WHO strata A & B)	2		Rate Ratio (Fixed, 95% CI)	0.63 [0.56, 0.71]
7 All-cause death	30	105778	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.30]
7.1 Low-mortality countries (WHO strata A & B)	22	97597	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.87, 1.71]
7.2 High-mortality countries (WHO strata D & E)	8	8181	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.22]
8 All serious adverse events	31	103714	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.93]
8.1 Low-mortality countries (WHO strata A & B)	24	96233	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.93]

8.2 High-mortality countries (WHO strata D & E)	7	7481	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
9 Serious adverse events: intussusception	21		Risk Ratio (Fixed, 95% CI)	0.70 [0.46, 1.05]
9.1 Low-mortality countries (WHO strata A & B)	17		Risk Ratio (Fixed, 95% CI)	0.69 [0.45, 1.04]
9.2 High-mortality countries (WHO stratum E)	4		Risk Ratio (Fixed, 95% CI)	1.49 [0.06, 36.63]
10 Serious adverse events: Kawasaki disease	3	13117	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.30, 10.61]
11 Serious adverse events requiring hospitalization	2	63675	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.81, 0.96]
12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up)	12	4294	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.69, 2.00]
12.1 Low-mortality countries (WHO strata A & B)	9	3537	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.66, 2.50]
12.2 High-mortality countries (WHO strata D & E)	3	757	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.41, 2.41]
13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	8	15197	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.23, 0.50]
13.1 Low-mortality countries (WHO strata A & B)	4	9083	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.13, 0.40]
13.2 High-mortality countries (WHO stratum E)	4	6114	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.68]
14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	7	11692	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.28, 0.47]
14.1 Low-mortality countries (WHO strata A & B)	6	10441	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
14.2 High-mortality countries (WHO stratum E)	1	1251	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.28, 0.62]
15 All-cause diarrhoea: all cases (up to 2 months follow-up)	7	3132	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.10]
15.1 Low-mortality countries (WHO strata A & B)	6	3032	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.09]
15.2 High-mortality countries (WHO stratum E)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.58]
16 All-cause diarrhoea: all cases (up to 1 year follow-up)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Low-mortality countries (WHO strata A & B)	2	2204	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.03]
16.2 High-mortality countries (WHO strata D & E)	1	700	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.93, 1.05]
17 All-cause diarrhoea: all cases (up to 2 years follow-up)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Low-mortality countries (WHO strata A & B)	3	5937	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 1.00]
18 All-cause diarrhoea: all episodes (up to 1 year follow-up)	2		Rate Ratio (Fixed, 95% CI)	Subtotals only

18.1 Low-mortality countries (WHO strata A & B)	2		Rate Ratio (Fixed, 95% CI)	0.98 [0.88, 1.10]
19 All-cause diarrhoea: all episodes (up to 2 years follow-up)	1		Rate Ratio (Fixed, 95% CI)	Totals not selected
19.1 Low-mortality countries (WHO strata A & B)	1		Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
20 All-cause hospitalizations (up to 2 years follow-up)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 Low-mortality countries (WHO strata A & B)	2	65646	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.27, 1.47]
21 Rotavirus diarrhoea: requiring hospitalization	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Up to 1 year follow-up (at least 1 rotavirus season)	8	48718	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.09, 0.33]
21.2 Second year follow-up (at least 2 rotavirus seasons)	7	35331	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.11, 0.22]
22 Rotavirus diarrhoea: requiring medical attention	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Up to 1 year follow-up (at least 1 rotavirus season)	1	3874	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.04, 0.16]
22.2 Second year follow-up (at least 2 rotavirus seasons)	3	7017	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.16, 0.31]
23 All-cause diarrhoea: cases requiring hospitalization	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Up to one year of follow-up (at least 1 rotavirus season)	2	14393	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.11]
23.2 Second year of follow-up (at least 2 rotavirus seasons)	2	14367	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.99]
24 All-cause diarrhoea: episodes requiring hospitalization	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
24.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1		Rate Ratio (Fixed, 95% CI)	0.58 [0.47, 0.71]
24.2 Second year of follow-up (at least 2 rotavirus seasons)	1		Rate Ratio (Fixed, 95% CI)	0.53 [0.46, 0.61]
25 Reactogenicity: fever	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 After dose 1	25	16192	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.17]
25.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
25.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.13]
25.4 End of follow-up	18	11926	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
26 Reactogenicity: diarrhoea	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 After dose 1	25	18732	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.17]
26.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.21]
26.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.36]
26.4 End of follow-up	17	14305	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
27 Reactogenicity: vomiting	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 After dose 1	25	18732	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
27.2 After dose 2	24	15630	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.05]
27.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.71, 2.50]
27.4 End of follow-up	17	14305	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.04]

28 Adverse events requiring discontinuation (end of follow-up)	26	94980	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.26]
29 Immunogenicity: rotavirus vaccine shedding (end of follow-up)	16	2638	Risk Ratio (M-H, Random, 95% CI)	10.94 [4.90, 24.43]
30 Immunogenicity: seroconversion	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.1 After dose 1	9	2537	Risk Ratio (M-H, Random, 95% CI)	20.39 [8.48, 49.01]
30.2 After dose 2	27	8742	Risk Ratio (M-H, Random, 95% CI)	11.44 [8.01, 16.32]
30.3 After dose 3	5	1137	Risk Ratio (M-H, Random, 95% CI)	6.89 [3.59, 13.24]
31 Dropouts before the end of the trial	28	93106	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.90, 1.00]
32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 G1	6	27583	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.44]
32.2 G2	5	26835	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.31, 0.56]
32.3 G3	4	8968	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.39]
32.4 G4	2	5720	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.59]
32.5 G9	3	8868	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.75]
33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 G1	7	39428	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.16, 0.38]
33.2 G2	7	44682	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.18, 0.50]
33.3 G3	5	20505	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.05, 0.56]
33.4 G4	1	2421	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.00, 2.95]
33.5 G8	2	4417	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.37]
33.6 G9	6	26815	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.13, 0.40]
33.7 G12	2	4417	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.97]
34 Subgroup analysis: rotavirus diarrhoea in malnourished children	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
34.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.78]

Comparison 2. RV5 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	9	10048	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.22, 0.44]
1.1 Low-mortality countries (WHO strata A & B)	5	4132	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.03, 0.22]

1.2 High-mortality countries (WHO strata D & E)	4	5916	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.29, 0.62]
2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	8	13203	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.60]
2.1 Low-mortality countries (WHO strata A & B)	4	7318	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.08, 0.39]
2.2 High-mortality countries (WHO strata D & E)	4	5885	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.82]
3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	3	4085	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.11]
3.1 Low-mortality countries (WHO stratum A)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 High-mortality countries (WHO strata D & E)	3	4085	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.11]
4 All-cause diarrhoea: severe cases (up to 2 years follow-up)	4	5977	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.98]
4.1 Low-mortality countries (WHO strata A & B)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 High-mortality countries (WHO strata D & E)	4	5977	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.98]
5 All-cause death	14	84448	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.74, 1.25]
5.1 Low-mortality countries (WHO strata A & B)	9	77642	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.65, 1.96]
5.2 High-mortality countries (WHO strata D & E)	5	6806	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.24]
6 All serious adverse events	14	82502	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.86, 1.01]
6.1 Low-mortality countries (WHO strata A & B)	8	75672	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.86, 1.02]
6.2 High-mortality countries (WHO strata D & E)	6	6830	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.28]
7 Serious adverse events: intussusception	16	85495	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.45]
7.1 Low-mortality countries (WHO strata A & B)	12	78907	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.45]
7.2 High-mortality countries (WHO strata D & E)	4	6588	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	8	13450	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.28, 0.50]
8.1 Low-mortality countries (WHO strata A & B)	5	8644	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.25, 0.37]
8.2 High-mortality countries (WHO strata D & E)	3	4806	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.94]
9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	7	12888	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.65]
9.1 Low-mortality countries (WHO strata A & B)	3	6144	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.26, 0.43]
9.2 High-mortality countries (WHO strata D & E)	4	6744	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.83]
10 All-cause diarrhoea: of any severity (up to 1 year follow-up)	1	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]

10.1 Low-mortality countries (WHO strata A & B)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 High-mortality countries (WHO stratum E)	1	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
11 All-cause diarrhoea: of any severity (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 High-mortality countries (WHO stratum E)	1	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.16]
12 All-cause hospitalizations (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 High-mortality countries (WHO strata D & E)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Rotavirus diarrhoea: requiring hospitalization	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Up to 1 year of follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Rotavirus diarrhoea: requiring medical attention	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Up to 1 year of follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Reactogenicity: fever	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 After dose 1	4	7124	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.91, 1.45]
15.2 After dose 2	2	4322	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.01]
15.3 After dose 3	2	4294	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]
15.4 End of follow-up	11	18391	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]
16 Reactogenicity: diarrhoea	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 After dose 1	2	4745	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.32]
16.2 After dose 2	1	3905	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.10]
16.3 End of follow-up	10	17087	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.10]
17 Reactogenicity: vomiting	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 After dose 1	2	4745	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.12]
17.2 After dose 2	1	3905	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.32, 1.49]
17.3 After dose 3	1	3878	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.16, 1.32]
17.4 End of follow-up	9	16294	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.06]
18 Adverse events requiring discontinuation (end of follow-up)	10	15471	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.57, 1.39]
19 Immunogenicity: rotavirus vaccine shedding (after dose 3)	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20 Immunogenicity: seroconversion	10		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.1 After dose 3	10		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Dropouts before the end of the trial	13	85855	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.08]
22 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 G1	4	11022	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.21, 0.32]
22.2 G2	3	9907	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.16, 0.78]
22.3 G3	4	11022	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 2.02]
22.4 G4	3	9907	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.33]
22.5 G9	2	9537	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.20, 0.54]

23 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 G1	3	76606	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.03, 1.74]
23.2 G2	3	76606	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.37]
23.3 G3	3	76606	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.05, 2.74]
23.4 G4	3	76606	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.03, 0.46]
23.5 G9	3	76606	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.05, 0.34]
24 Subgroup analysis: HIV-infected children	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Rotavirus diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.11, 56.68]
24.2 All-cause diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [0.52, 31.43]
24.3 All-cause death	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.51, 3.21]
24.4 Serious adverse events (up to 24 weeks)	2	113	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.59, 3.97]

Comparison 3. Rotavac versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 All-cause death	2	8155	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.52, 1.62]
5 All serious adverse events	3	8210	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.85, 1.02]
6 Serious adverse events: intussusception	4	8582	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.35, 5.02]
7 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Rotavirus diarrhoea: requiring medical attention	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Up to 1 year follow-up (at least 1 rotavirus season)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Reactogenicity: fever	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 After dose 1	2	427	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.35, 1.94]
10.2 After dose 2	1	356	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.33, 1.77]
10.3 After dose 3	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.52, 2.36]
11 Reactogenicity: diarrhoea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

11.1 After dose 1	2	427	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.62, 1.30]
11.2 After dose 2	1	356	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.00, 2.41]
11.3 After dose 3	1	358	Risk Ratio (M-H, Fixed, 95% CI)	4.09 [2.11, 7.92]
12 Reactogenicity: vomiting	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 After dose 1	2	427	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.71, 2.55]
12.2 After dose 2	1	356	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.64, 3.66]
12.3 After dose 3	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.39, 2.66]
13 Immunogenicity: rotavirus vaccine shedding (end of follow-up)	2	427	Risk Ratio (M-H, Random, 95% CI)	9.86 [2.58, 37.63]
14 Immunogenicity: seroconversion	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 After dose 1	1	121	Risk Ratio (M-H, Fixed, 95% CI)	3.58 [2.03, 6.29]
14.2 After dose 2	1	117	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [1.78, 4.98]
14.3 After dose 3	3	1699	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [2.26, 3.51]
15 Dropouts before the end of the trial	3	8215	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.06]
16 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 1 year follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 G1P[8]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.36, 1.20]
16.2 G2P[4]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.22, 0.69]
16.3 G12P[6]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.74]
16.4 G12P[8]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.07, 1.26]
17 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 G1P[8]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.38, 0.93]
17.2 G2P[4]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.23, 0.62]
17.3 G9P[4]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	4.52 [0.57, 35.66]
17.4 G12P[6]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.74]
17.5 G12P[8]	1	6541	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.96]

Analysis 1.1. Comparison 1 RV1 versus placebo, Outcome 1 Rotavirus diarrhoea: severe (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 1 Rotavirus diarrhoea: severe (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Bernstein 1999-USA	2/108	9/107		5.4 %	0.22 [0.05, 1.00]
RV1 Li 2014-CHN	8/1575	32/1573		9.9 %	0.25 [0.12, 0.54]
RV1 Phua 2009-AS	0/5263	15/5256		2.1 %	0.03 [0.00, 0.54]
RV1 Ruiz-Palac 06-LA/EU (1)	12/9009	77/8858		11.2 %	0.15 [0.08, 0.28]
RV1 Salinas 2005-LA	27/1392	34/454		12.0 %	0.26 [0.16, 0.42]
RV1 Tregnaghi 2011-LA	7/4211	19/2099		9.2 %	0.18 [0.08, 0.44]
RV1 Vesikari 2007a-EU	5/2572	60/1302		8.9 %	0.04 [0.02, 0.10]
Subtotal (95% CI)	**24130**	**19649**		**58.8 %**	**0.16 [0.09, 0.26]**
Total events: 61 (RV1), 246 (Placebo)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 15.41, df = 6 (P = 0.02); I^2 =61%					
Test for overall effect: Z = 6.91 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV1 Colgate 2016-BGD	14/350	39/350		11.3 %	0.36 [0.20, 0.65]
RV1 Madhi 2010-MWI (2)	52/1182	47/591		12.8 %	0.55 [0.38, 0.81]
RV1 Madhi 2010-ZAF (3)	16/2116	36/1050		11.3 %	0.22 [0.12, 0.40]
RV1 Steele 2010b-ZAF	5/379	3/96		5.9 %	0.42 [0.10, 1.74]
Subtotal (95% CI)	**4027**	**2087**		**41.2 %**	**0.37 [0.23, 0.60]**
Total events: 87 (RV1), 125 (Placebo)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 6.91, df = 3 (P = 0.07); I^2 =57%					
Test for overall effect: Z = 4.09 (P = 0.000044)					
Total (95% CI)	**28157**	**21736**		**100.0 %**	**0.22 [0.14, 0.34]**
Total events: 148 (RV1), 371 (Placebo)					
Heterogeneity: Tau^2 = 0.37; Chi^2 = 39.86, df = 10 (P = 0.00002); I^2 =75%					
Test for overall effect: Z = 6.63 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 5.84, df = 1 (P = 0.02), I^2 =83%					

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort in Malawi

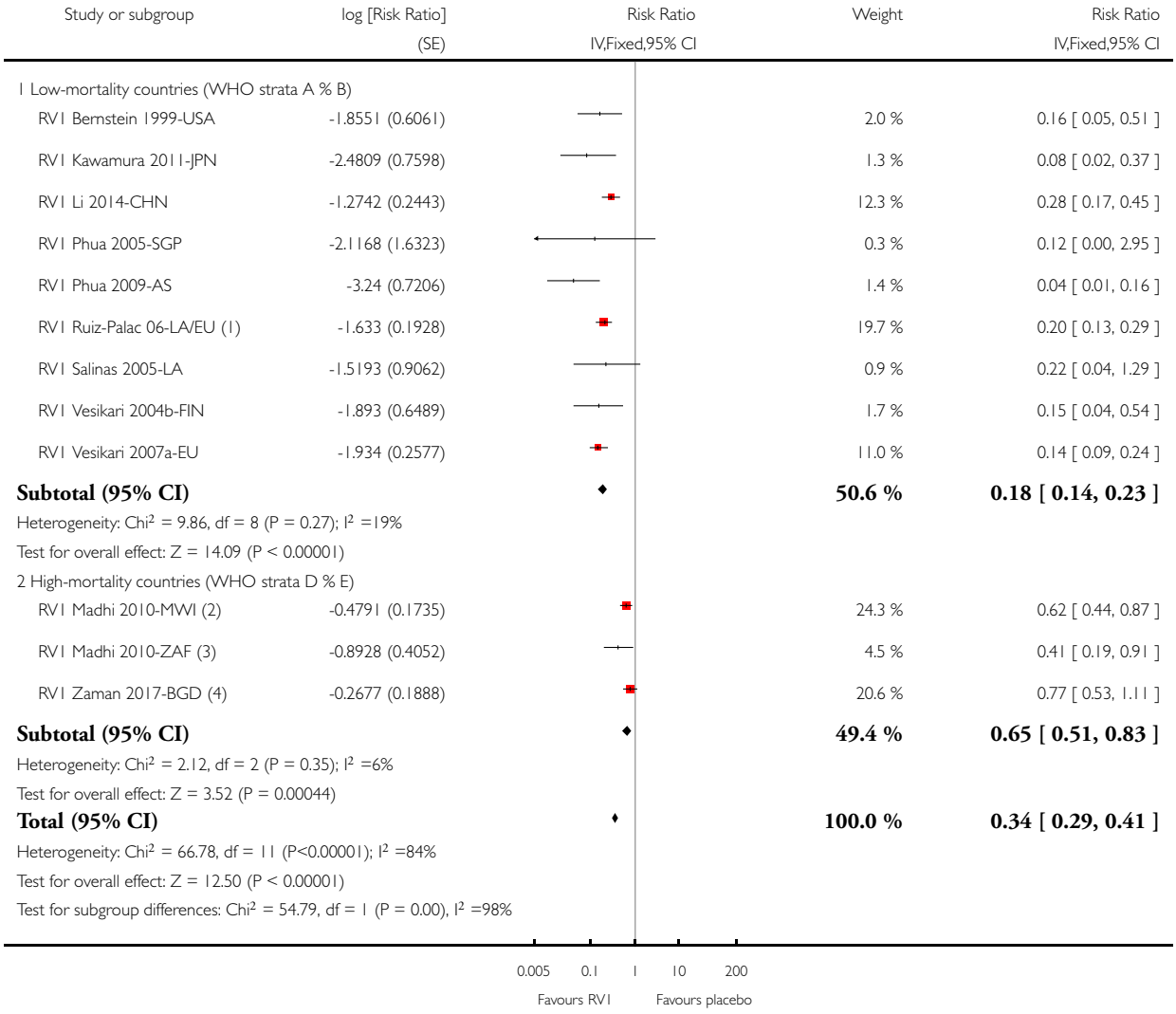
(3) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort in South Africa

Analysis 1.2. Comparison 1 RV1 versus placebo, Outcome 2 Rotavirus diarrhoea: severe (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 2 Rotavirus diarrhoea: severe (up to 2 years follow-up)



(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) Data from Malawi cohort only

(3) Assessment of vaccine effiicacy up to two years follow-up available from cohort 2 subjects only in South Africa

(4) Adjusted for clustering: design effect of 2.53, villages randomised to RV1 versus no intervention

Analysis 1.3. Comparison 1 RV1 versus placebo, Outcome 3 All-cause diarrhoea: severe cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 3 All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Ruiz-Palac 06-LA/EU	183/9009	300/8858		18.4 %	0.60 [0.50, 0.72]
RV1 Tregnaghi 2011-LA	116/4211	78/2099		14.9 %	0.74 [0.56, 0.98]
RV1 Vesikari 2007a-EU	116/2572	123/1302		16.2 %	0.48 [0.37, 0.61]
Subtotal (95% CI)	**15792**	**12259**		**49.5 %**	**0.59 [0.47, 0.74]**
Total events: 415 (RV1), 501 (Placebo)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.42$, df = 2 (P = 0.07); $I^2 = 63\%$					
Test for overall effect: Z = 4.63 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV1 Colgate 2016-BGD	110/350	126/350		17.5 %	0.87 [0.71, 1.08]
RV1 Madhi 2010-MWI (1)	221/1182	139/591		18.2 %	0.79 [0.66, 0.96]
RV1 Madhi 2010-ZAF (2)	92/2116	86/1050		14.8 %	0.53 [0.40, 0.71]
Subtotal (95% CI)	**3648**	**1991**		**50.5 %**	**0.73 [0.56, 0.95]**
Total events: 423 (RV1), 351 (Placebo)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.11$, df = 2 (P = 0.02); $I^2 = 75\%$					
Test for overall effect: Z = 2.37 (P = 0.018)					
Total (95% CI)	**19440**	**14250**		**100.0 %**	**0.66 [0.54, 0.80]**
Total events: 838 (RV1), 852 (Placebo)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 21.45$, df = 5 (P = 0.00066); $I^2 = 77\%$					
Test for overall effect: Z = 4.30 (P = 0.000017)					
Test for subgroup differences: $Chi^2 = 1.45$, df = 1 (P = 0.23), $I^2 = 31\%$					

(1) Data taken from main paper Supplementary Appendix, Table 6 - total vaccinated cohort in Malawi

(2) Data taken from main paper Supplementary Appendix, Table 6 - total vaccinated cohort in South Africa

Analysis 1.4. Comparison 1 RV1 versus placebo, Outcome 4 All-cause diarrhoea: severe cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 4 All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Li 2014-CHN	187/1575	206/1573		24.5 %	0.91 [0.75, 1.09]
RV1 Phua 2005-SGP	11/1779	10/642		7.4 %	0.40 [0.17, 0.93]
RV1 Vesikari 2007a-EU	149/2554	153/1294		23.6 %	0.49 [0.40, 0.61]
Subtotal (95% CI)	**5908**	**3509**		**55.5 %**	**0.60 [0.36, 1.02]**
Total events: 347 (RV1), 369 (Placebo)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 19.27, df = 2 (P = 0.00007); I^2 =90%					
Test for overall effect: Z = 1.89 (P = 0.059)					
2 High-mortality countries (WHO strata D % E)					
RV1 Madhi 2010-MWI (1)	287/1030	160/483		25.2 %	0.84 [0.72, 0.99]
RV1 Madhi 2010-ZAF (2)	76/843	48/408		19.2 %	0.77 [0.54, 1.08]
Subtotal (95% CI)	**1873**	**891**		**44.5 %**	**0.83 [0.72, 0.96]**
Total events: 363 (RV1), 208 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.56 (P = 0.010)					
Total (95% CI)	**7781**	**4400**		**100.0 %**	**0.70 [0.54, 0.92]**
Total events: 710 (RV1), 577 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 22.70, df = 4 (P = 0.00015); I^2 =82%					
Test for overall effect: Z = 2.56 (P = 0.011)					
Test for subgroup differences: Chi^2 = 1.29, df = 1 (P = 0.26), I^2 =22%					

(1) Data from Malawi cohort only

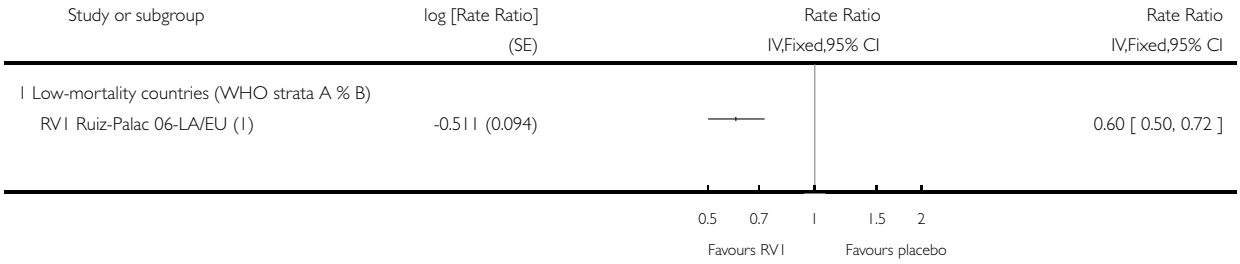
(2) Data from South Africa cohort only

Analysis 1.5. Comparison 1 RV1 versus placebo, Outcome 5 All-cause diarrhoea: severe episodes (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 5 All-cause diarrhoea: severe episodes (up to 1 year follow-up)



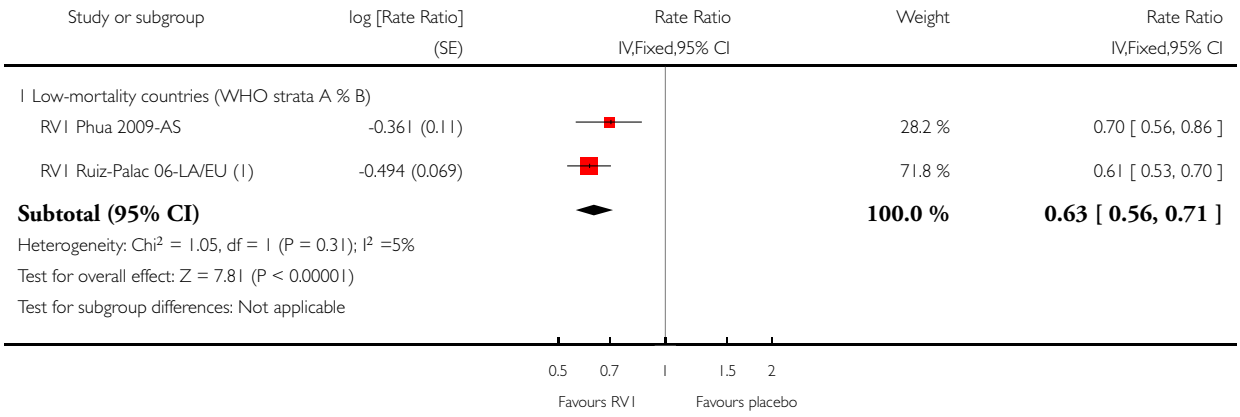
(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

Analysis 1.6. Comparison 1 RV1 versus placebo, Outcome 6 All-cause diarrhoea: severe episodes (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 6 All-cause diarrhoea: severe episodes (up to 2 years follow-up)



(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

Analysis 1.7. Comparison 1 RV1 versus placebo, Outcome 7 All-cause death.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 7 All-cause death

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Anh 2011-PHL	1/281	0/64		0.6 %	0.69 [0.03, 16.78]
RV1 Anh 2011-VNM	0/279	0/73			Not estimable
RV1 Bernstein 1999-USA	1/108	0/107		0.4 %	2.97 [0.12, 72.16]
RV1 GSK[021] 2007-PAN	0/177	0/51			Not estimable
RV1 GSK[041] 2007-KOR	0/103	0/52			Not estimable
RV1 GSK[101555] 2008-PHL	0/100	0/50			Not estimable
RV1 Kawamura 2011-JPN	0/507	0/257			Not estimable
RV1 Kerdpanich 2010-THA	0/395	0/26			Not estimable
RV1 Kim 2012-KOR	0/508	0/176			Not estimable
RV1 Li 2013b-CHN	0/25	0/25			Not estimable
RV1 Li 2014-CHN	6/1666	7/1667		5.1 %	0.86 [0.29, 2.55]
RV1 NCT00158756-RUS	0/161	0/48			Not estimable
RV1 Omenaca 2012-EU	0/670	1/339		1.4 %	0.17 [0.01, 4.14]
RV1 Phua 2005-SGP	3/1779	0/642		0.5 %	2.53 [0.13, 48.89]
RV1 Phua 2009-AS	1/5263	3/5256		2.2 %	0.33 [0.03, 3.20]
RV1 Rivera 2011-DOM	0/100	0/100			Not estimable
RV1 Ruiz-Palac 06-LA/EU (1)	56/31673	43/31552		31.3 %	1.30 [0.87, 1.93]
RV1 Salinas 2005-LA	2/1618	1/537		1.1 %	0.66 [0.06, 7.31]
RV1 Tregnaghi 2011-LA	10/4376	2/2192		1.9 %	2.50 [0.55, 11.42]
RV1 Vesikari 2004b-FIN	0/267	0/133			Not estimable
RV1 Vesikari 2007a-EU	0/2613	0/1331			Not estimable
RV1 Vesikari 2011-FIN	0/200	0/50			Not estimable
Subtotal (95% CI)	**52869**	**44728**		**44.5 %**	**1.22 [0.87, 1.71]**
Total events: 80 (RV1), 57 (Placebo)					
Heterogeneity: Chi^2 = 4.99, df = 8 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-mortality countries (WHO strata D % E)					
RV1 Colgate 2016-BGD	1/350	1/350		0.7 %	1.00 [0.06, 15.92]
RV1 GSK[033] 2007-LA (2)	3/730	0/124		0.6 %	1.20 [0.06, 23.03]
RV1 Madhi 2010-AF	83/3298	43/1641		41.7 %	0.96 [0.67, 1.38]
RV1 Narang 2009-IND	0/182	0/181			Not estimable
RV1 Steele 2008-ZAF	3/300	5/150		4.8 %	0.30 [0.07, 1.24]
RV1 Steele 2010a-ZAF	6/50	9/50		6.5 %	0.67 [0.26, 1.73]
RV1 Steele 2010b-ZAF	3/379	0/96		0.6 %	1.79 [0.09, 34.30]
RV1 Zaman 2009-BGD	1/200	0/100		0.5 %	1.51 [0.06, 36.68]
Subtotal (95% CI)	**5489**	**2692**		**55.5 %**	**0.88 [0.64, 1.22]**
Total events: 100 (RV1), 58 (Placebo)					
Heterogeneity: Chi^2 = 3.14, df = 6 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.75 (P = 0.45)					
Total (95% CI)	**58358**	**47420**		**100.0 %**	**1.03 [0.82, 1.30]**
Total events: 180 (RV1), 115 (Placebo)					
Heterogeneity: Chi^2 = 9.92, df = 15 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.78)					
Test for subgroup differences: Chi^2 = 1.84, df = 1 (P = 0.18), I^2 =46%					

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) This study was conducted in four study centres in a high mortality country (Peru), but also in three study centres in two low mortality countries (Colombia and Mexico)

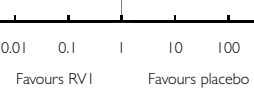
Analysis 1.8. Comparison 1 RV1 versus placebo, Outcome 8 All serious adverse events.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 8 All serious adverse events

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Anh 2011-PHL	1/281	1/64		0.1 %	0.23 [0.01, 3.59]
RV1 Anh 2011-VNM	15/279	1/73		0.1 %	3.92 [0.53, 29.23]
RV1 Bernstein 1998-USA	0/21	0/20			Not estimable
RV1 Dennehy 2005-NA	15/421	8/108		0.5 %	0.48 [0.21, 1.10]
RV1 GSK[021] 2007-PAN	18/177	9/51		0.6 %	0.58 [0.28, 1.20]
RV1 GSK[041] 2007-KOR	9/103	2/52		0.1 %	2.27 [0.51, 10.14]
RV1 GSK[101555] 2008-PHL	5/100	0/50		0.0 %	5.55 [0.31, 98.50]
RV1 Kawamura 2011-JPN	72/508	44/257		2.3 %	0.83 [0.59, 1.17]
RV1 Kerdpanich 2010-THA	11/396	4/51		0.3 %	0.35 [0.12, 1.07]
RV1 Kim 2012-KOR	17/508	13/176		0.8 %	0.45 [0.22, 0.91]
RV1 Li 2013b-CHN	2/25	0/25		0.0 %	5.00 [0.25, 99.16]
RV1 Li 2014-CHN	183/1666	246/1667		9.8 %	0.74 [0.62, 0.89]
RV1 NCT00158756-RUS	8/161	0/48		0.0 %	5.14 [0.30, 87.50]
RV1 Omenaca 2012-EU	34/670	23/339		1.2 %	0.75 [0.45, 1.25]
RV1 Phua 2005-SGP	144/1811	40/653		2.3 %	1.30 [0.93, 1.82]
RV1 Phua 2009-AS	10/4272	11/4226		0.4 %	0.90 [0.38, 2.12]
RV1 Rivera 2011-DOM	5/100	6/100		0.2 %	0.83 [0.26, 2.64]
RV1 Ruiz-Palac 06-LA/EU (1)	928/31673	1047/31552		41.8 %	0.88 [0.81, 0.96]
RV1 Salinas 2005-LA	156/1618	64/537		3.8 %	0.81 [0.62, 1.06]
RV1 Tregnaghi 2011-LA	505/4376	265/2192		14.1 %	0.95 [0.83, 1.10]
RV1 Vesikari 2004a-FIN	2/128	1/64		0.1 %	1.00 [0.09, 10.82]
RV1 Vesikari 2004b-FIN	28/267	9/133		0.5 %	1.55 [0.75, 3.19]
RV1 Vesikari 2007a-EU	290/2646	176/1348		9.3 %	0.84 [0.70, 1.00]
RV1 Vesikari 2011-FIN	3/193	0/47		0.0 %	1.73 [0.09, 32.97]
Subtotal (95% CI)	**52400**	**43833**		**88.3 %**	**0.88 [0.83, 0.93]**



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 2461 (RV1), 1970 (Placebo)					
Heterogeneity: Chi² = 31.78, df = 22 (P = 0.08); I² =31%					
Test for overall effect: Z = 4.28 (P = 0.000018)					
2 High-mortality countries (WHO strata D % E)					
RV1 GSK[033] 2007-LA (2)	3/730	0/124		0.0 %	1.20 [0.06, 23.03]
RV1 Madhi 2010-AF	319/3298	189/1641		10.0 %	0.84 [0.71, 1.00]
RV1 Narang 2009-IND	3/182	2/181		0.1 %	1.49 [0.25, 8.82]
RV1 Steele 2008-ZAF	30/300	14/150		0.7 %	1.07 [0.59, 1.96]
RV1 Steele 2010a-ZAF	17/50	12/50		0.5 %	1.42 [0.76, 2.65]
RV1 Steele 2010b-ZAF	19/379	5/96		0.3 %	0.96 [0.37, 2.51]
RV1 Zaman 2009-BGD	1/200	0/100		0.0 %	1.51 [0.06, 36.68]
Subtotal (95% CI)	**5139**	**2342**		**11.7 %**	**0.89 [0.76, 1.04]**
Total events: 392 (RV1), 222 (Placebo)					
Heterogeneity: Chi² = 3.42, df = 6 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 1.50 (P = 0.13)					
Total (95% CI)	**57539**	**46175**		**100.0 %**	**0.88 [0.83, 0.93]**
Total events: 2853 (RV1), 2192 (Placebo)					
Heterogeneity: Chi² = 35.23, df = 29 (P = 0.20); I² =18%					
Test for overall effect: Z = 4.54 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² =0.0%					

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

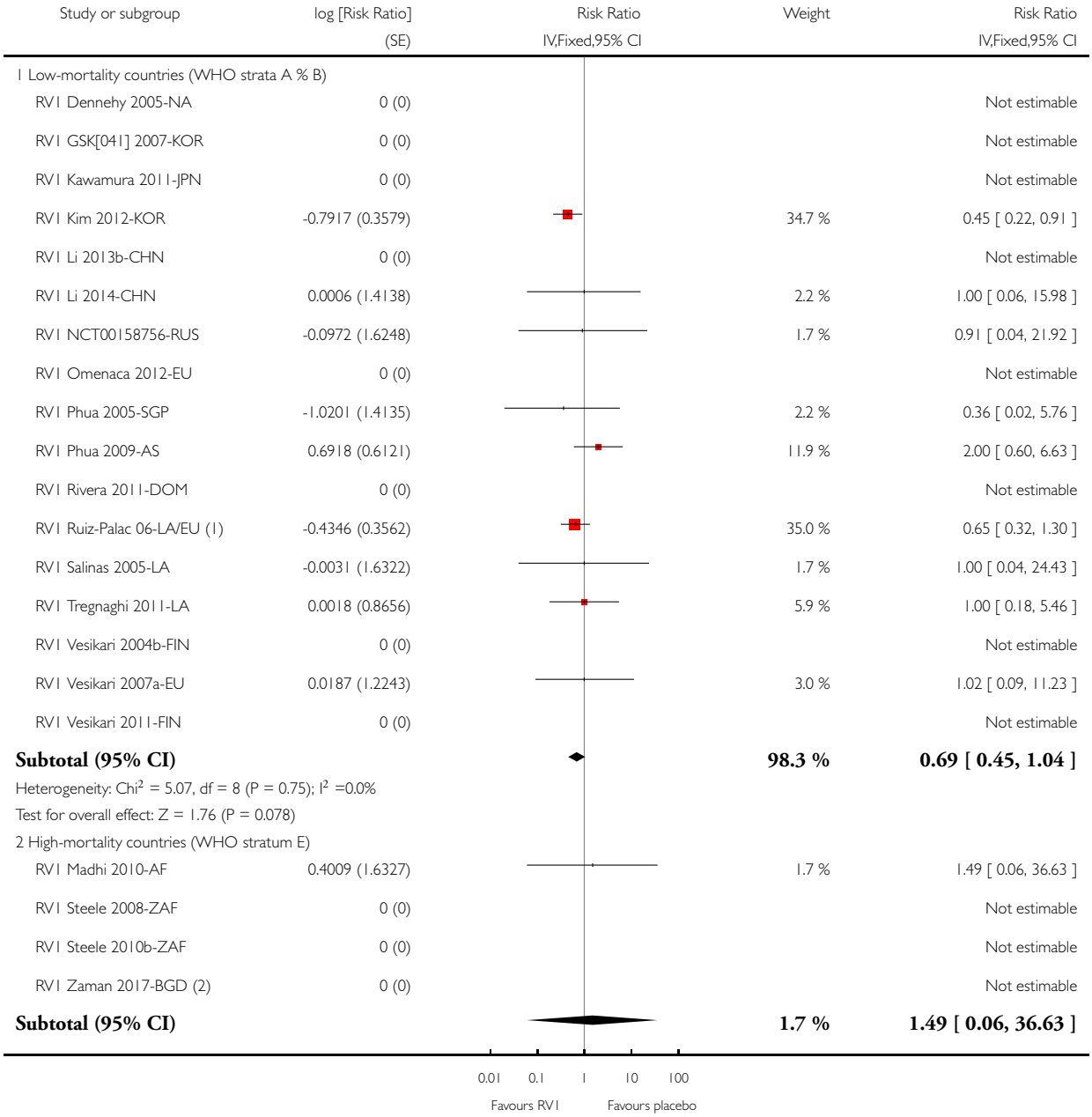
(2) This study was conducted in four study centres in a high mortality country (Peru), but also in three study centres in two low mortality countries (Colombia and Mexico)

Analysis 1.9. Comparison 1 RV1 versus placebo, Outcome 9 Serious adverse events: intussusception.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 9 Serious adverse events: intussusception



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Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 0.25 (P = 0.81)				
Total (95% CI)			**100.0 %**	**0.70 [0.46, 1.05]**
Heterogeneity: Chi^2 = 5.30, df = 9 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 1.72 (P = 0.086)				
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%				

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru). Data updated from www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm134142.htm

(2) Adjusted for clustering: design effect of 2.53, villages randomised to RV1 versus no intervention

Analysis 1.10. Comparison 1 RV1 versus placebo, Outcome 10 Serious adverse events: Kawasaki disease.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 10 Serious adverse events: Kawasaki disease

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Phua 2005-SGP	2/1811	0/653		37.0 %	1.80 [0.09, 37.54]
RV1 Phua 2009-AS	1/4272	0/4226		25.3 %	2.97 [0.12, 72.83]
RV1 Salinas 2005-LA	1/1618	0/537		37.8 %	1.00 [0.04, 24.44]
Total (95% CI)	**7701**	**5416**		**100.0 %**	**1.79 [0.30, 10.61]**
Total events: 4 (RV1), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.22, df = 2 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Not applicable					

Analysis 1.11. Comparison 1 RV1 versus placebo, Outcome 11 Serious adverse events requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 11 Serious adverse events requiring hospitalization

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Ruiz-Palac 06-LA/EU	886/31673	1003/31552		99.9 %	0.88 [0.81, 0.96]
RV1 Steele 2008-ZAF	1/300	0/150		0.1 %	1.50 [0.06, 36.72]
Total (95% CI)	**31973**	**31702**		**100.0 %**	**0.88 [0.81, 0.96]**

Total events: 887 (RV1), 1003 (Placebo)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 2.81 (P = 0.0050)

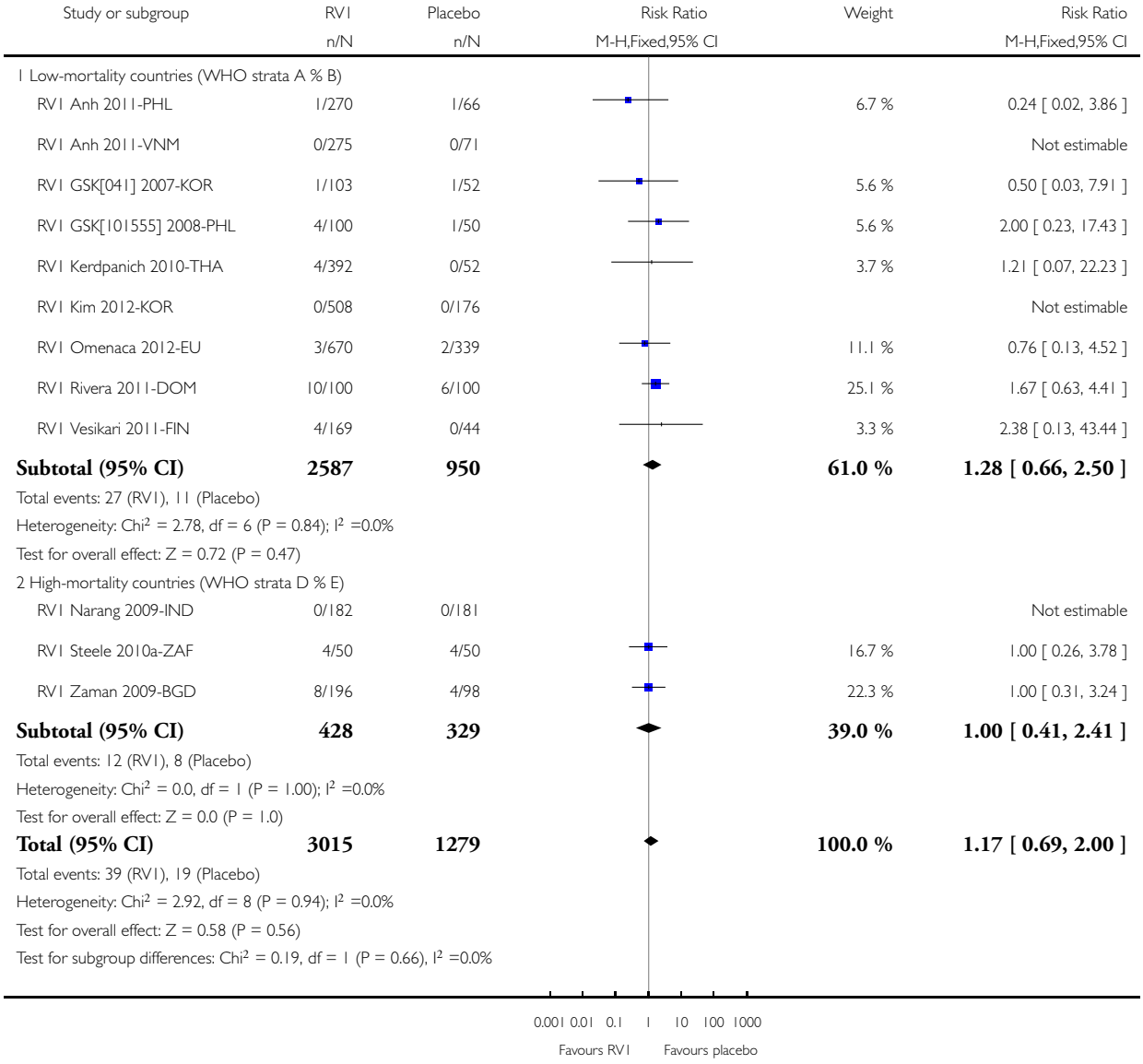
Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 RV1 versus placebo, Outcome 12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up)



Analysis 1.13. Comparison 1 RV1 versus placebo, Outcome 13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Bernstein 1999-USA	2/108	18/107		4.8 %	0.11 [0.03, 0.46]
RV1 Li 2014-CHN	27/1575	90/1573		13.5 %	0.30 [0.20, 0.46]
RV1 Salinas 2005-LA	58/1392	51/454		14.1 %	0.37 [0.26, 0.53]
RV1 Vesikari 2007a-EU	24/2572	94/1302		13.3 %	0.13 [0.08, 0.20]
Subtotal (95% CI)	**5647**	**3436**		**45.7 %**	**0.22 [0.13, 0.40]**
Total events: 111 (RV1), 253 (Placebo)					
Heterogeneity: Tau^2 = 0.25; Chi^2 = 15.34, df = 3 (P = 0.002); I^2 =80%					
Test for overall effect: Z = 5.03 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Colgate 2016-BGD	67/350	114/350		15.1 %	0.59 [0.45, 0.76]
RV1 Madhi 2010-MWI (1)	109/1182	85/591		15.0 %	0.64 [0.49, 0.84]
RV1 Madhi 2010-ZAF (2)	91/2116	128/1050		15.1 %	0.35 [0.27, 0.46]
RV1 Steele 2010b-ZAF	13/379	9/96		9.2 %	0.37 [0.16, 0.83]
Subtotal (95% CI)	**4027**	**2087**		**54.3 %**	**0.49 [0.35, 0.68]**
Total events: 280 (RV1), 336 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 12.38, df = 3 (P = 0.01); I^2 =76%					
Test for overall effect: Z = 4.20 (P = 0.000026)					
Total (95% CI)	**9674**	**5523**		**100.0 %**	**0.34 [0.23, 0.50]**
Total events: 391 (RV1), 589 (Placebo)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 52.06, df = 7 (P<0.00001); I^2 =87%					
Test for overall effect: Z = 5.62 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 5.25, df = 1 (P = 0.02), I^2 =81%					

(1) Data taken from main paper Supplementary Appendix, Table 5 - total vaccinated cohort in Malawi

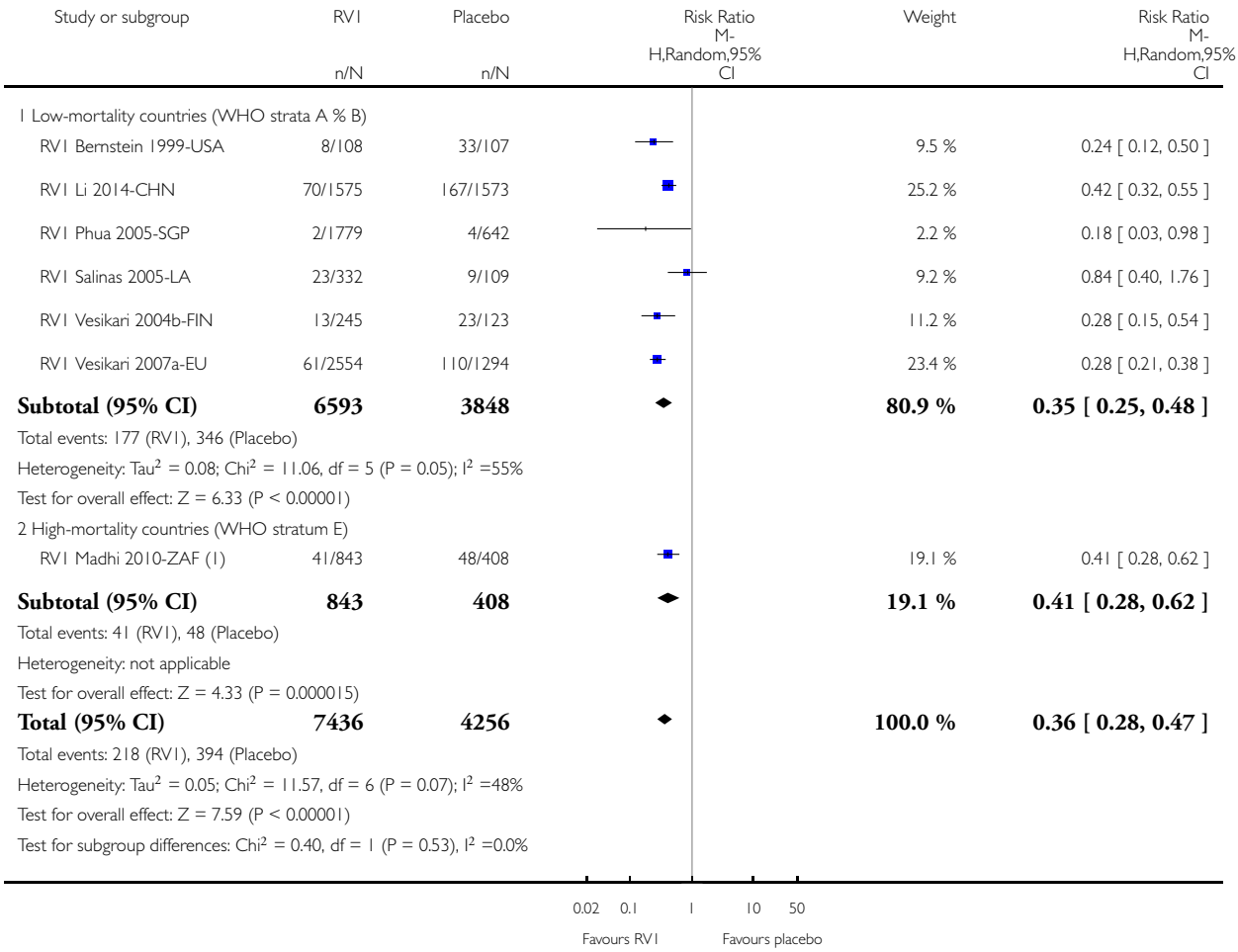
(2) Data taken from main paper Supplementary Appendix, Table 5 - total vaccinated cohort in South Africa

Analysis 1.14. Comparison 1 RV1 versus placebo, Outcome 14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)



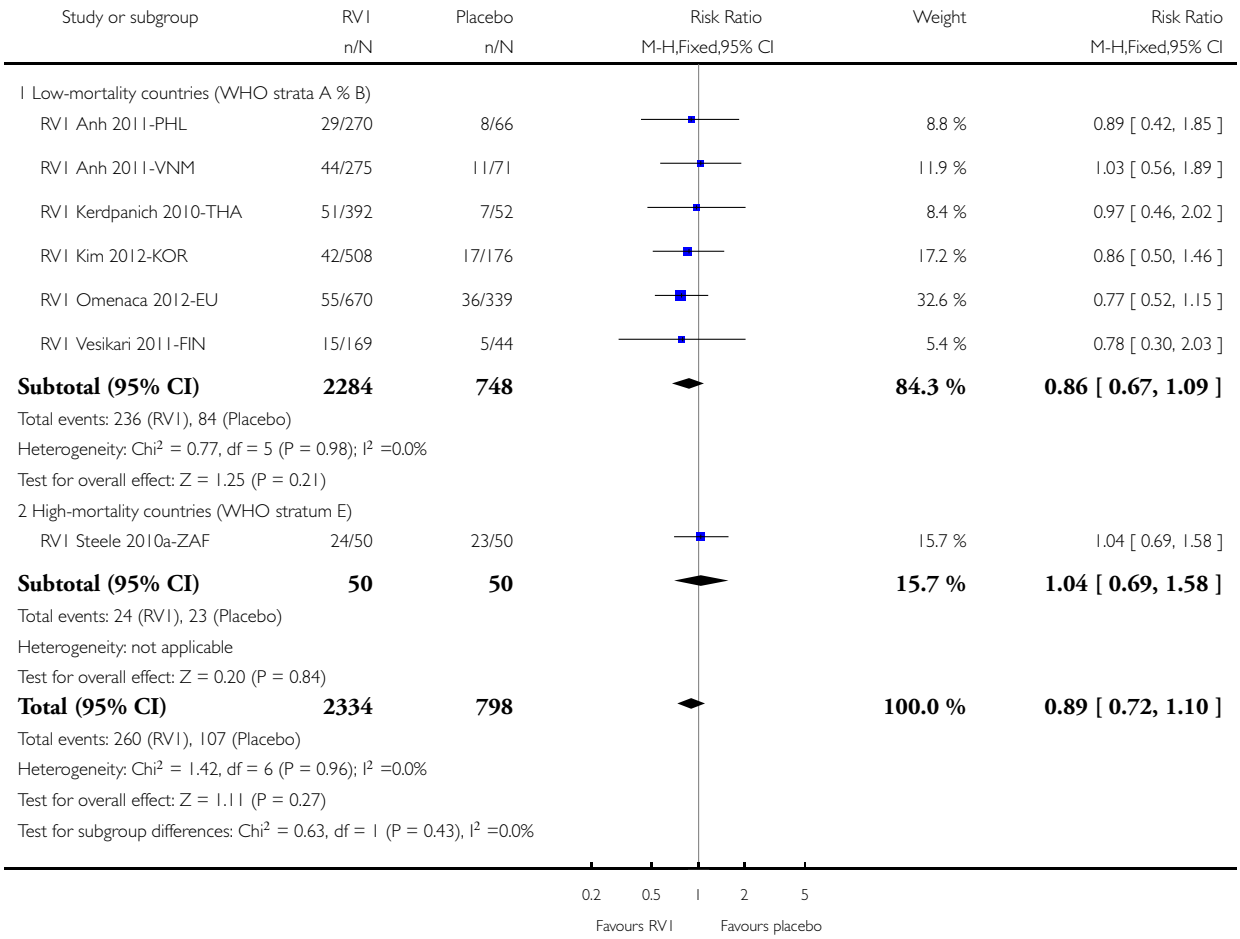
(1) Data from South Africa cohort only

Analysis 1.15. Comparison 1 RV1 versus placebo, Outcome 15 All-cause diarrhoea: all cases (up to 2 months follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 15 All-cause diarrhoea: all cases (up to 2 months follow-up)



Analysis 1.16. Comparison 1 RV1 versus placebo, Outcome 16 All-cause diarrhoea: all cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 16 All-cause diarrhoea: all cases (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Rivera 2011-DOM	32/100	31/100		8.8 %	1.03 [0.69, 1.55]
RV1 Salinas 2005-LA	573/1498	214/506		91.2 %	0.90 [0.80, 1.02]
Subtotal (95% CI)	**1598**	**606**		**100.0 %**	**0.92 [0.82, 1.03]**
Total events: 605 (RV1), 245 (Placebo)					
Heterogeneity: Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.49 (P = 0.14)					
2 High-mortality countries (WHO strata D % E)					
RV1 Colgate 2016-BGD (1)	298/350	302/350		100.0 %	0.99 [0.93, 1.05]
Subtotal (95% CI)	**350**	**350**		**100.0 %**	**0.99 [0.93, 1.05]**
Total events: 298 (RV1), 302 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					

(1) no intervention control group

Analysis 1.17. Comparison 1 RV1 versus placebo, Outcome 17 All-cause diarrhoea: all cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 17 All-cause diarrhoea: all cases (up to 2 years follow-up)

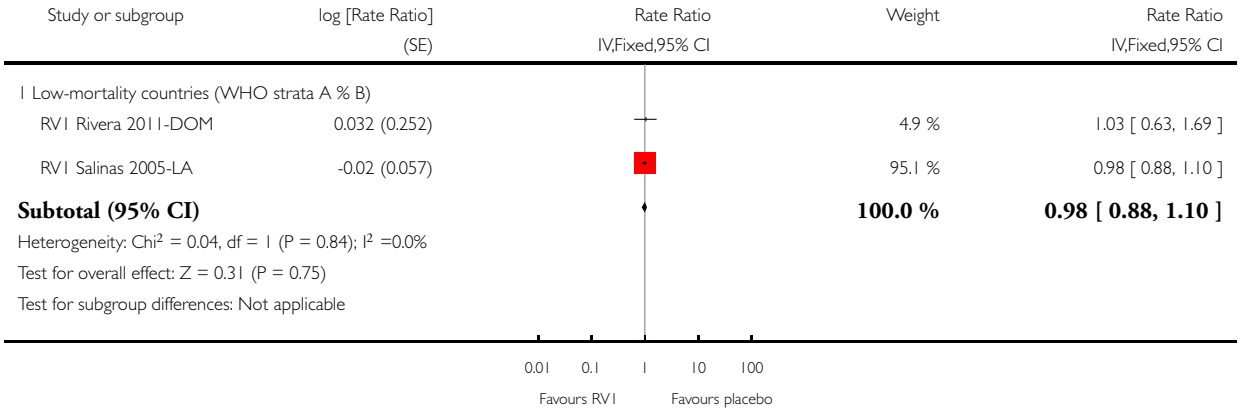
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Li 2014-CHN	728/1575	759/1573		82.5 %	0.96 [0.89, 1.03]
RV1 Phua 2005-SGP	231/1779	100/642		16.0 %	0.83 [0.67, 1.04]
RV1 Vesikari 2004b-FIN	12/245	11/123		1.6 %	0.55 [0.25, 1.21]
Subtotal (95% CI)	**3599**	**2338**		**100.0 %**	**0.93 [0.87, 1.00]**
Total events: 971 (RV1), 870 (Placebo)					
Heterogeneity: Chi^2 = 3.30, df = 2 (P = 0.19); I^2 =39%					
Test for overall effect: Z = 1.97 (P = 0.049)					

Analysis 1.18. Comparison 1 RV1 versus placebo, Outcome 18 All-cause diarrhoea: all episodes (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 18 All-cause diarrhoea: all episodes (up to 1 year follow-up)

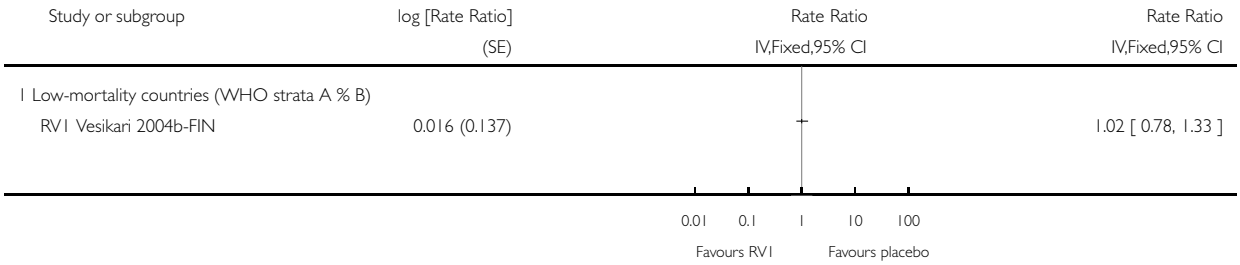


Analysis 1.19. Comparison 1 RV1 versus placebo, Outcome 19 All-cause diarrhoea: all episodes (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 19 All-cause diarrhoea: all episodes (up to 2 years follow-up)

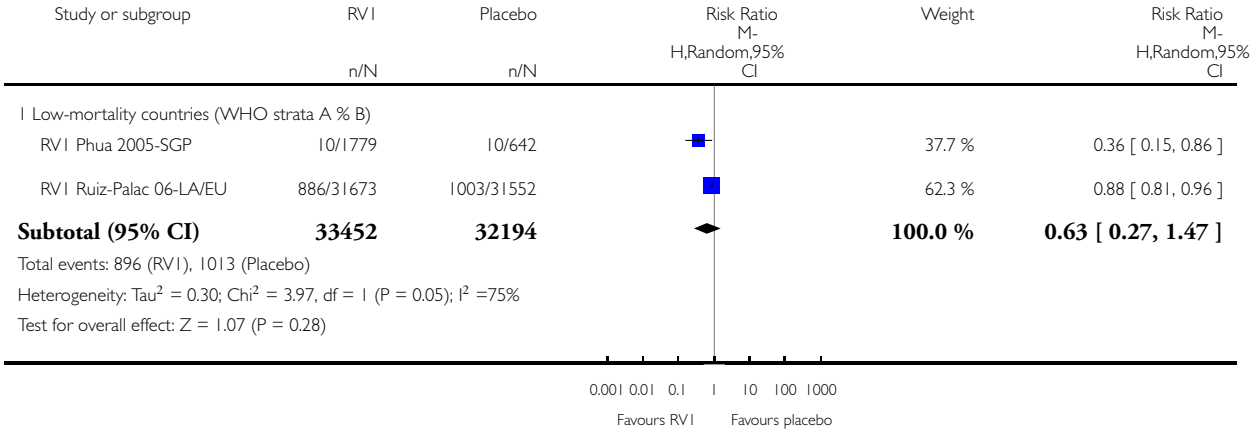


Analysis 1.20. Comparison 1 RV1 versus placebo, Outcome 20 All-cause hospitalizations (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 20 All-cause hospitalizations (up to 2 years follow-up)

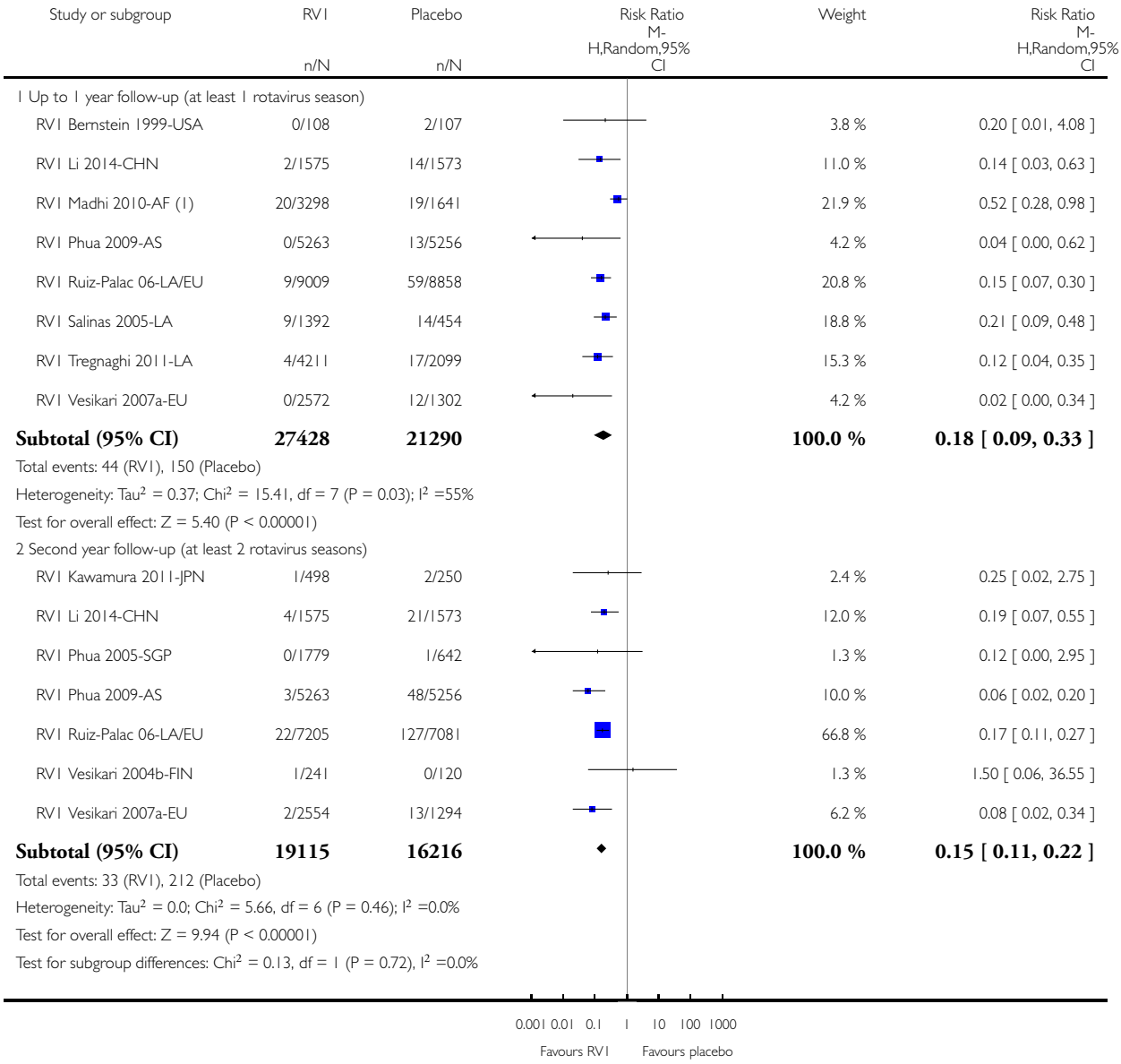


Analysis 1.21. Comparison 1 RV1 versus placebo, Outcome 21 Rotavirus diarrhoea: requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 21 Rotavirus diarrhoea: requiring hospitalization



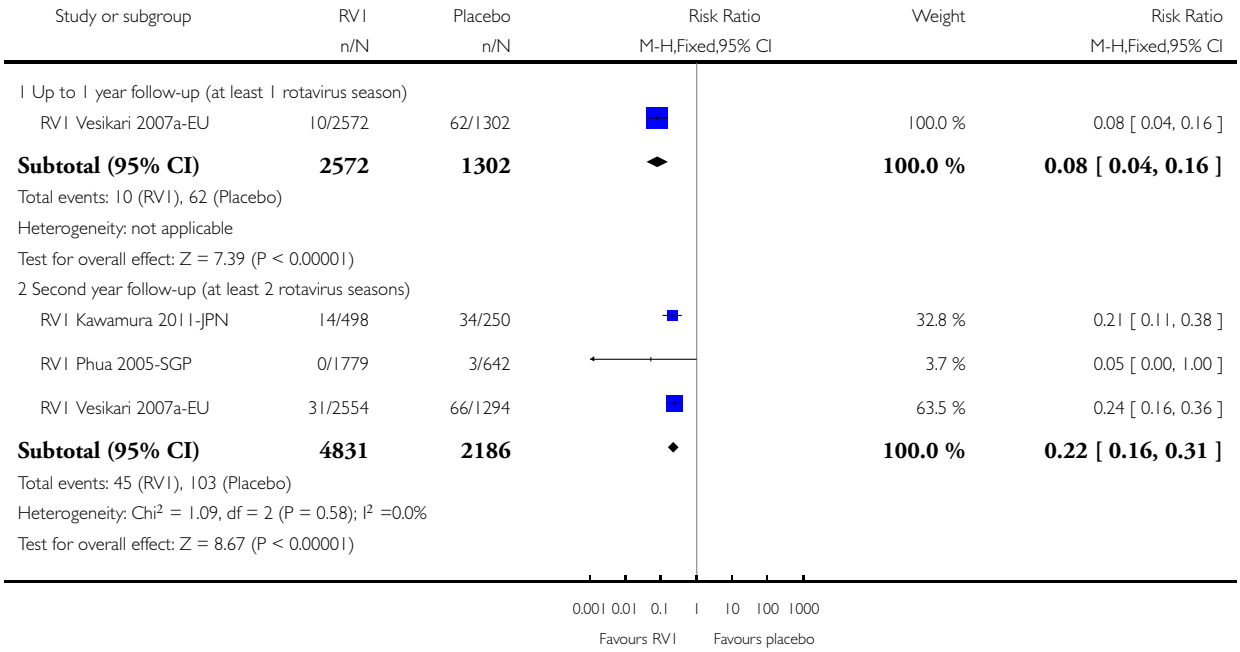
(1) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort.

Analysis 1.22. Comparison 1 RV1 versus placebo, Outcome 22 Rotavirus diarrhoea: requiring medical attention.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 22 Rotavirus diarrhoea: requiring medical attention

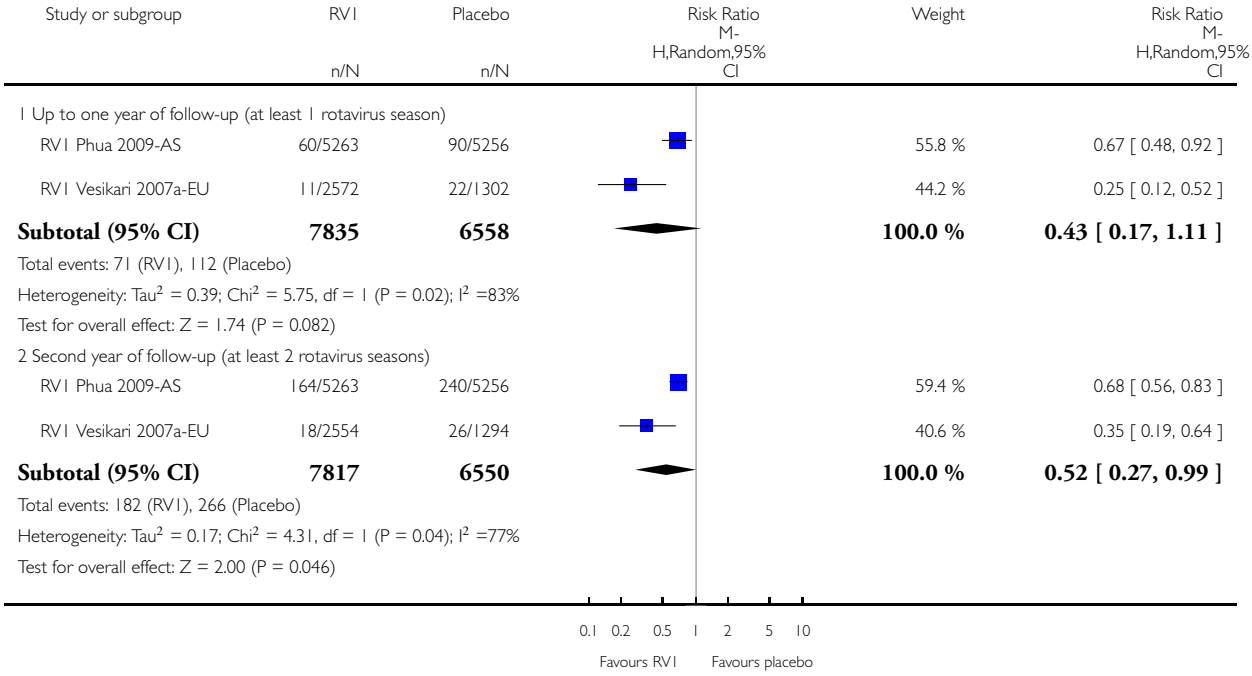


Analysis 1.23. Comparison 1 RV1 versus placebo, Outcome 23 All-cause diarrhoea: cases requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 23 All-cause diarrhoea: cases requiring hospitalization

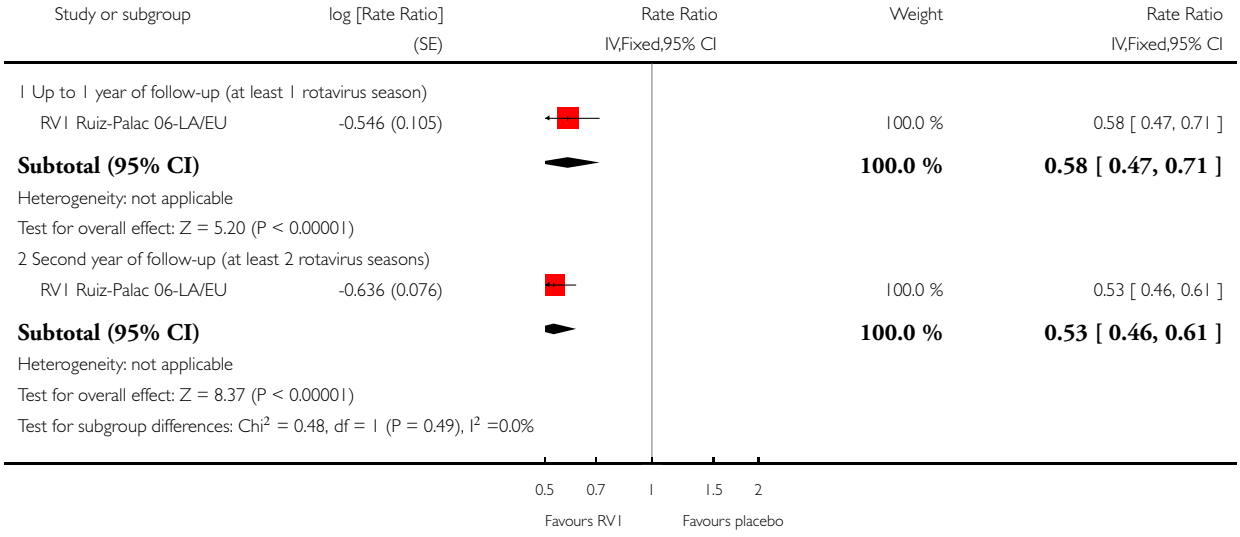


Analysis 1.24. Comparison 1 RV1 versus placebo, Outcome 24 All-cause diarrhoea: episodes requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 24 All-cause diarrhoea: episodes requiring hospitalization



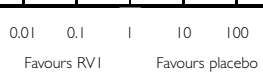
Analysis 1.25. Comparison 1 RV1 versus placebo, Outcome 25 Reactogenicity: fever.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 25 Reactogenicity: fever

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	239/300	54/75		11.9 %	1.11 [0.95, 1.29]
RV1 Anh 2011-VNM	182/297	44/78		9.1 %	1.09 [0.88, 1.35]
RV1 Bernstein 1998-USA	3/21	6/20		0.6 %	0.48 [0.14, 1.65]
RV1 Bernstein 1999-USA	21/108	5/107		1.0 %	4.16 [1.63, 10.63]
RV1 Dennehy 2005-NA	83/421	21/108		3.8 %	1.01 [0.66, 1.56]
RV1 GSK[021] 2007-PAN	91/177	18/51		4.3 %	1.46 [0.98, 2.17]
RV1 GSK[033] 2007-LA	98/730	15/124		2.9 %	1.11 [0.67, 1.85]
RV1 GSK[041] 2007-KOR	10/100	3/52		0.6 %	1.73 [0.50, 6.03]
RV1 GSK[101555] 2008-PHL	39/100	11/50		2.3 %	1.77 [1.00, 3.16]
RV1 Kawamura 2011-JPN	38/508	12/257		2.0 %	1.60 [0.85, 3.01]
RV1 Kerdpanich 2010-THA	68/348	6/52		1.4 %	1.69 [0.77, 3.70]
RV1 Kim 2012-KOR	43/508	13/176		2.2 %	1.15 [0.63, 2.08]
RV1 Li 2013b-CHN	1/25	0/25		0.1 %	3.00 [0.13, 70.30]
RV1 Li 2014-CHN	41/1513	66/1514		4.5 %	0.62 [0.42, 0.91]
RV1 Narang 2009-IND	14/182	6/181		1.0 %	2.32 [0.91, 5.90]
RV1 NCT00158756-RUS	43/78	13/25		3.8 %	1.06 [0.69, 1.62]
RV1 Phua 2005-SGP	497/1811	183/653		12.3 %	0.98 [0.85, 1.13]
RV1 Salinas 2005-LA	1002/1618	346/537		15.5 %	0.96 [0.89, 1.03]
RV1 Steele 2008-ZAF	37/297	21/150		3.0 %	0.89 [0.54, 1.46]
RV1 Steele 2010b-ZAF	62/189	30/96		4.9 %	1.05 [0.73, 1.50]
RV1 Vesikari 2004a-FIN	8/122	3/62		0.5 %	1.36 [0.37, 4.93]
RV1 Vesikari 2004b-FIN	32/265	14/133		2.2 %	1.15 [0.63, 2.07]
RV1 Vesikari 2007a-EU	166/914	91/490		8.5 %	0.98 [0.78, 1.23]
RV1 Vesikari 2011-FIN	9/200	1/50		0.2 %	2.25 [0.29, 17.35]



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Zaman 2009-BGD	16/196	12/98		1.6 %	0.67 [0.33, 1.35]
Subtotal (95% CI)	**11028**	**5164**		**100.0 %**	**1.06 [0.97, 1.17]**
Total events: 2843 (RV1), 994 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 38.19, df = 24 (P = 0.03); I^2 =37%					
Test for overall effect: Z = 1.30 (P = 0.20)					
2 After dose 2					
RV1 Anh 2011-PHL	197/296	45/75		9.8 %	1.11 [0.91, 1.36]
RV1 Anh 2011-VNM	141/286	36/73		6.5 %	1.00 [0.77, 1.30]
RV1 Bernstein 1998-USA	4/21	5/20		0.4 %	0.76 [0.24, 2.44]
RV1 Dennehy 2005-NA	82/394	31/101		3.9 %	0.68 [0.48, 0.96]
RV1 GSK[021] 2007-PAN	57/168	13/47		1.9 %	1.23 [0.74, 2.04]
RV1 GSK[033] 2007-LA	129/683	28/112		3.8 %	0.76 [0.53, 1.08]
RV1 GSK[041] 2007-KOR	8/99	6/52		0.5 %	0.70 [0.26, 1.91]
RV1 GSK[101555] 2008-PHL	29/98	22/50		2.6 %	0.67 [0.43, 1.04]
RV1 Kawamura 2011-JPN	33/499	12/250		1.2 %	1.38 [0.72, 2.62]
RV1 Kerdpanich 2010-THA	69/342	12/52		1.7 %	0.87 [0.51, 1.50]
RV1 Kim 2012-KOR	33/508	8/176		0.9 %	1.43 [0.67, 3.03]
RV1 Li 2013b-CHN	0/23	3/22		0.1 %	0.14 [0.01, 2.51]
RV1 Li 2014-CHN	46/1449	42/1446		2.9 %	1.09 [0.72, 1.65]
RV1 Narang 2009-IND	18/175	12/173		1.0 %	1.48 [0.74, 2.98]
RV1 NCT00158756-RUS	22/76	10/25		1.4 %	0.72 [0.40, 1.31]
RV1 Phua 2005-SGP	536/1779	186/642		16.2 %	1.04 [0.90, 1.20]
RV1 Salinas 2005-LA	826/1534	288/522		25.1 %	0.98 [0.89, 1.07]
RV1 Steele 2008-ZAF	34/282	12/143		1.3 %	1.44 [0.77, 2.69]
RV1 Steele 2010b-ZAF	91/369	13/90		1.8 %	1.71 [1.00, 2.91]
RV1 Vesikari 2004a-FIN	5/111	4/60		0.3 %	0.68 [0.19, 2.42]
RV1 Vesikari 2004b-FIN	69/255	31/124		3.6 %	1.08 [0.75, 1.56]
RV1 Vesikari 2007a-EU	244/905	142/486		12.1 %	0.92 [0.77, 1.10]
RV1 Vesikari 2011-FIN	10/196	3/49		0.3 %	0.83 [0.24, 2.91]
RV1 Zaman 2009-BGD	14/195	6/97		0.6 %	1.16 [0.46, 2.93]
Subtotal (95% CI)	**10743**	**4887**		**100.0 %**	**0.99 [0.92, 1.06]**
Total events: 2697 (RV1), 970 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 26.11, df = 23 (P = 0.30); I^2 =12%					

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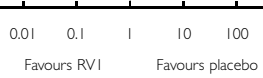
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.33 (P = 0.74)					
3 After dose 3					
RV1 Anh 2011-PHL	182/293	48/75		50.0 %	0.97 [0.80, 1.18]
RV1 Anh 2011-VNM	146/283	40/73		32.8 %	0.94 [0.74, 1.19]
RV1 GSK[021] 2007-PAN	63/168	18/46		10.9 %	0.96 [0.64, 1.44]
RV1 Steele 2010b-ZAF	76/364	13/88		6.3 %	1.41 [0.82, 2.43]
Subtotal (95% CI)	**1108**	**282**		**100.0 %**	**0.98 [0.86, 1.13]**
Total events: 467 (RV1), 119 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.03, df = 3 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.25 (P = 0.80)					
4 End of follow-up					
RV1 Dennehy 2005-NA	136/421	38/108		2.2 %	0.92 [0.69, 1.23]
RV1 GSK[033] 2007-LA	199/730	33/124		1.9 %	1.02 [0.75, 1.40]
RV1 GSK[041] 2007-KOR	17/100	8/52		0.3 %	1.11 [0.51, 2.39]
RV1 GSK[101555] 2008-PHL	47/100	24/50		1.5 %	0.98 [0.69, 1.40]
RV1 Kawamura 2011-JPN	62/508	22/257		0.9 %	1.43 [0.90, 2.26]
RV1 Kerdpanich 2010-THA	114/348	16/52		1.0 %	1.06 [0.69, 1.64]
RV1 Li 2014-CHN	83/1513	104/1514		2.4 %	0.80 [0.60, 1.06]
RV1 Narang 2009-IND	29/182	18/181		0.6 %	1.60 [0.92, 2.78]
RV1 Omenaca 2012-EU	54/203	29/100		1.3 %	0.92 [0.63, 1.34]
RV1 Rivera 2011-DOM	32/100	32/100		1.2 %	1.00 [0.67, 1.50]
RV1 Salinas 2005-LA	1238/1618	425/537		72.4 %	0.97 [0.92, 1.02]
RV1 Steele 2008-ZAF	64/297	28/150		1.2 %	1.15 [0.78, 1.72]
RV1 Steele 2010a-ZAF	30/50	28/50		1.7 %	1.07 [0.77, 1.50]
RV1 Vesikari 2004a-FIN	8/122	6/62		0.2 %	0.68 [0.25, 1.87]
RV1 Vesikari 2004b-FIN	86/265	33/133		1.6 %	1.31 [0.93, 1.84]
RV1 Vesikari 2007a-EU	310/914	192/490		9.3 %	0.87 [0.75, 1.00]
RV1 Vesikari 2011-FIN	18/200	4/50		0.2 %	1.13 [0.40, 3.18]
RV1 Zaman 2009-BGD	10/196	3/49		0.1 %	0.83 [0.24, 2.91]
Subtotal (95% CI)	**7867**	**4059**		**100.0 %**	**0.97 [0.93, 1.01]**
Total events: 2537 (RV1), 1043 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 15.47, df = 17 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 1.47 (P = 0.14)					



Analysis 1.26. Comparison 1 RV1 versus placebo, Outcome 26 Reactogenicity: diarrhoea.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 26 Reactogenicity: diarrhoea

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	9/300	6/75		2.0 %	0.38 [0.14, 1.02]
RV1 Anh 2011-VNM	21/297	5/78		2.2 %	1.10 [0.43, 2.83]
RV1 Bernstein 1998-USA	2/21	1/20		0.4 %	1.90 [0.19, 19.40]
RV1 Bernstein 1999-USA	18/108	9/107		3.5 %	1.98 [0.93, 4.21]
RV1 Dennehy 2005-NA	28/421	10/108		4.2 %	0.72 [0.36, 1.43]
RV1 GSK[021] 2007-PAN	33/177	2/51		1.0 %	4.75 [1.18, 19.14]
RV1 GSK[033] 2007-LA	42/730	5/124		2.4 %	1.43 [0.58, 3.54]
RV1 GSK[041] 2007-KOR	5/100	3/52		1.0 %	0.87 [0.22, 3.49]
RV1 GSK[101555] 2008-PHL	6/100	3/50		1.1 %	1.00 [0.26, 3.83]
RV1 Kawamura 2011-JPN	26/508	8/257		3.3 %	1.64 [0.76, 3.58]
RV1 Kerdpanich 2010-THA	7/348	1/52		0.5 %	1.05 [0.13, 8.33]
RV1 Kim 2012-KOR	16/508	6/176		2.3 %	0.92 [0.37, 2.32]
RV1 Li 2013b-CHN	4/25	2/25		0.8 %	2.00 [0.40, 9.95]
RV1 Li 2014-CHN	80/1513	87/1514		22.8 %	0.92 [0.68, 1.24]
RV1 Narang 2009-IND	11/182	8/181		2.5 %	1.37 [0.56, 3.32]
RV1 NCT00158756-RUS	6/78	0/25		0.2 %	4.28 [0.25, 73.38]
RV1 Phua 2005-SGP	31/1811	13/653		4.8 %	0.86 [0.45, 1.63]
RV1 Salinas 2005-LA	111/1618	45/537		18.0 %	0.82 [0.59, 1.14]
RV1 Steele 2008-ZAF	29/297	14/150		5.4 %	1.05 [0.57, 1.92]
RV1 Steele 2010b-ZAF	19/189	11/96		4.0 %	0.88 [0.44, 1.77]
RV1 Vesikari 2004a-FIN	11/122	5/62		1.9 %	1.12 [0.41, 3.08]
RV1 Vesikari 2004b-FIN	20/265	7/133		2.8 %	1.43 [0.62, 3.31]
RV1 Vesikari 2007a-EU	68/2613	29/1331		10.7 %	1.19 [0.78, 1.84]

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Vesikari 2011-FIN	10/200	2/50		0.9 %	1.25 [0.28, 5.53]
RV1 Zaman 2009-BGD	5/196	4/98		1.2 %	0.63 [0.17, 2.28]
Subtotal (95% CI)	**12727**	**6005**		**100.0 %**	**1.01 [0.88, 1.17]**
Total events: 618 (RV1), 286 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 21.56, df = 24 (P = 0.61); I² =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
2 After dose 2					
RV1 Anh 2011-PHL	4/296	0/75		0.3 %	2.30 [0.13, 42.31]
RV1 Anh 2011-VNM	8/286	0/73		0.4 %	4.38 [0.26, 75.08]
RV1 Bernstein 1998-USA	2/21	1/20		0.5 %	1.90 [0.19, 19.40]
RV1 Dennehy 2005-NA	16/394	5/101		3.1 %	0.82 [0.31, 2.19]
RV1 GSK[021] 2007-PAN	21/168	9/47		5.9 %	0.65 [0.32, 1.33]
RV1 GSK[033] 2007-LA	35/683	6/112		4.2 %	0.96 [0.41, 2.22]
RV1 GSK[041] 2007-KOR	5/99	6/52		2.3 %	0.44 [0.14, 1.37]
RV1 GSK[101555] 2008-PHL	6/98	4/50		2.0 %	0.77 [0.23, 2.59]
RV1 Kawamura 2011-JPN	23/499	8/250		4.7 %	1.44 [0.65, 3.17]
RV1 Kerdpanich 2010-THA	15/342	1/52		0.7 %	2.28 [0.31, 16.90]
RV1 Kim 2012-KOR	6/508	1/176		0.7 %	2.08 [0.25, 17.15]
RV1 Li 2013b-CHN	4/23	4/22		1.9 %	0.96 [0.27, 3.36]
RV1 Li 2014-CHN	57/1449	45/1446		20.1 %	1.26 [0.86, 1.86]
RV1 Narang 2009-IND	5/175	8/173		2.5 %	0.62 [0.21, 1.85]
RV1 NCT00158756-RUS	1/76	0/25		0.3 %	1.01 [0.04, 24.11]
RV1 Phua 2005-SGP	36/1779	7/642		4.6 %	1.86 [0.83, 4.15]
RV1 Salinas 2005-LA	116/1534	46/522		27.7 %	0.86 [0.62, 1.19]
RV1 Steele 2008-ZAF	22/282	9/143		5.3 %	1.24 [0.59, 2.62]
RV1 Steele 2010b-ZAF	33/369	7/90		4.8 %	1.15 [0.53, 2.51]
RV1 Vesikari 2004a-FIN	3/111	2/60		1.0 %	0.81 [0.14, 4.72]
RV1 Vesikari 2004b-FIN	11/255	2/124		1.3 %	2.67 [0.60, 11.88]
RV1 Vesikari 2007a-EU	15/905	9/486		4.4 %	0.90 [0.39, 2.03]
RV1 Vesikari 2011-FIN	5/196	2/49		1.1 %	0.63 [0.12, 3.13]
RV1 Zaman 2009-BGD	0/195	1/97		0.3 %	0.17 [0.01, 4.05]
Subtotal (95% CI)	**10743**	**4887**		**100.0 %**	**1.02 [0.86, 1.21]**
Total events: 449 (RV1), 183 (Placebo)					

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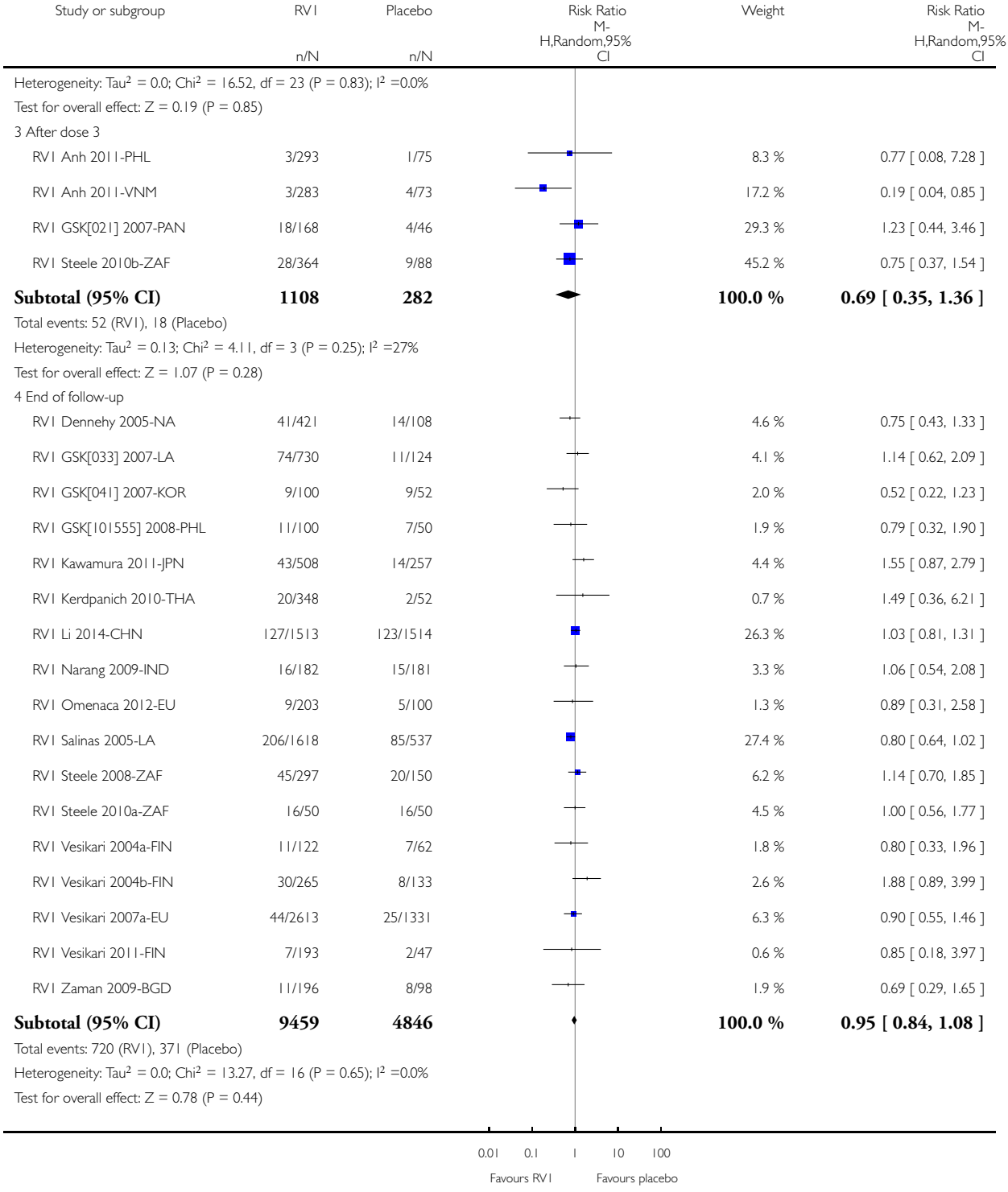

Analysis 1.27. Comparison 1 RV1 versus placebo, Outcome 27 Reactogenicity: vomiting.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 27 Reactogenicity: vomiting

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	56/300	5/75		0.9 %	2.80 [1.16, 6.74]
RV1 Anh 2011-VNM	39/297	6/78		1.1 %	1.71 [0.75, 3.89]
RV1 Bernstein 1998-USA	4/21	2/20		0.3 %	1.90 [0.39, 9.28]
RV1 Bernstein 1999-USA	16/108	10/107		1.3 %	1.59 [0.75, 3.33]
RV1 Dennehy 2005-NA	56/421	19/108		3.2 %	0.76 [0.47, 1.22]
RV1 GSK[021] 2007-PAN	36/177	10/51		1.8 %	1.04 [0.55, 1.94]
RV1 GSK[033] 2007-LA	115/730	22/124		4.2 %	0.89 [0.59, 1.34]
RV1 GSK[041] 2007-KOR	18/100	11/52		1.6 %	0.85 [0.43, 1.66]
RV1 GSK[101555] 2008-PHL	15/100	9/50		1.3 %	0.83 [0.39, 1.77]
RV1 Kawamura 2011-JPN	58/508	28/257		4.0 %	1.05 [0.68, 1.60]
RV1 Kerdpanich 2010-THA	103/348	13/52		2.9 %	1.18 [0.72, 1.95]
RV1 Kim 2012-KOR	78/508	30/176		4.9 %	0.90 [0.61, 1.32]
RV1 Li 2013b-CHN	2/25	1/25		0.1 %	2.00 [0.19, 20.67]
RV1 Li 2014-CHN	165/1513	176/1514		18.0 %	0.94 [0.77, 1.15]
RV1 Narang 2009-IND	24/182	24/181		2.6 %	0.99 [0.59, 1.68]
RV1 NCT00158756-RUS	9/78	1/25		0.2 %	2.88 [0.38, 21.66]
RV1 Phua 2005-SGP	102/1811	39/653		5.6 %	0.94 [0.66, 1.35]
RV1 Salinas 2005-LA	285/1618	89/537		15.3 %	1.06 [0.86, 1.32]
RV1 Steele 2008-ZAF	55/297	21/150		3.4 %	1.32 [0.83, 2.10]
RV1 Steele 2010b-ZAF	24/189	14/96		1.9 %	0.87 [0.47, 1.61]
RV1 Vesikari 2004a-FIN	20/122	14/62		1.9 %	0.73 [0.39, 1.34]
RV1 Vesikari 2004b-FIN	23/265	6/133		0.9 %	1.92 [0.80, 4.61]
RV1 Vesikari 2007a-EU	290/2613	141/1331		20.0 %	1.05 [0.87, 1.27]

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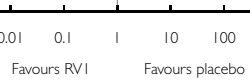
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Vesikari 2011-FIN	39/200	7/50		1.3 %	1.39 [0.66, 2.93]
RV1 Zaman 2009-BGD	22/196	8/98		1.2 %	1.38 [0.64, 2.98]
Subtotal (95% CI)	**12727**	**6005**		**100.0 %**	**1.03 [0.94, 1.12]**
Total events: 1654 (RV1), 706 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 20.22$, df = 24 (P = 0.68); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.65 (P = 0.52)					
2 After dose 2					
RV1 Anh 2011-PHL	32/296	5/75		2.0 %	1.62 [0.65, 4.02]
RV1 Anh 2011-VNM	27/286	7/73		2.5 %	0.98 [0.45, 2.17]
RV1 Bernstein 1998-USA	4/21	0/20		0.2 %	8.59 [0.49, 150.00]
RV1 Dennehy 2005-NA	30/394	15/101		4.3 %	0.51 [0.29, 0.92]
RV1 GSK[021] 2007-PAN	33/168	6/47		2.4 %	1.54 [0.69, 3.45]
RV1 GSK[033] 2007-LA	82/683	17/112		5.8 %	0.79 [0.49, 1.28]
RV1 GSK[041] 2007-KOR	21/99	10/52		3.3 %	1.10 [0.56, 2.16]
RV1 GSK[101555] 2008-PHL	8/98	1/50		0.4 %	4.08 [0.53, 31.73]
RV1 Kawamura 2011-JPN	32/499	14/250		4.0 %	1.15 [0.62, 2.11]
RV1 Kerdpanich 2010-THA	65/342	15/52		5.8 %	0.66 [0.41, 1.06]
RV1 Kim 2012-KOR	45/508	17/176		5.0 %	0.92 [0.54, 1.56]
RV1 Li 2013b-CHN	1/23	1/22		0.2 %	0.96 [0.06, 14.37]
RV1 Li 2014-CHN	91/1449	100/1446		12.1 %	0.91 [0.69, 1.19]
RV1 Narang 2009-IND	12/175	13/173		2.7 %	0.91 [0.43, 1.94]
RV1 NCT00158756-RUS	3/76	0/25		0.2 %	2.36 [0.13, 44.25]
RV1 Phua 2005-SGP	77/1779	26/642		6.8 %	1.07 [0.69, 1.65]
RV1 Salinas 2005-LA	189/1534	59/522		12.1 %	1.09 [0.83, 1.43]
RV1 Steele 2008-ZAF	47/282	14/143		4.5 %	1.70 [0.97, 2.99]
RV1 Steele 2010b-ZAF	60/369	17/90		5.7 %	0.86 [0.53, 1.40]
RV1 Vesikari 2004a-FIN	16/111	12/60		3.3 %	0.72 [0.37, 1.42]
RV1 Vesikari 2004b-FIN	16/255	11/124		2.8 %	0.71 [0.34, 1.48]
RV1 Vesikari 2007a-EU	53/905	46/486		8.2 %	0.62 [0.42, 0.90]
RV1 Vesikari 2011-FIN	31/196	6/49		2.4 %	1.29 [0.57, 2.92]
RV1 Zaman 2009-BGD	17/195	12/97		3.1 %	0.70 [0.35, 1.42]
Subtotal (95% CI)	**10743**	**4887**		**100.0 %**	**0.92 [0.81, 1.05]**
Total events: 992 (RV1), 424 (Placebo)					



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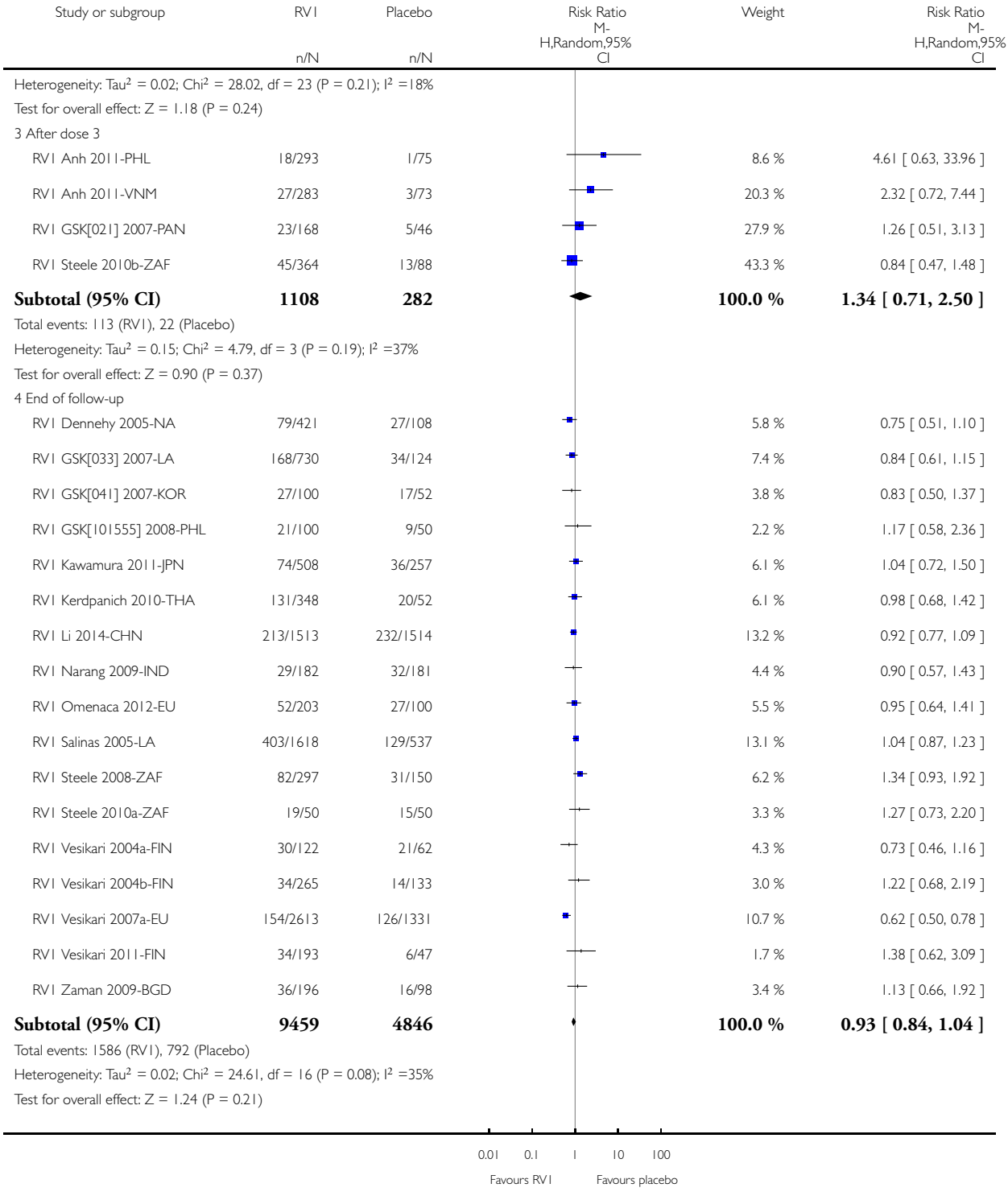


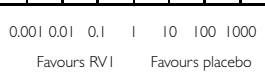
Analysis 1.28. Comparison 1 RV1 versus placebo, Outcome 28 Adverse events requiring discontinuation (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 28 Adverse events requiring discontinuation (end of follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Anh 2011-PHL	1/300	0/75		0.5 %	0.76 [0.03, 18.41]
RV1 Anh 2011-VNM	1/297	0/78		0.5 %	0.80 [0.03, 19.34]
RV1 Bernstein 1998-USA	1/21	0/20		0.3 %	2.86 [0.12, 66.44]
RV1 Dennehy 2005-NA	5/421	1/108		0.9 %	1.28 [0.15, 10.86]
RV1 GSK[021] 2007-PAN	0/177	1/51		1.3 %	0.10 [0.00, 2.35]
RV1 GSK[033] 2007-LA	4/730	0/122		0.5 %	1.51 [0.08, 27.95]
RV1 GSK[041] 2007-KOR	0/103	0/52			Not estimable
RV1 GSK[101555] 2008-PHL	0/100	0/50			Not estimable
RV1 Kawamura 2011-JPN	1/508	1/257		0.8 %	0.51 [0.03, 8.06]
RV1 Kerdpanich 2010-THA	0/348	0/52			Not estimable
RV1 Kim 2012-KOR	1/508	0/176		0.4 %	1.04 [0.04, 25.49]
RV1 Li 2013b-CHN	0/25	0/25			Not estimable
RV1 Li 2014-CHN	10/1666	15/1667		8.7 %	0.67 [0.30, 1.48]
RV1 Narang 2009-IND	1/182	0/181		0.3 %	2.98 [0.12, 72.76]
RV1 NCT00158756-RUS	2/161	0/48		0.4 %	1.51 [0.07, 30.97]
RV1 Phua 2009-AS	7/5263	12/5256		6.9 %	0.58 [0.23, 1.48]
RV1 Ruiz-Palac 06-LA/EU	118/31673	104/31552		60.2 %	1.13 [0.87, 1.47]
RV1 Steele 2008-ZAF	4/300	4/150		3.1 %	0.50 [0.13, 1.97]
RV1 Steele 2010a-ZAF	6/50	8/50		4.6 %	0.75 [0.28, 2.00]
RV1 Steele 2010b-ZAF	4/379	1/95		0.9 %	1.00 [0.11, 8.87]
RV1 Tregnaghi 2011-LA	12/4376	3/2192		2.3 %	2.00 [0.57, 7.09]
RV1 Vesikari 2004a-FIN	5/128	0/64		0.4 %	5.54 [0.31, 98.71]
RV1 Vesikari 2004b-FIN	6/270	2/135		1.5 %	1.50 [0.31, 7.33]



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Vesikari 2007a-EU	7/2646	6/1348		4.6 %	0.59 [0.20, 1.77]
RV1 Vesikari 2011-FIN	1/200	0/50		0.5 %	0.76 [0.03, 18.41]
RV1 Zaman 2009-BGD	1/196	0/98		0.4 %	1.51 [0.06, 36.67]
Total (95% CI)	**51028**	**43952**		**100.0 %**	**1.03 [0.83, 1.26]**
Total events: 198 (RV1), 158 (Placebo)					
Heterogeneity: Chi² = 11.59, df = 21 (P = 0.95); I² =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
Test for subgroup differences: Not applicable					

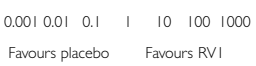
Analysis 1.29. Comparison 1 RV1 versus placebo, Outcome 29 Immunogenicity: rotavirus vaccine shedding (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 29 Immunogenicity: rotavirus vaccine shedding (end of follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Bernstein 1998-USA	17/20	0/20		4.7 %	35.00 [2.25, 544.92]
RV1 Bernstein 1999-USA	75/100	1/107		6.4 %	80.25 [11.37, 566.35]
RV1 Dennehy 2005-NA	184/328	2/78		7.9 %	21.88 [5.55, 86.22]
RV1 GSK[021] 2007-PAN	35/88	0/26		4.6 %	21.54 [1.37, 339.58]
RV1 GSK[033] 2007-LA	14/26	1/6		6.7 %	3.23 [0.52, 20.02]
RV1 GSK[101555] 2008-PHL	50/86	7/40		9.5 %	3.32 [1.66, 6.67]
RV1 Kerdpanich 2010-THA	198/337	1/51		6.4 %	29.96 [4.29, 209.08]
RV1 Li 2013b-CHN	2/15	1/17		5.6 %	2.27 [0.23, 22.56]
RV1 Salinas 2005-LA	44/267	1/93		6.3 %	15.33 [2.14, 109.68]



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Steele 2008-ZAF	19/76	0/39		4.6 %	20.26 [1.26, 326.90]
RV1 Steele 2010a-ZAF	15/23	7/22		9.5 %	2.05 [1.04, 4.05]
RV1 Steele 2010b-ZAF	41/109	0/23		4.6 %	18.11 [1.15, 284.20]
RV1 Vesikari 2004a-FIN	9/122	0/62		4.5 %	9.73 [0.58, 164.51]
RV1 Vesikari 2011-FIN	101/193	0/46		4.6 %	49.18 [3.11, 777.27]
RV1 Ward 2006-USA	74/75	0/36		4.6 %	72.54 [4.62, 1138.35]
RV1 Zaman 2009-BGD	45/71	7/36		9.5 %	3.26 [1.64, 6.49]
Total (95% CI)	**1936**	**702**		**100.0 %**	**10.94 [4.90, 24.43]**

Total events: 923 (RV1), 28 (Placebo)

Heterogeneity: $Tau^2 = 1.65$; $Chi^2 = 62.38$, df = 15 ($P<0.00001$); $I^2 = 76\%$

Test for overall effect: $Z = 5.84$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

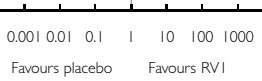
Analysis 1.30. Comparison 1 RV1 versus placebo, Outcome 30 Immunogenicity: seroconversion.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 30 Immunogenicity: seroconversion

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Bernstein 1998-USA	16/20	0/21		6.9 %	34.57 [2.21, 540.36]
RV1 GSK[021] 2007-PAN	59/140	2/38		14.3 %	8.01 [2.05, 31.29]
RV1 GSK[101555] 2008-PHL	34/77	4/39		17.3 %	4.31 [1.65, 11.26]
RV1 Phua 2005-SGP	357/442	3/155		16.1 %	41.73 [13.60, 128.09]
RV1 Salinas 2005-LA	157/405	1/139		10.5 %	53.88 [7.61, 381.29]
RV1 Steele 2008-ZAF	72/201	2/110		14.2 %	19.70 [4.93, 78.76]
RV1 Steele 2010b-ZAF	30/283	0/65		6.8 %	14.18 [0.88, 228.86]
RV1 Vesikari 2004a-FIN	85/122	0/62		6.9 %	87.59 [5.53, 1388.36]
RV1 Vesikari 2011-FIN	130/176	0/42		6.9 %	63.41 [4.02, 998.86]
Subtotal (95% CI)	**1866**	**671**		**100.0 %**	**20.39 [8.48, 49.01]**
Total events: 940 (RV1), 12 (Placebo)					
Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 18.72$, df = 8 (P = 0.02); $I^2 = 57\%$					
Test for overall effect: Z = 6.74 (P < 0.00001)					
2 After dose 2					
RV1 Bernstein 1998-USA	19/21	0/20		1.3 %	37.23 [2.40, 578.09]
RV1 Bernstein 1999-USA	98/107	0/106		1.3 %	195.18 [12.28, 3102.13]
RV1 Dennehy 2005-NA	197/271	4/63		4.3 %	11.45 [4.42, 29.64]
RV1 GSK[021] 2007-PAN	96/139	2/37		3.3 %	12.78 [3.30, 49.41]
RV1 GSK[033] 2007-LA	355/494	9/91		5.3 %	7.27 [3.90, 13.54]
RV1 GSK[041] 2007-KOR	32/48	1/24		2.2 %	16.00 [2.32, 110.13]
RV1 GSK[101555] 2008-PHL	60/76	6/39		4.9 %	5.13 [2.44, 10.81]
RV1 Kawamura 2011-JPN	29/34	1/20		2.2 %	17.06 [2.51, 115.83]
RV1 Kerdpanich 2010-THA	290/352	0/51		1.3 %	85.59 [5.42, 1350.73]
RV1 Kim 2012-KOR	280/318	5/114		4.6 %	20.08 [8.51, 47.35]
RV1 Li 2013b-CHN	18/20	2/21		3.4 %	9.45 [2.51, 35.60]
RV1 Li 2014-CHN	278/391	22/393		5.8 %	12.70 [8.42, 19.16]



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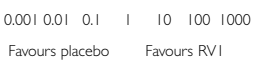
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Narang 2009-IND	67/115	7/112		5.0 %	9.32 [4.48, 19.42]
RV1 NCT00158756-RUS	83/115	0/34		1.3 %	50.39 [3.21, 791.58]
RV1 Omenaca 2012-EU	126/147	13/81		5.6 %	5.34 [3.23, 8.83]
RV1 Phua 2005-SGP	379/445	4/151		4.3 %	32.15 [12.22, 84.62]
RV1 Phua 2009-AS (1)	88/90	1/96		2.2 %	93.87 [13.36, 659.74]
RV1 Rivera 2011-DOM	50/80	17/80		5.7 %	2.94 [1.87, 4.63]
RV1 Ruiz-Palac 06-LA/EU	302/393	33/341		6.0 %	7.94 [5.72, 11.03]
RV1 Salinas 2005-LA	246/391	5/132		4.6 %	16.61 [7.01, 39.37]
RV1 Steele 2008-ZAF	86/182	5/106		4.6 %	10.02 [4.20, 23.89]
RV1 Tregnaghi 2011-LA	108/176	14/89		5.6 %	3.90 [2.38, 6.40]
RV1 Vesikari 2004a-FIN	106/122	0/62		1.3 %	109.10 [6.89, 1726.59]
RV1 Vesikari 2004b-FIN	168/209	0/112		1.3 %	181.34 [11.40, 2883.75]
RV1 Vesikari 2007a-EU	687/794	28/422		5.9 %	13.04 [9.11, 18.67]
RV1 Vesikari 2011-FIN	144/166	0/44		1.3 %	77.87 [4.94, 1226.73]
RV1 Zaman 2009-BGD	83/135	13/70		5.6 %	3.31 [1.99, 5.50]
Subtotal (95% CI)	**5831**	**2911**		**100.0 %**	**11.44 [8.01, 16.32]**
Total events: 4475 (RV1), 192 (Placebo)					
Heterogeneity: Tau^2 = 0.52; Chi^2 = 126.68, df = 26 (P<0.00001); I^2 =79%					
Test for overall effect: Z = 13.43 (P < 0.00001)					
3 After dose 3					
RV1 Anh 2011-PHL	155/240	3/52		19.0 %	11.19 [3.72, 33.71]
RV1 Anh 2011-VNM	178/247	10/65		31.2 %	4.68 [2.63, 8.33]
RV1 GSK[021] 2007-PAN	111/130	3/37		19.2 %	10.53 [3.55, 31.23]
RV1 Steele 2010a-ZAF	12/21	4/22		21.8 %	3.14 [1.20, 8.21]
RV1 Steele 2010b-ZAF	117/264	1/59		8.8 %	26.15 [3.73, 183.41]
Subtotal (95% CI)	**902**	**235**		**100.0 %**	**6.89 [3.59, 13.24]**
Total events: 573 (RV1), 21 (Placebo)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 8.24, df = 4 (P = 0.08); I^2 =51%					
Test for overall effect: Z = 5.79 (P < 0.00001)					



(1) Singapore and Hong Kong cohorts

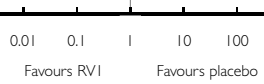
Analysis 1.31. Comparison 1 RV1 versus placebo, Outcome 31 Dropouts before the end of the trial.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 31 Dropouts before the end of the trial

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Anh 2011-PHL	8/300	1/75		0.1 %	2.00 [0.25, 15.75]
RV1 Anh 2011-VNM	16/297	5/78		0.3 %	0.84 [0.32, 2.22]
RV1 Colgate 2016-BGD	58/350	49/350		1.7 %	1.18 [0.83, 1.68]
RV1 GSK[021] 2007-PAN	19/177	6/51		0.3 %	0.91 [0.38, 2.16]
RV1 GSK[033] 2007-LA	47/730	12/124		0.7 %	0.67 [0.36, 1.22]
RV1 GSK[041] 2007-KOR	4/103	0/52		0.0 %	4.59 [0.25, 83.60]
RV1 GSK[101555] 2008-PHL	5/100	0/50		0.0 %	5.55 [0.31, 98.50]
RV1 Kawamura 2011-JPN	32/508	16/257		0.8 %	1.01 [0.57, 1.81]
RV1 Kerdpanich 2010-THA	9/348	0/52		0.0 %	2.89 [0.17, 48.85]
RV1 Kim 2012-KOR	5/508	0/76		0.0 %	1.66 [0.09, 29.80]
RV1 Li 2013b-CHN	2/25	3/25		0.1 %	0.67 [0.12, 3.65]
RV1 Li 2014-CHN	148/1666	168/1667		6.0 %	0.88 [0.71, 1.09]
RV1 Madhi 2010-AF	324/3298	198/1641		9.4 %	0.81 [0.69, 0.96]
RV1 Narang 2009-IND	9/182	10/181		0.4 %	0.90 [0.37, 2.15]
RV1 NCT00158756-RUS	13/161	1/48		0.1 %	3.88 [0.52, 28.88]
RV1 Omenaca 2012-EU	15/670	6/339		0.3 %	1.26 [0.50, 3.23]
RV1 Phua 2005-SGP	69/1811	25/653		1.3 %	1.00 [0.64, 1.56]
RV1 Rivera 2011-DOM	5/100	5/100		0.2 %	1.00 [0.30, 3.35]
RV1 Ruiz-Palac 06-LA/EU	1920/31673	1997/31552		71.2 %	0.96 [0.90, 1.02]
RV1 Steele 2008-ZAF	30/300	14/150		0.7 %	1.07 [0.59, 1.96]
RV1 Steele 2010a-ZAF	14/50	12/50		0.4 %	1.17 [0.60, 2.27]
RV1 Steele 2010b-ZAF	42/379	13/96		0.7 %	0.82 [0.46, 1.46]
RV1 Tregnaghi 2011-LA	142/4376	77/2192		3.7 %	0.92 [0.70, 1.21]
RV1 Vesikari 2004a-FIN	12/128	2/64		0.1 %	3.00 [0.69, 13.00]
RV1 Vesikari 2004b-FIN	21/270	12/135		0.6 %	0.88 [0.44, 1.72]
RV1 Vesikari 2007a-EU	33/2646	17/1348		0.8 %	0.99 [0.55, 1.77]



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Vesikari 2011-FIN	5/200	1/50		0.1 %	1.25 [0.15, 10.46]
RV1 Zaman 2009-BGD	3/196	1/98		0.0 %	1.50 [0.16, 14.23]
Total (95% CI)	**51552**	**41554**		**100.0 %**	**0.95 [0.90, 1.00]**
Total events: 3010 (RV1), 2651 (Placebo)					
Heterogeneity: Chi^2 = 16.56, df = 27 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 2.02 (P = 0.044)					
Test for subgroup differences: Not applicable					

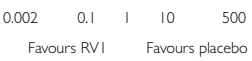
Analysis 1.32. Comparison 1 RV1 versus placebo, Outcome 32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV1 Kawamura 2011-JPN	5/498	19/250		16.7 %	0.13 [0.05, 0.35]
RV1 Li 2014-CHN	22/1575	46/1573		21.4 %	0.48 [0.29, 0.79]
RV1 Ruiz-Palac 06-LA/EU	3/9009	36/8858		14.6 %	0.08 [0.03, 0.27]
RV1 Salinas 2005-LA	25/1392	30/454		21.3 %	0.27 [0.16, 0.46]
RV1 Steele 2010a-ZAF	2/50	0/50		4.6 %	5.00 [0.25, 101.58]
RV1 Vesikari 2007a-EU	18/2572	89/1302		21.4 %	0.10 [0.06, 0.17]
Subtotal (95% CI)	**15096**	**12487**		**100.0 %**	**0.21 [0.10, 0.44]**
Total events: 75 (RV1), 220 (Placebo)					
Heterogeneity: Tau^2 = 0.57; Chi^2 = 26.82, df = 5 (P = 0.00006); I^2 =81%					
Test for overall effect: Z = 4.22 (P = 0.000025)					



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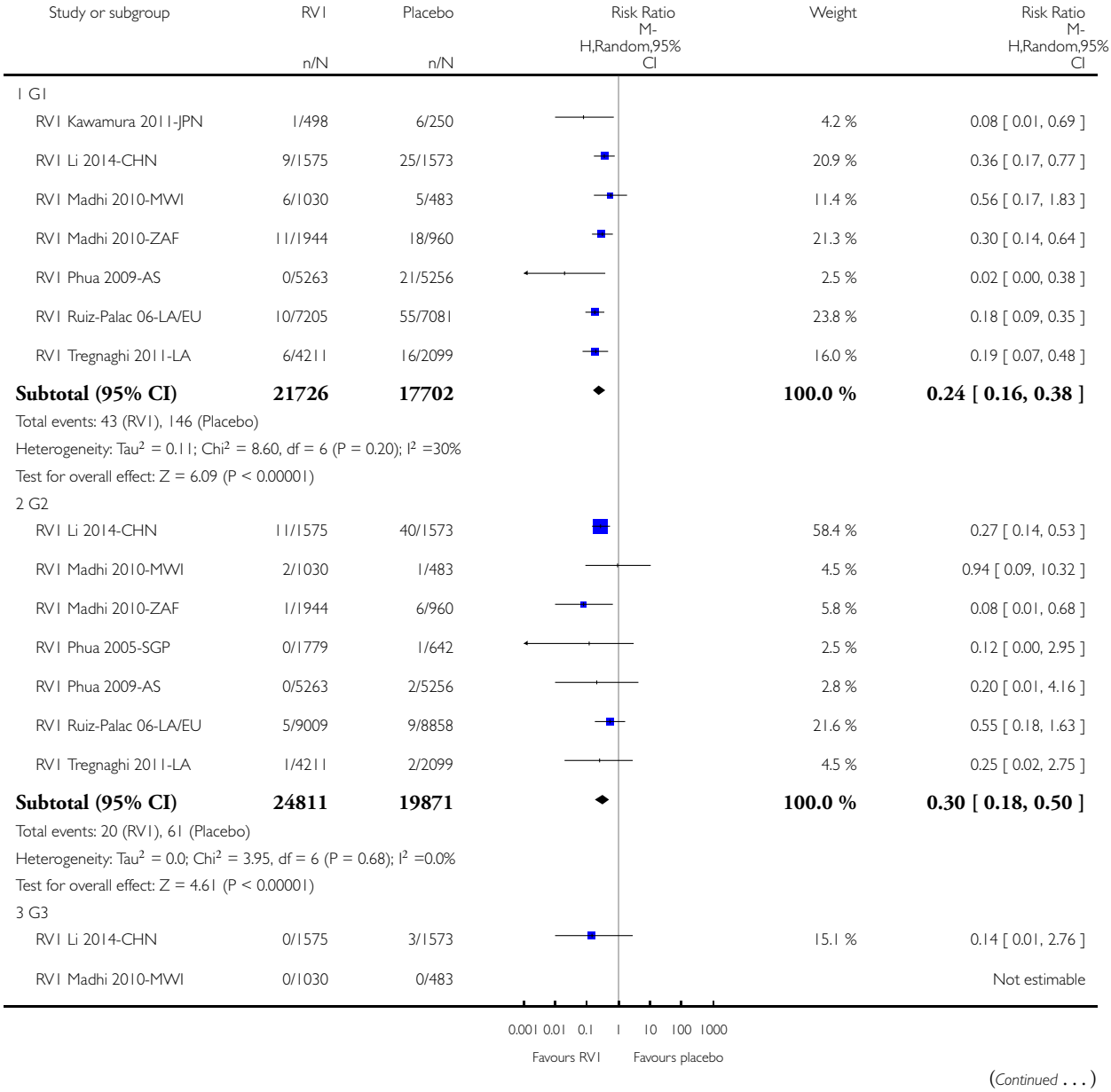
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 G2					
RV1 Li 2014-CHN	42/1575	102/1573		71.0 %	0.41 [0.29, 0.59]
RV1 Ruiz-Palac 06-LA/EU	6/9009	10/8858		8.6 %	0.59 [0.21, 1.62]
RV1 Salinas 2005-LA	1/1392	3/454		1.7 %	0.11 [0.01, 1.04]
RV1 Steele 2010a-ZAF	0/50	1/50		0.9 %	0.33 [0.01, 7.99]
RV1 Vesikari 2007a-EU	14/2572	17/1302		17.8 %	0.42 [0.21, 0.84]
Subtotal (95% CI)	**14598**	**12237**		**100.0 %**	**0.41 [0.31, 0.56]**
Total events: 63 (RV1), 133 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.83$, df = 4 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.81 (P < 0.00001)					
3 G3					
RV1 Li 2014-CHN	0/1575	11/1573		12.5 %	0.04 [0.00, 0.74]
RV1 Salinas 2005-LA	1/1392	2/454		17.4 %	0.16 [0.01, 1.79]
RV1 Steele 2010a-ZAF	0/50	1/50		9.9 %	0.33 [0.01, 7.99]
RV1 Vesikari 2007a-EU	3/2572	10/1302		60.2 %	0.15 [0.04, 0.55]
Subtotal (95% CI)	**5589**	**3379**		**100.0 %**	**0.14 [0.05, 0.39]**
Total events: 4 (RV1), 24 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.09$, df = 3 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.82 (P = 0.00013)					
4 G4					
RV1 Salinas 2005-LA	1/1392	0/454		10.5 %	0.98 [0.04, 24.01]
RV1 Vesikari 2007a-EU	6/2572	18/1302		89.5 %	0.17 [0.07, 0.42]
Subtotal (95% CI)	**3964**	**1756**		**100.0 %**	**0.20 [0.07, 0.59]**
Total events: 7 (RV1), 18 (Placebo)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 1.07$, df = 1 (P = 0.30); $I^2 = 7\%$					
Test for overall effect: Z = 2.95 (P = 0.0032)					
5 G9					
RV1 Li 2014-CHN	1/1575	5/1573		9.1 %	0.20 [0.02, 1.71]
RV1 Salinas 2005-LA	29/1392	15/454		40.8 %	0.63 [0.34, 1.17]
RV1 Vesikari 2007a-EU	38/2572	71/1302		50.1 %	0.27 [0.18, 0.40]
Subtotal (95% CI)	**5539**	**3329**		**100.0 %**	**0.37 [0.18, 0.75]**
Total events: 68 (RV1), 91 (Placebo)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 5.44$, df = 2 (P = 0.07); $I^2 = 63\%$					
Test for overall effect: Z = 2.76 (P = 0.0058)					
Test for subgroup differences: $Chi^2 = 7.26$, df = 4 (P = 0.12), $I^2 = 45\%$					

Analysis 1.33. Comparison 1 RV1 versus placebo, Outcome 33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)



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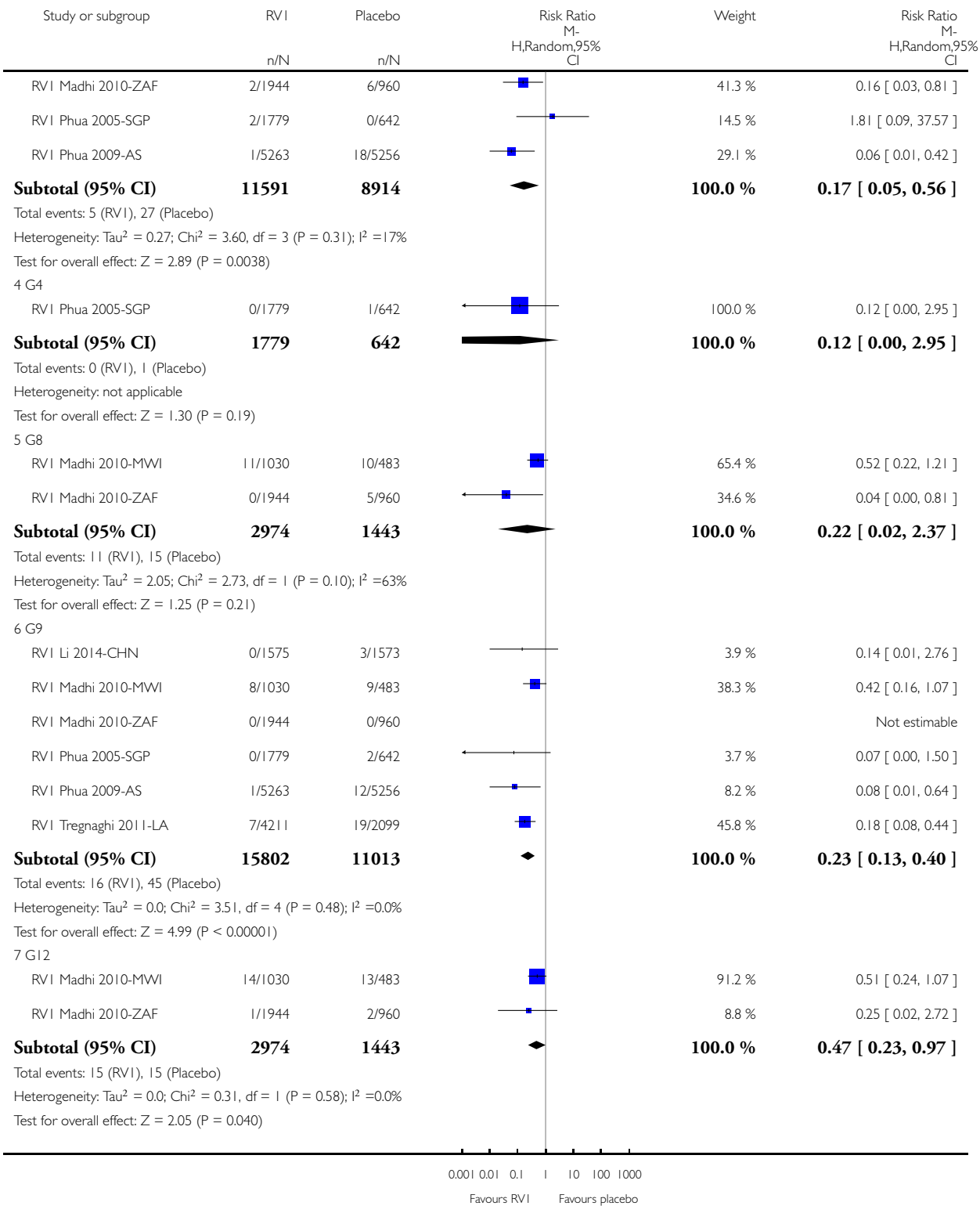


Analysis 1.34. Comparison 1 RV1 versus placebo, Outcome 34 Subgroup analysis: rotavirus diarrhoea in malnourished children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 34 Subgroup analysis: rotavirus diarrhoea in malnourished children

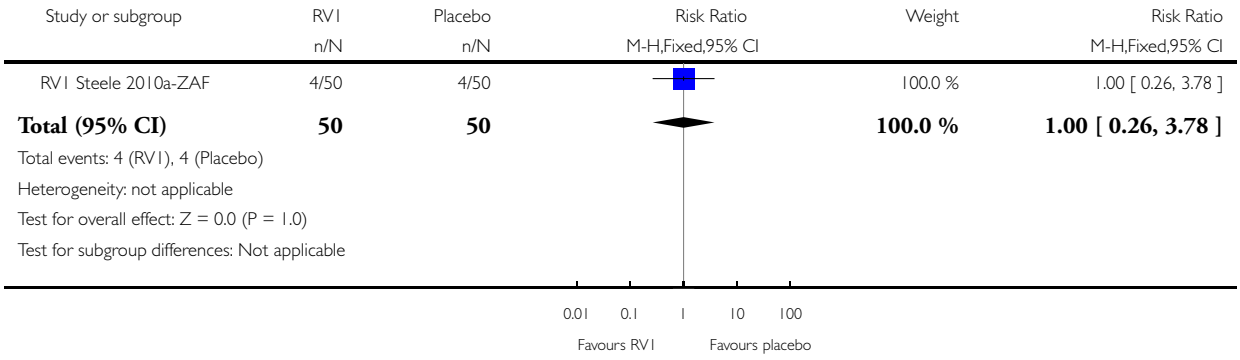
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year of follow-up (at least 1 rotavirus season)				
RV1 Salinas 2005-LA	14/211	13/76		0.39 [0.19, 0.79]

Analysis 1.35. Comparison 1 RV1 versus placebo, Outcome 35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children

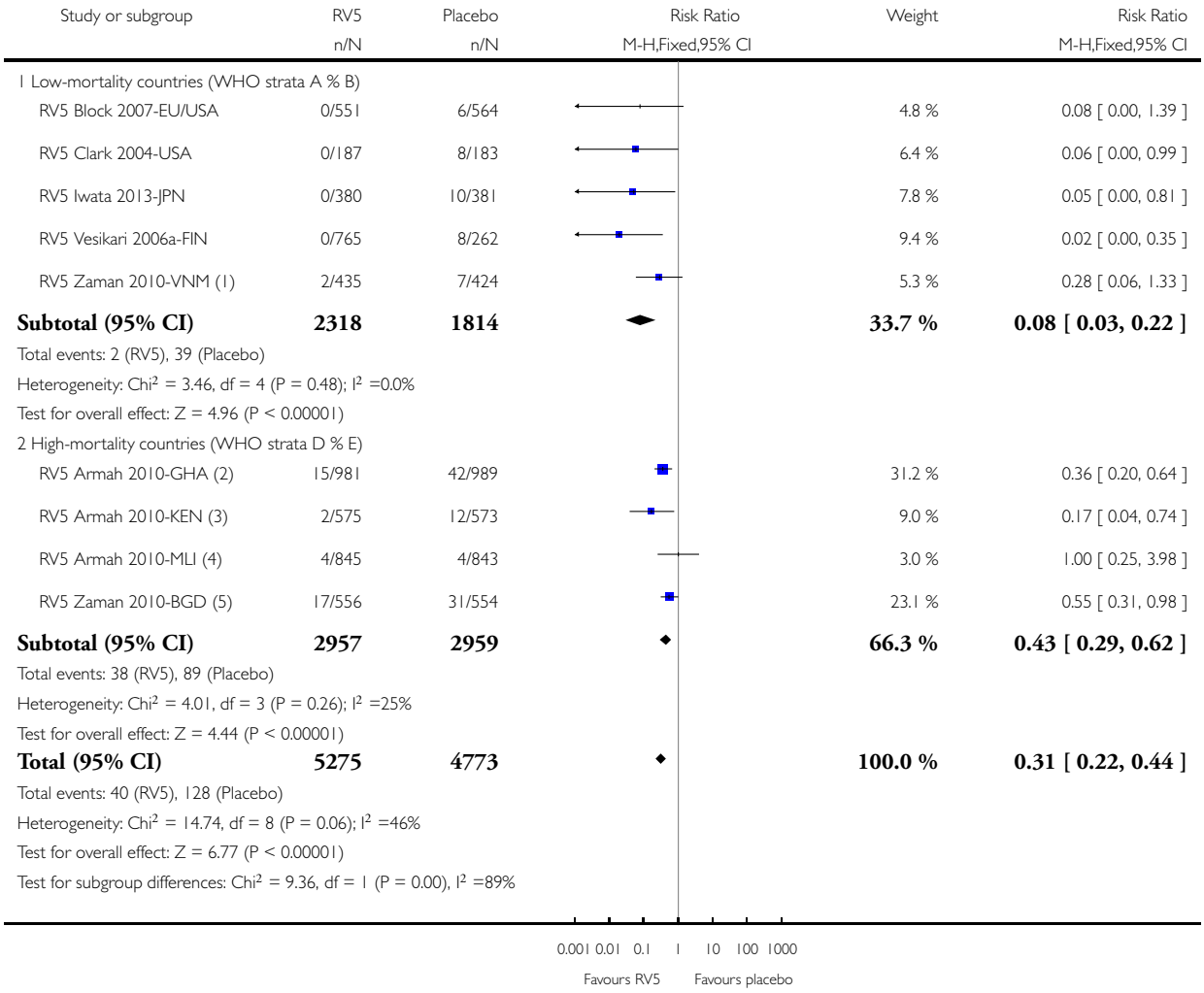


Analysis 2.1. Comparison 2 RV5 versus placebo, Outcome 1 Rotavirus diarrhoea: severe (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 1 Rotavirus diarrhoea: severe (up to 1 year follow-up)



(1) Data from RV5 Zaman 2010-AS for Vietnam only

(2) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.

(3) Total number of participants taken from Tapia et al. 2012, Table 4, data for Kenya only.

(4) Total number of participants taken from Tapia et al. 2012, Table 4, data for Mali only.

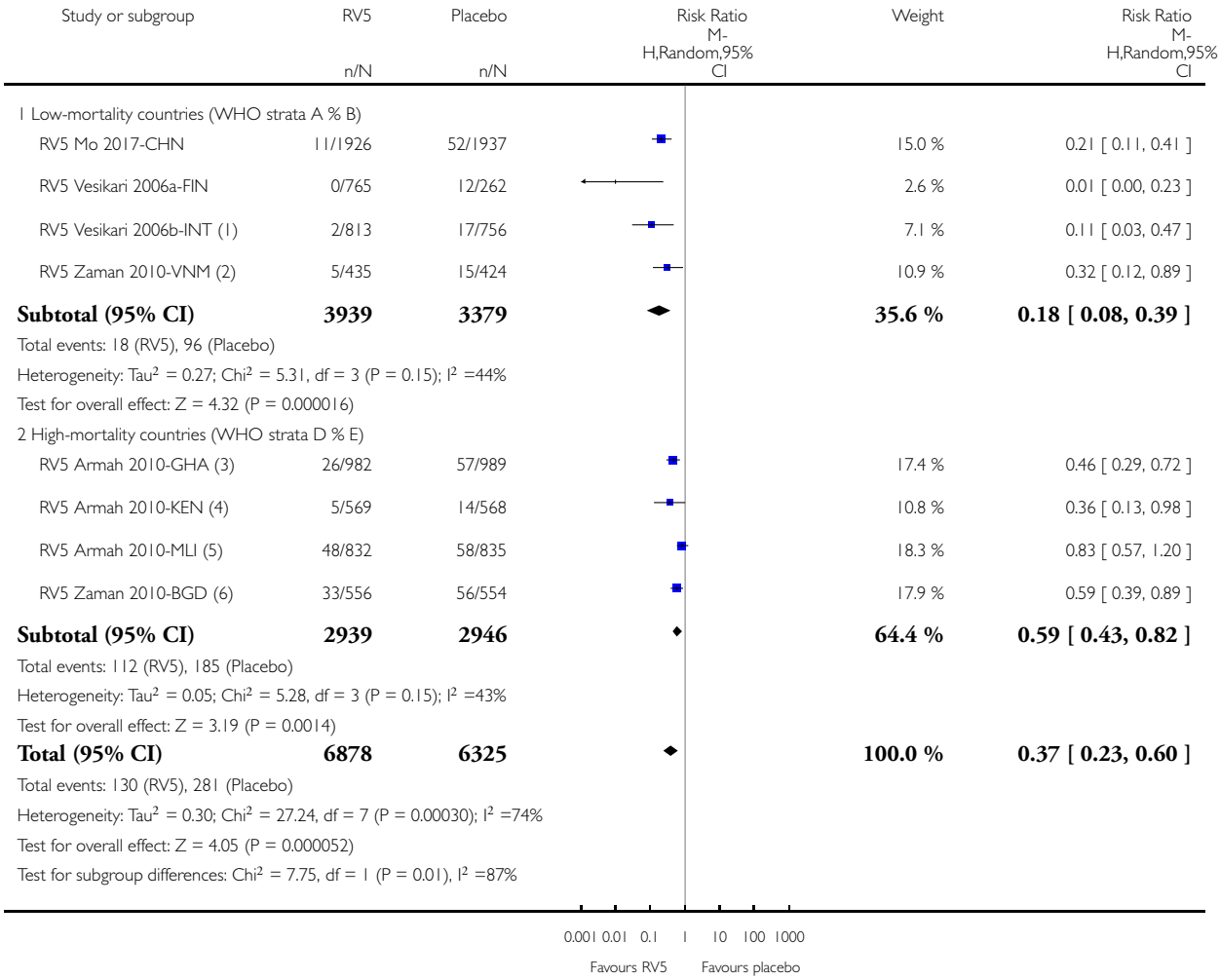
(5) Data from RV5 Zaman 2010-AS for Bangladesh only

Analysis 2.2. Comparison 2 RV5 versus placebo, Outcome 2 Rotavirus diarrhoea: severe (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 2 Rotavirus diarrhoea: severe (up to 2 years follow-up)



(1) This study was conducted mainly in European and Latin American low-mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.

(4) Total number of participants taken from Tapia et al. 2012, Table 4, data for Kenya only.

(5) Total number of participants taken from Tapia et al. 2012, Table 4, data for Mali only.

(6) Data from RV5 Zaman 2010-AS for Bangladesh only

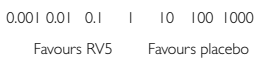
Analysis 2.3. Comparison 2 RV5 versus placebo, Outcome 3 All-cause diarrhoea: severe cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 3 All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO stratum A)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (RV5), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (1)	49/753	78/737		40.1 %	0.61 [0.44, 0.87]
RV5 Armah 2010-KEN (2)	21/481	22/477		21.6 %	0.95 [0.53, 1.70]
RV5 Armah 2010-MLI (3)	55/823	56/814		38.4 %	0.97 [0.68, 1.39]
Subtotal (95% CI)	**2057**	**2028**		**100.0 %**	**0.80 [0.58, 1.11]**
Total events: 125 (RV5), 156 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.70, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.32 (P = 0.19)					
Total (95% CI)	**2057**	**2028**		**100.0 %**	**0.80 [0.58, 1.11]**
Total events: 125 (RV5), 156 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.70, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.32 (P = 0.19)					
Test for subgroup differences: Not applicable					



(1) Data collected from Tapia et al. 2012, Table 3, data for Ghana only.

(2) Data collected from Tapia et al. 2012, Table 3, data for Kenya only.

(3) Data collected from Tapia et al. 2012, Table 3, data for Mali only.

Analysis 2.4. Comparison 2 RV5 versus placebo, Outcome 4 All-cause diarrhoea: severe cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 4 All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (RV5), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (1)	80/747	101/725		26.5 %	0.77 [0.58, 1.01]
RV5 Armah 2010-KEN (2)	25/472	29/472		7.5 %	0.86 [0.51, 1.45]
RV5 Armah 2010-MLI (3)	147/797	148/795		38.3 %	0.99 [0.81, 1.22]
RV5 Zaman 2010-AS (4)	81/991	107/978		27.8 %	0.75 [0.57, 0.98]
Subtotal (95% CI)	**3007**	**2970**		**100.0 %**	**0.85 [0.75, 0.98]**
Total events: 333 (RV5), 385 (Placebo)					
Heterogeneity: Chi^2 = 3.47, df = 3 (P = 0.32); I^2 =14%					
Test for overall effect: Z = 2.26 (P = 0.024)					
Total (95% CI)	**3007**	**2970**		**100.0 %**	**0.85 [0.75, 0.98]**
Total events: 333 (RV5), 385 (Placebo)					
Heterogeneity: Chi^2 = 3.47, df = 3 (P = 0.32); I^2 =14%					
Test for overall effect: Z = 2.26 (P = 0.024)					
Test for subgroup differences: Not applicable					

(1) Data collected from Tapia et al. 2012, Table 3, data for Ghana only.

(2) Data collected from Tapia et al. 2012, Table 3, data for Kenya only.

(3) Data collected from Tapia et al. 2012, Table 3, data for Mali only.

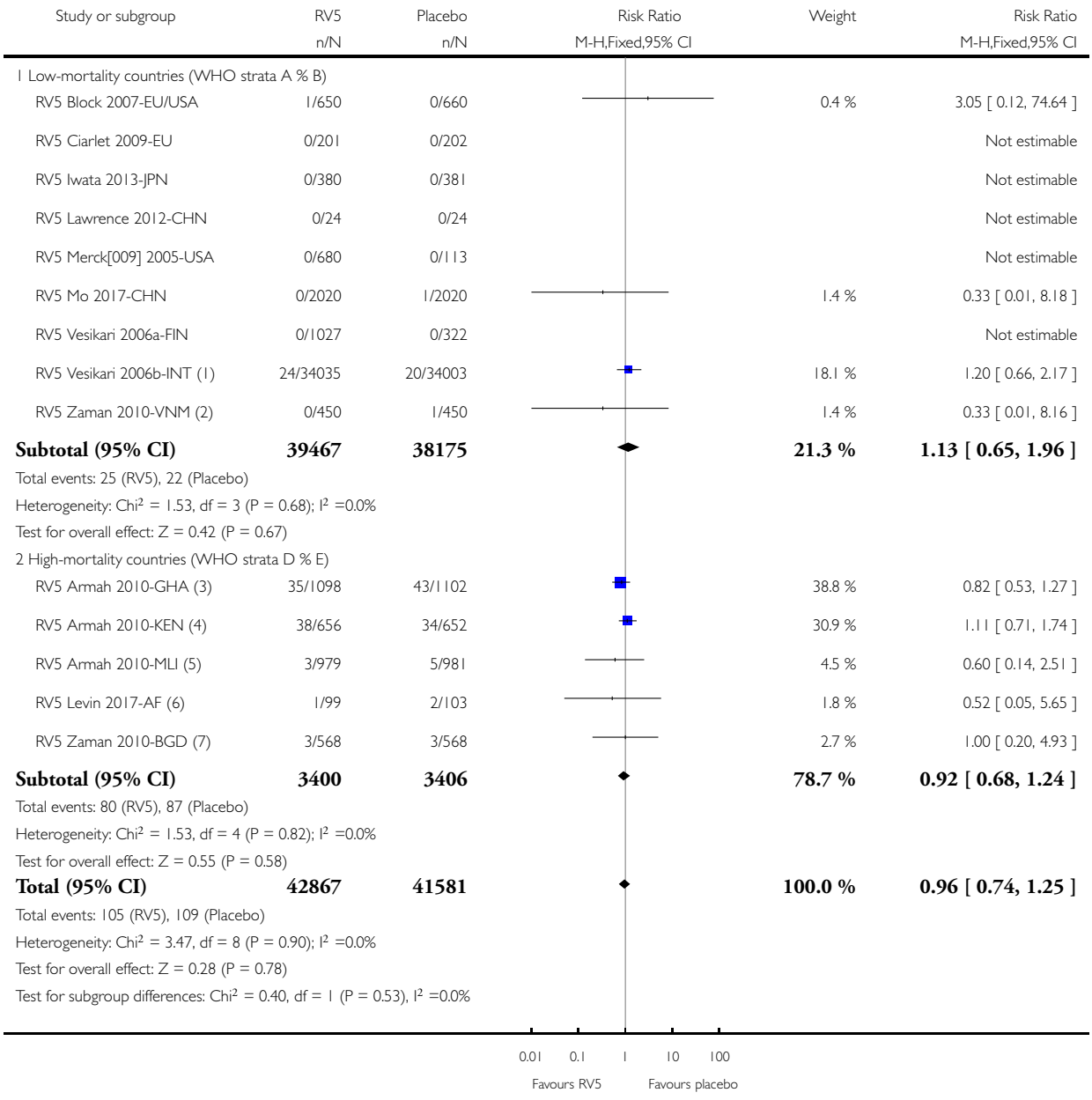
(4) This study was mainly conducted in high mortality Bangladesh, but also in low mortality Vietnam.

Analysis 2.5. Comparison 2 RV5 versus placebo, Outcome 5 All-cause death.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 5 All-cause death



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

(6) HIV positive infants and HIV exposed but uninfected infants

(7) Data from RV5 Zaman 2010-AS for Bangladesh only

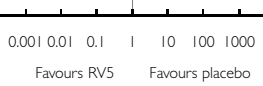
Analysis 2.6. Comparison 2 RV5 versus placebo, Outcome 6 All serious adverse events.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 6 All serious adverse events

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	21/650	27/660		2.4 %	0.79 [0.45, 1.38]
RV5 Ciarlet 2009-EU	3/201	6/202		0.5 %	0.50 [0.13, 1.98]
RV5 Iwata 2013-JPN	7/380	9/381		0.8 %	0.78 [0.29, 2.07]
RV5 Kim 2008-KOR	6/115	7/63		0.8 %	0.47 [0.16, 1.34]
RV5 Lawrence 2012-CHN	0/24	3/24		0.3 %	0.14 [0.01, 2.62]
RV5 Mo 2017-CHN	116/2015	116/2019		10.5 %	1.00 [0.78, 1.29]
RV5 Vesikari 2006b-INT (1)	803/34035	859/34003		77.8 %	0.93 [0.85, 1.03]
RV5 Zaman 2010-VNM (2)	9/450	3/450		0.3 %	3.00 [0.82, 11.01]
Subtotal (95% CI)	**37870**	**37802**		**93.5 %**	**0.93 [0.86, 1.02]**
Total events: 965 (RV5), 1030 (Placebo)					
Heterogeneity: Chi^2 = 7.92, df = 7 (P = 0.34); I^2 =12%					
Test for overall effect: Z = 1.57 (P = 0.12)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (3)	17/1098	18/1102		1.6 %	0.95 [0.49, 1.83]
RV5 Armah 2010-KEN (4)	20/649	21/643		1.9 %	0.94 [0.52, 1.72]



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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV5 Armah 2010-MLI (5)	5/979	6/981		0.5 %	0.84 [0.26, 2.73]
RV5 Dhingra 2014-IND	0/20	1/20		0.1 %	0.33 [0.01, 7.72]
RV5 Levin 2017-AF (6)	7/99	8/103		0.7 %	0.91 [0.34, 2.42]
RV5 Zaman 2010-BGD (7)	16/568	17/568		1.5 %	0.94 [0.48, 1.84]
Subtotal (95% CI)	**3413**	**3417**		**6.5 %**	**0.92 [0.66, 1.28]**
Total events: 65 (RV5), 71 (Placebo)					
Heterogeneity: Chi^2 = 0.45, df = 5 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.50 (P = 0.61)					
Total (95% CI)	**41283**	**41219**		**100.0 %**	**0.93 [0.86, 1.01]**
Total events: 1030 (RV5), 1101 (Placebo)					
Heterogeneity: Chi^2 = 8.37, df = 13 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					

(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

(6) Includes HIV positive infants and HIV exposed but uninfected infants

(7) Data from RV5 Zaman 2010-AS for Bangladesh only

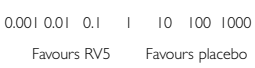
Analysis 2.7. Comparison 2 RV5 versus placebo, Outcome 7 Serious adverse events: intussusception.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 7 Serious adverse events: intussusception

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	0/650	0/660			Not estimable
RV5 Ciarlet 2009-EU	0/201	0/202			Not estimable
RV5 Clark 2003-USA	0/573	0/148			Not estimable
RV5 Clark 2004-USA	0/218	0/221			Not estimable
RV5 Iwata 2013-JPN	0/380	0/381			Not estimable
RV5 Kim 2008-KOR	0/115	0/63			Not estimable
RV5 Lawrence 2012-CHN	0/24	0/24			Not estimable
RV5 Merck[009] 2005-USA	0/680	0/113			Not estimable
RV5 Mo 2017-CHN	2/2015	0/2019		2.3 %	5.01 [0.24, 104.29]
RV5 Vesikari 2006a-FIN	1/1027	0/322		3.5 %	0.94 [0.04, 23.08]
RV5 Vesikari 2006b-INT (1)	13/34002	19/33969		87.3 %	0.68 [0.34, 1.38]
RV5 Zaman 2010-VNM (2)	0/450	1/450		6.9 %	0.33 [0.01, 8.16]
Subtotal (95% CI)	**40335**	**38572**		**100.0 %**	**0.77 [0.41, 1.45]**
Total events: 16 (RV5), 20 (Placebo)					
Heterogeneity: Chi^2 = 1.85, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (3)	0/1098	0/1102			Not estimable
RV5 Armah 2010-KEN (4)	0/649	0/643			Not estimable
RV5 Armah 2010-MLI (5)	0/979	0/981			Not estimable
RV5 Zaman 2010-BGD (6)	0/568	0/568			Not estimable
Subtotal (95% CI)	**3294**	**3294**			**Not estimable**
Total events: 0 (RV5), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**43629**	**41866**		**100.0 %**	**0.77 [0.41, 1.45]**
Total events: 16 (RV5), 20 (Placebo)					
Heterogeneity: Chi^2 = 1.85, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
Test for subgroup differences: Not applicable					



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

(6) Data from RV5 Zaman 2010-AS for Bangladesh only

Analysis 2.8. Comparison 2 RV5 versus placebo, Outcome 8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	21/551	63/564		13.9 %	0.34 [0.21, 0.55]
RV5 Clark 2003-USA	5/342	7/114		5.3 %	0.24 [0.08, 0.74]
RV5 Clark 2004-USA	11/187	39/183		10.9 %	0.28 [0.15, 0.52]
RV5 Vesikari 2006a-FIN	51/766	43/264		16.1 %	0.41 [0.28, 0.60]
RV5 Vesikari 2006b-INT (1)	82/2834	315/2839		19.2 %	0.26 [0.21, 0.33]
Subtotal (95% CI)	**4680**	**3964**		**65.3 %**	**0.30 [0.25, 0.37]**
Total events: 170 (RV5), 467 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.45$, df = 4 (P = 0.35); $I^2 = 10\%$					
Test for overall effect: Z = 11.90 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (2)	31/981	70/989		15.3 %	0.45 [0.30, 0.68]
RV5 Armah 2010-KEN (3)	6/575	21/573		7.3 %	0.28 [0.12, 0.70]
RV5 Armah 2010-MLI (4)	22/845	24/843		12.1 %	0.91 [0.52, 1.62]
Subtotal (95% CI)	**2401**	**2405**		**34.7 %**	**0.52 [0.28, 0.94]**
Total events: 59 (RV5), 115 (Placebo)					

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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.18; Chi^2 = 6.02, df = 2 (P = 0.05); I^2 =67%					
Test for overall effect: Z = 2.16 (P = 0.031)					
Total (95% CI)	**7081**	**6369**	♦	**100.0 %**	**0.37 [0.28, 0.50]**
Total events: 229 (RV5), 582 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 19.95, df = 7 (P = 0.01); I^2 =65%					
Test for overall effect: Z = 6.56 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.74, df = 1 (P = 0.10), I^2 =64%					

(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data collected from Tapia et al. 2012, Table 4 for Ghana only.

(3) Data collected from Tapia et al. 2012, Table 4 for Kenya only.

(4) Data collected from Tapia et al. 2012, Table 4 for Mali only.

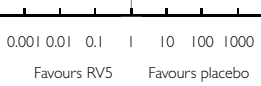
Analysis 2.9. Comparison 2 RV5 versus placebo, Outcome 9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Iwata 2013-JPN	7/355	27/356		9.0 %	0.26 [0.11, 0.59]
RV5 Mo 2017-CHN	34/1927	109/1937		15.4 %	0.31 [0.21, 0.46]
RV5 Vesikari 2006b-INT (1)	36/813	88/756		15.4 %	0.38 [0.26, 0.55]
Subtotal (95% CI)	**3095**	**3049**		**39.8 %**	**0.34 [0.26, 0.43]**
Total events: 77 (RV5), 224 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.93, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 8.42 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (2)	46/982	88/989		15.9 %	0.53 [0.37, 0.74]
RV5 Armah 2010-KEN (3)	9/569	24/568		9.7 %	0.37 [0.18, 0.80]
RV5 Armah 2010-MLI (4)	151/832	182/835		18.0 %	0.83 [0.69, 1.01]
RV5 Zaman 2010-AS (5)	65/991	109/978		16.7 %	0.59 [0.44, 0.79]
Subtotal (95% CI)	**3374**	**3370**		**60.2 %**	**0.61 [0.45, 0.83]**
Total events: 271 (RV5), 403 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 9.72, df = 3 (P = 0.02); I^2 =69%					
Test for overall effect: Z = 3.21 (P = 0.0013)					
Total (95% CI)	**6469**	**6419**		**100.0 %**	**0.46 [0.33, 0.65]**
Total events: 348 (RV5), 627 (Placebo)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 34.28, df = 6 (P<0.00001); I^2 =82%					
Test for overall effect: Z = 4.48 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 8.85, df = 1 (P = 0.00), I^2 =89%					



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data collected from Tapia et al. 2012, Table 4 for Ghana only.

(3) Data collected from Tapia et al. 2012, Table 4 for Kenya only.

(4) Data collected from Tapia et al. 2012, Table 4 for Mali only.

(5) This study was mainly conducted in high mortality Bangladesh, but also in low mortality Vietnam.

Analysis 2.10. Comparison 2 RV5 versus placebo, Outcome 10 All-cause diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 10 All-cause diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (RV5), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-mortality countries (WHO stratum E)					
RV5 Armah 2010-KEN (1)	66/525	82/534		100.0 %	0.82 [0.61, 1.11]
Subtotal (95% CI)	**525**	**534**		**100.0 %**	**0.82 [0.61, 1.11]**
Total events: 66 (RV5), 82 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Total (95% CI)	**525**	**534**		**100.0 %**	**0.82 [0.61, 1.11]**
Total events: 66 (RV5), 82 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Test for subgroup differences: Not applicable					

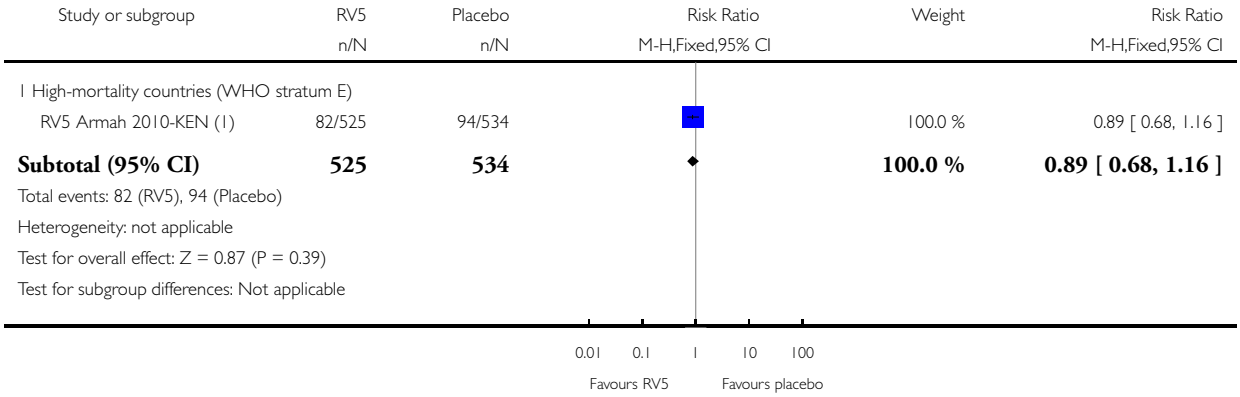
(1) Data from RV5 Armah 2010-AF for Kenya only

Analysis 2.11. Comparison 2 RV5 versus placebo, Outcome 11 All-cause diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 11 All-cause diarrhoea: of any severity (up to 2 years follow-up)



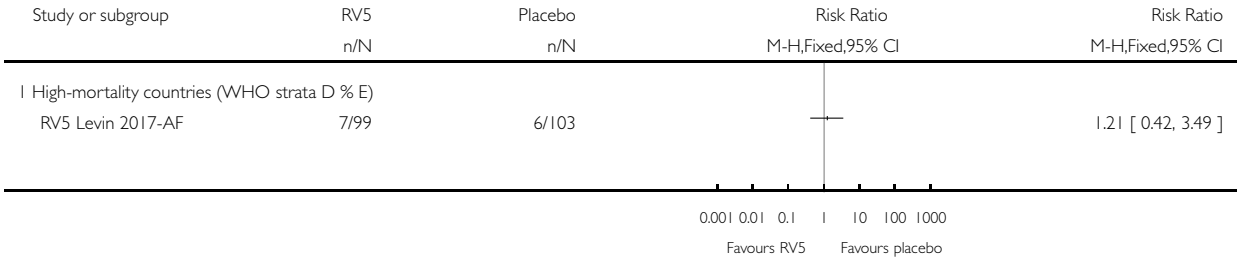
(1) Data from RV5 Armah 2010-AF for Kenya only

Analysis 2.12. Comparison 2 RV5 versus placebo, Outcome 12 All-cause hospitalizations (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 12 All-cause hospitalizations (up to 2 years follow-up)



Analysis 2.13. Comparison 2 RV5 versus placebo, Outcome 13 Rotavirus diarrhoea: requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 13 Rotavirus diarrhoea: requiring hospitalization

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year of follow-up				
RV5 Vesikari 2006b-INT	6/28646	138/28488		0.04 [0.02, 0.10]

Analysis 2.14. Comparison 2 RV5 versus placebo, Outcome 14 Rotavirus diarrhoea: requiring medical attention.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 14 Rotavirus diarrhoea: requiring medical attention

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year of follow-up				
RV5 Vesikari 2006b-INT	13/28646	191/28488		0.07 [0.04, 0.12]

Analysis 2.15. Comparison 2 RV5 versus placebo, Outcome 15 Reactogenicity: fever.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 15 Reactogenicity: fever

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV5 Block 2007-EU/USA	87/650	58/660		24.4 %	1.52 [1.11, 2.09]
RV5 Clark 2004-USA	25/213	27/218		14.2 %	0.95 [0.57, 1.58]
RV5 Mo 2017-CHN	154/2015	165/2019		32.0 %	0.94 [0.76, 1.15]
RV5 Vesikari 2006a-FIN	255/1027	64/322		29.4 %	1.25 [0.98, 1.59]
Subtotal (95% CI)	**3905**	**3219**		**100.0 %**	**1.15 [0.91, 1.45]**
Total events: 521 (RV5), 314 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 7.67, df = 3 (P = 0.05); I^2 =61%					
Test for overall effect: Z = 1.16 (P = 0.25)					
2 After dose 2					
RV5 Clark 2004-USA	26/208	35/209		16.8 %	0.75 [0.47, 1.19]
RV5 Mo 2017-CHN	146/1946	173/1959		83.2 %	0.85 [0.69, 1.05]
Subtotal (95% CI)	**2154**	**2168**		**100.0 %**	**0.83 [0.69, 1.01]**
Total events: 172 (RV5), 208 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.24, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.88 (P = 0.060)					
3 After dose 3					
RV5 Clark 2004-USA	47/207	43/209		21.7 %	1.10 [0.77, 1.59]
RV5 Mo 2017-CHN	191/1932	182/1946		78.3 %	1.06 [0.87, 1.28]
Subtotal (95% CI)	**2139**	**2155**		**100.0 %**	**1.07 [0.90, 1.27]**
Total events: 238 (RV5), 225 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
4 End of follow-up					
RV5 Block 2007-EU/USA	195/650	158/660		11.3 %	1.25 [1.05, 1.50]
RV5 Ciarlet 2009-EU	106/201	115/202		11.5 %	0.93 [0.78, 1.11]
RV5 Clark 2003-USA	157/568	36/147		4.7 %	1.13 [0.82, 1.54]
RV5 Clark 2004-USA	70/218	73/220		6.0 %	0.97 [0.74, 1.27]
RV5 Dhingra 2014-IND	7/20	6/20		0.6 %	1.17 [0.48, 2.86]
RV5 Iwata 2013-JPN	29/380	31/381		2.1 %	0.94 [0.58, 1.52]

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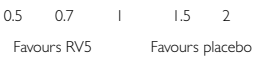
Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV5 Lawrence 2012-CHN	9/24	5/24		0.6 %	1.80 [0.71, 4.59]
RV5 Levin 2017-AF	27/99	27/103		2.3 %	1.04 [0.66, 1.64]
RV5 Merck[009] 2005-USA	370/680	53/113		9.1 %	1.16 [0.94, 1.43]
RV5 Mo 2017-CHN	440/2015	461/2019		19.2 %	0.96 [0.85, 1.07]
RV5 Vesikari 2006b-INT	1974/4826	2073/4821		32.5 %	0.95 [0.91, 1.00]
Subtotal (95% CI)	**9681**	**8710**		**100.0 %**	**1.01 [0.94, 1.09]**
Total events: 3384 (RV5), 3038 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.45$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.36 (P = 0.72)					



Analysis 2.16. Comparison 2 RV5 versus placebo, Outcome 16 Reactogenicity: diarrhoea.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 16 Reactogenicity: diarrhoea

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 After dose 1					
RV5 Clark 2003-USA	127/565	33/146		21.7 %	0.99 [0.71, 1.39]
RV5 Mo 2017-CHN	218/2015	189/2019		78.3 %	1.16 [0.96, 1.39]
Subtotal (95% CI)	**2580**	**2165**		**100.0 %**	**1.12 [0.95, 1.32]**
Total events: 345 (RV5), 222 (Placebo)					
Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.38 (P = 0.17)					
2 After dose 2					
RV5 Mo 2017-CHN	143/1946	162/1959		100.0 %	0.89 [0.72, 1.10]
Subtotal (95% CI)	**1946**	**1959**		**100.0 %**	**0.89 [0.72, 1.10]**

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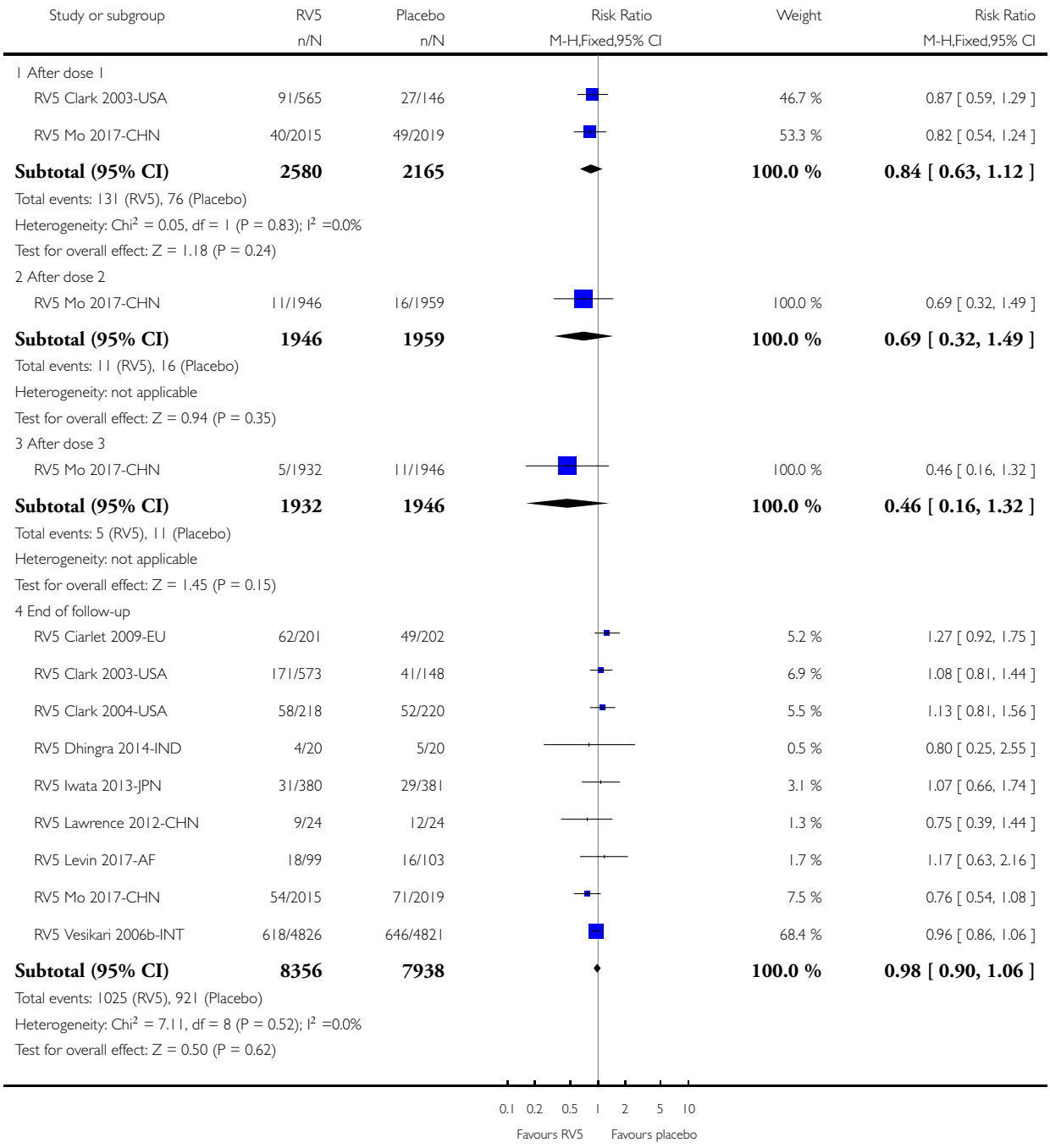
Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 143 (RV5), 162 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
3 End of follow-up					
RV5 Ciarlet 2009-EU	57/201	65/202		3.8 %	0.88 [0.65, 1.19]
RV5 Clark 2003-USA	205/573	52/148		4.8 %	1.02 [0.80, 1.30]
RV5 Clark 2004-USA	97/218	80/220		4.6 %	1.22 [0.97, 1.54]
RV5 Dhingra 2014-IND	4/20	3/20		0.2 %	1.33 [0.34, 5.21]
RV5 Iwata 2013-JPN	46/380	47/381		2.7 %	0.98 [0.67, 1.44]
RV5 Lawrence 2012-CHN	13/24	8/24		0.5 %	1.63 [0.83, 3.19]
RV5 Levin 2017-AF	33/99	25/103		1.4 %	1.37 [0.88, 2.13]
RV5 Merck[009] 2005-USA	367/680	51/113		5.1 %	1.20 [0.96, 1.48]
RV5 Mo 2017-CHN	406/2015	406/2019		23.5 %	1.00 [0.89, 1.13]
RV5 Vesikari 2006b-INT	951/4826	921/4821		53.4 %	1.03 [0.95, 1.12]
Subtotal (95% CI)	**9036**	**8051**		**100.0 %**	**1.04 [0.98, 1.10]**
Total events: 2179 (RV5), 1658 (Placebo)					
Heterogeneity: Chi^2 = 8.56, df = 9 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.40 (P = 0.16)					

Analysis 2.17. Comparison 2 RV5 versus placebo, Outcome 17 Reactogenicity: vomiting.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 17 Reactogenicity: vomiting



Analysis 2.18. Comparison 2 RV5 versus placebo, Outcome 18 Adverse events requiring discontinuation (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 18 Adverse events requiring discontinuation (end of follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV5 Armah 2010-AF	9/2733	15/2735		37.3 %	0.60 [0.26, 1.37]
RV5 Block 2007-EU/USA	1/650	5/660		12.4 %	0.20 [0.02, 1.73]
RV5 Ciarlet 2009-EU	1/201	0/202		1.2 %	3.01 [0.12, 73.57]
RV5 Clark 2004-USA	4/218	1/221		2.5 %	4.06 [0.46, 35.99]
RV5 Iwata 2013-JPN	1/381	3/381		7.5 %	0.33 [0.03, 3.19]
RV5 Kim 2008-KOR	0/115	0/63			Not estimable
RV5 Lawrence 2012-CHN	0/24	1/24		3.7 %	0.33 [0.01, 7.80]
RV5 Merck[009] 2005-USA	1/680	1/113		4.3 %	0.17 [0.01, 2.64]
RV5 Mo 2017-CHN	17/2015	12/2019		29.9 %	1.42 [0.68, 2.96]
RV5 Zaman 2010-AS	1/1018	0/1018		1.2 %	3.00 [0.12, 73.56]
Total (95% CI)	**8035**	**7436**		**100.0 %**	**0.89 [0.57, 1.39]**

Total events: 35 (RV5), 38 (Placebo)

Heterogeneity: $Chi^2 = 9.73$, df = 8 (P = 0.28); $I^2 = 18\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

Analysis 2.19. Comparison 2 RV5 versus placebo, Outcome 19 Immunogenicity: rotavirus vaccine shedding (after dose 3).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 19 Immunogenicity: rotavirus vaccine shedding (after dose 3)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
RV5 Clark 2003-USA	277/355	13/93		5.58 [3.36, 9.27]
RV5 Clark 2004-USA	104/159	2/155		50.69 [12.73, 201.81]
RV5 Dhingra 2014-IND	0/20	0/20		Not estimable
RV5 Lawrence 2012-CHN	6/23	0/24		13.54 [0.81, 227.50]
RV5 Levin 2017-AF	0/99	0/130		Not estimable

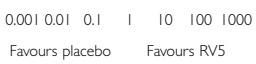
Analysis 2.20. Comparison 2 RV5 versus placebo, Outcome 20 Immunogenicity: seroconversion.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 20 Immunogenicity: seroconversion

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 After dose 3				
RV5 Armah 2010-AF	148/189	34/169		3.89 [2.86, 5.31]
RV5 Block 2007-EU/USA	64/67	9/73		7.75 [4.19, 14.32]
RV5 Ciarlet 2009-EU	184/201	12/202		15.41 [8.89, 26.72]
RV5 Clark 2003-USA	404/455	3/113		33.44 [10.95, 102.19]
RV5 Clark 2004-USA	162/185	3/185		54.00 [17.55, 166.11]
RV5 Dhingra 2014-IND	13/20	2/20		6.50 [1.68, 25.16]
RV5 Levin 2017-AF	72/89	22/89		3.27 [2.25, 4.77]
RV5 Vesikari 2006a-FIN	959/1027	43/322		6.99 [5.29, 9.24]
RV5 Vesikari 2006b-INT	180/189	23/161		6.67 [4.56, 9.75]
RV5 Zaman 2010-AS	115/131	24/132		4.83 [3.34, 6.97]



Analysis 2.21. Comparison 2 RV5 versus placebo, Outcome 21 Dropouts before the end of the trial.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 21 Dropouts before the end of the trial

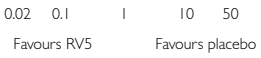
Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV5 Armah 2010-AF	376/2733	387/2735		21.2 %	0.97 [0.85, 1.11]
RV5 Block 2007-EU/USA	99/651	96/661		9.3 %	1.05 [0.81, 1.36]
RV5 Clark 2003-USA	97/581	36/150		6.0 %	0.70 [0.50, 0.98]
RV5 Clark 2004-USA	11/218	12/221		1.2 %	0.93 [0.42, 2.06]
RV5 Dhingra 2014-IND	1/20	1/20		0.1 %	1.00 [0.07, 14.90]
RV5 Iwata 2013-JPN	13/381	15/381		1.5 %	0.87 [0.42, 1.80]
RV5 Lawrence 2012-CHN	2/24	4/24		0.3 %	0.50 [0.10, 2.48]
RV5 Levin 2017-AF	1/99	4/103		0.2 %	0.26 [0.03, 2.29]
RV5 Merck[009] 2005-USA	71/680	16/113		3.0 %	0.74 [0.45, 1.22]
RV5 Mo 2017-CHN	90/2020	74/2020		7.3 %	1.22 [0.90, 1.64]
RV5 Vesikari 2006a-FIN	390/1624	60/322		10.1 %	1.29 [1.01, 1.65]
RV5 Vesikari 2006b-INT	5846/34035	5882/34003		36.6 %	0.99 [0.96, 1.03]
RV5 Zaman 2010-AS	27/1018	40/1018		3.2 %	0.68 [0.42, 1.09]
Total (95% CI)	**44084**	**41771**		**100.0 %**	**0.98 [0.90, 1.08]**

Total events: 7024 (RV5), 6627 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 16.79$, df = 12 (P = 0.16); $I^2 = 29\%$

Test for overall effect: Z = 0.34 (P = 0.74)

Test for subgroup differences: Not applicable



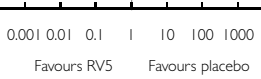
Analysis 2.22. Comparison 2 RV5 versus placebo, Outcome 22 Subgroup analysis: rotavirus diarrhoea of any severity (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 22 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV5 Block 2007-EU/USA	13/551	53/564		12.5 %	0.25 [0.14, 0.46]
RV5 Clark 2004-USA	10/187	26/183		9.0 %	0.38 [0.19, 0.76]
RV5 Mo 2017-CHN	10/1927	39/1937		9.3 %	0.26 [0.13, 0.51]
RV5 Vesikari 2006b-INT	72/2834	286/2839		69.2 %	0.25 [0.20, 0.32]
Subtotal (95% CI)	**5499**	**5523**		**100.0 %**	**0.26 [0.21, 0.32]**
Total events: 105 (RV5), 404 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.14, df = 3 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 12.47 (P < 0.00001)					
2 G2					
RV5 Clark 2004-USA	1/187	2/183		11.3 %	0.49 [0.04, 5.35]
RV5 Mo 2017-CHN	1/1927	4/1937		13.5 %	0.25 [0.03, 2.25]
RV5 Vesikari 2006b-INT	6/2834	17/2839		75.1 %	0.35 [0.14, 0.90]
Subtotal (95% CI)	**4948**	**4959**		**100.0 %**	**0.35 [0.16, 0.78]**
Total events: 8 (RV5), 23 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 2 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
3 G3					
RV5 Block 2007-EU/USA	2/551	1/564		24.0 %	2.05 [0.19, 22.51]
RV5 Clark 2004-USA	0/187	10/183		19.9 %	0.05 [0.00, 0.79]
RV5 Mo 2017-CHN	2/1927	2/1937		29.0 %	1.01 [0.14, 7.13]
RV5 Vesikari 2006b-INT	1/2834	6/2839		27.1 %	0.17 [0.02, 1.39]
Subtotal (95% CI)	**5499**	**5523**		**100.0 %**	**0.40 [0.08, 2.02]**
Total events: 5 (RV5), 19 (Placebo)					
Heterogeneity: Tau² = 1.38; Chi² = 6.03, df = 3 (P = 0.11); I² =50%					
Test for overall effect: Z = 1.11 (P = 0.27)					
4 G4					
RV5 Clark 2004-USA	0/187	1/183		13.5 %	0.33 [0.01, 7.96]
RV5 Mo 2017-CHN	0/1927	2/1937		14.9 %	0.20 [0.01, 4.18]



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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV5 Vesikari 2006b-INT	3/2834	6/2839		71.6 %	0.50 [0.13, 2.00]
Subtotal (95% CI)	**4948**	**4959**		**100.0 %**	**0.41 [0.13, 1.33]**
Total events: 3 (RV5), 9 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 2 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 1.48 (P = 0.14)					
5 G9					
RV5 Mo 2017-CHN	20/1927	61/1937		95.3 %	0.33 [0.20, 0.54]
RV5 Vesikari 2006b-INT	1/2834	3/2839		4.7 %	0.33 [0.03, 3.21]
Subtotal (95% CI)	**4761**	**4776**		**100.0 %**	**0.33 [0.20, 0.54]**
Total events: 21 (RV5), 64 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 4.44 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.71, df = 4 (P = 0.79), I^2 =0.0%					

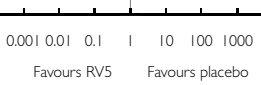
Analysis 2.23. Comparison 2 RV5 versus placebo, Outcome 23 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 23 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)

Study or subgroup	Favours RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV5 Armah 2010-AF	42/2357	62/2348		34.2 %	0.67 [0.46, 0.99]
RV5 Mo 2017-CHN	5/1926	14/1937		31.9 %	0.36 [0.13, 1.00]
RV5 Vesikari 2006b-INT	16/34035	328/34003		33.9 %	0.05 [0.03, 0.08]
Subtotal (95% CI)	**38318**	**38288**		**100.0 %**	**0.23 [0.03, 1.74]**
Total events: 63 (Favours RV5), 404 (Placebo)					
Heterogeneity: Tau^2 = 3.13; Chi^2 = 78.22, df = 2 (P<0.00001); I^2 =97%					
Test for overall effect: Z = 1.43 (P = 0.15)					
2 G2					
RV5 Armah 2010-AF	32/2357	44/2348		64.7 %	0.72 [0.46, 1.14]
RV5 Mo 2017-CHN	0/1926	2/1937		12.7 %	0.20 [0.01, 4.19]
RV5 Vesikari 2006b-INT	1/34035	8/34003		22.6 %	0.12 [0.02, 1.00]
Subtotal (95% CI)	**38318**	**38288**		**100.0 %**	**0.41 [0.13, 1.37]**
Total events: 33 (Favours RV5), 54 (Placebo)					
Heterogeneity: Tau^2 = 0.52; Chi^2 = 3.29, df = 2 (P = 0.19); I^2 =39%					
Test for overall effect: Z = 1.45 (P = 0.15)					
3 G3					
RV5 Armah 2010-AF	3/2357	8/2348		42.7 %	0.37 [0.10, 1.41]
RV5 Mo 2017-CHN	2/1926	0/1937		23.4 %	5.03 [0.24, 104.67]
RV5 Vesikari 2006b-INT	1/34035	15/34003		33.9 %	0.07 [0.01, 0.50]
Subtotal (95% CI)	**38318**	**38288**		**100.0 %**	**0.38 [0.05, 2.74]**
Total events: 6 (Favours RV5), 23 (Placebo)					
Heterogeneity: Tau^2 = 1.90; Chi^2 = 5.61, df = 2 (P = 0.06); I^2 =64%					
Test for overall effect: Z = 0.96 (P = 0.34)					
4 G4					
RV5 Armah 2010-AF	0/2357	0/2348			Not estimable
RV5 Mo 2017-CHN	0/1926	2/1937		18.8 %	0.20 [0.01, 4.19]
RV5 Vesikari 2006b-INT	2/34035	18/34003		81.2 %	0.11 [0.03, 0.48]
Subtotal (95% CI)	**38318**	**38288**		**100.0 %**	**0.12 [0.03, 0.46]**



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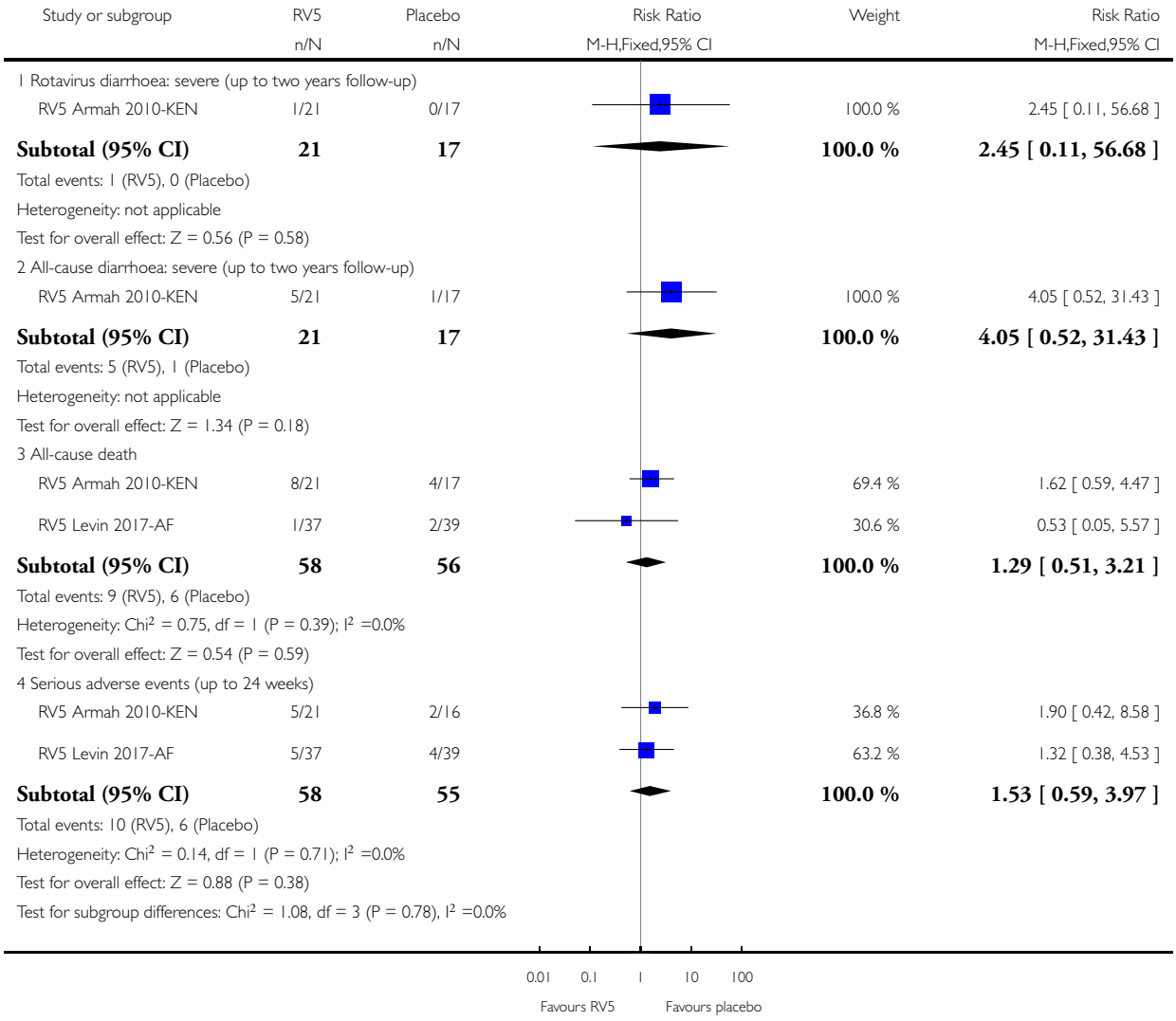
Study or subgroup	Favours RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 2 (Favours RV5), 20 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.11 (P = 0.0019)					
5 G9					
RV5 Armah 2010-AF	1/2357	2/2348		15.5 %	0.50 [0.05, 5.49]
RV5 Mo 2017-CHN	4/1926	34/1937		73.2 %	0.12 [0.04, 0.33]
RV5 Vesikari 2006b-INT	0/34035	13/34003		11.3 %	0.04 [0.00, 0.62]
Subtotal (95% CI)	**38318**	**38288**		**100.0 %**	**0.13 [0.05, 0.34]**
Total events: 5 (Favours RV5), 49 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.09$, df = 2 (P = 0.35); $I^2 = 4\%$					
Test for overall effect: Z = 4.17 (P = 0.000031)					

Analysis 2.24. Comparison 2 RV5 versus placebo, Outcome 24 Subgroup analysis: HIV-infected children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 24 Subgroup analysis: HIV-infected children

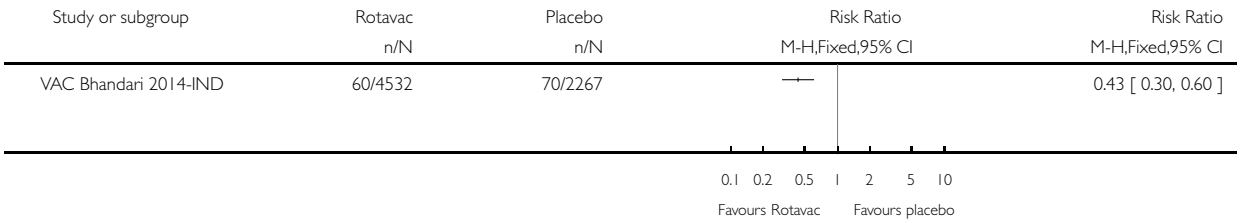


Analysis 3.1. Comparison 3 Rotavac versus placebo, Outcome 1 Rotavirus diarrhoea: severe (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 1 Rotavirus diarrhoea: severe (up to 1 year follow-up)

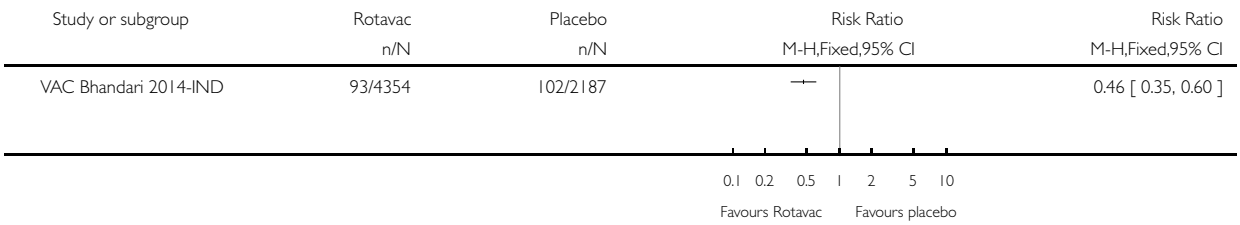


Analysis 3.2. Comparison 3 Rotavac versus placebo, Outcome 2 Rotavirus diarrhoea: severe (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 2 Rotavirus diarrhoea: severe (up to 2 years follow-up)



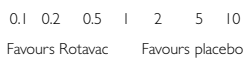
Analysis 3.3. Comparison 3 Rotavac versus placebo, Outcome 3 All-cause diarrhoea: severe cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 3 All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2014-IND	353/4532	211/2267		0.84 [0.71, 0.98]



Analysis 3.4. Comparison 3 Rotavac versus placebo, Outcome 4 All-cause death.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 4 All-cause death

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2014-IND	30/4532	18/2267		97.0 %	0.83 [0.47, 1.49]
VAC Chandola 2017-IND	5/1017	0/339		3.0 %	3.67 [0.20, 66.27]
Total (95% CI)	**5549**	**2606**		**100.0 %**	**0.92 [0.52, 1.62]**
Total events: 35 (Rotavac), 18 (Placebo)					
Heterogeneity: Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Not applicable					

Analysis 3.5. Comparison 3 Rotavac versus placebo, Outcome 5 All serious adverse events.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 5 All serious adverse events

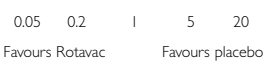
Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2006-IND (1)	1/30	2/28		0.3 %	0.47 [0.04, 4.87]
VAC Bhandari 2014-IND	947/4531	515/2265		95.7 %	0.92 [0.84, 1.01]
VAC Chandola 2017-IND	72/1017	19/339		4.0 %	1.26 [0.77, 2.06]
Total (95% CI)	**5578**	**2632**		**100.0 %**	**0.93 [0.85, 1.02]**

Total events: 1020 (Rotavac), 536 (Placebo)

Heterogeneity: Chi^2 = 1.89, df = 2 (P = 0.39); I^2 =0.0%

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Not applicable



(1) intervention: 1 dose only

Analysis 3.6. Comparison 3 Rotavac versus placebo, Outcome 6 Serious adverse events: intussusception.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 6 Serious adverse events: intussusception

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2006-IND (1)	0/30	0/28			Not estimable
VAC Bhandari 2009-IND (2)	0/185	0/184			Not estimable
VAC Bhandari 2014-IND	8/4532	3/2267		100.0 %	1.33 [0.35, 5.02]
VAC Chandola 2017-IND	0/1017	0/339			Not estimable
Total (95% CI)	**5764**	**2818**		**100.0 %**	**1.33 [0.35, 5.02]**
Total events: 8 (Rotavac), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					

(1) intervention: 1 dose only

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

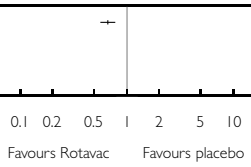
Analysis 3.7. Comparison 3 Rotavac versus placebo, Outcome 7 Rotavirus diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 7 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2014-IND	313/4532	236/2267		0.66 [0.56, 0.78]

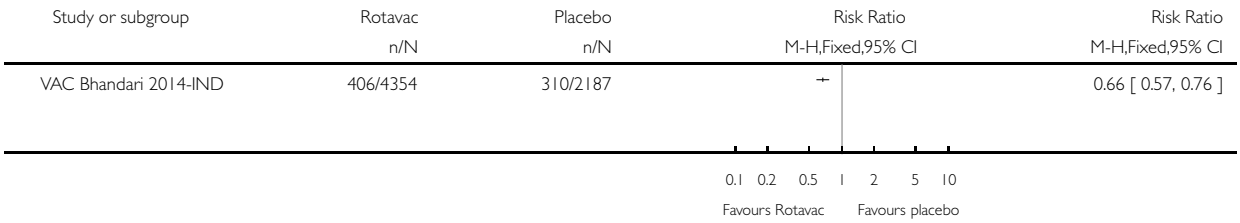


Analysis 3.8. Comparison 3 Rotavac versus placebo, Outcome 8 Rotavirus diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 8 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

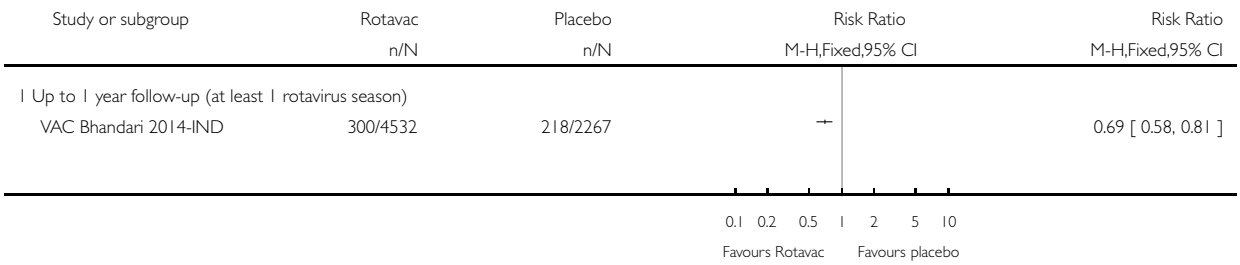


Analysis 3.9. Comparison 3 Rotavac versus placebo, Outcome 9 Rotavirus diarrhoea: requiring medical attention.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 9 Rotavirus diarrhoea: requiring medical attention

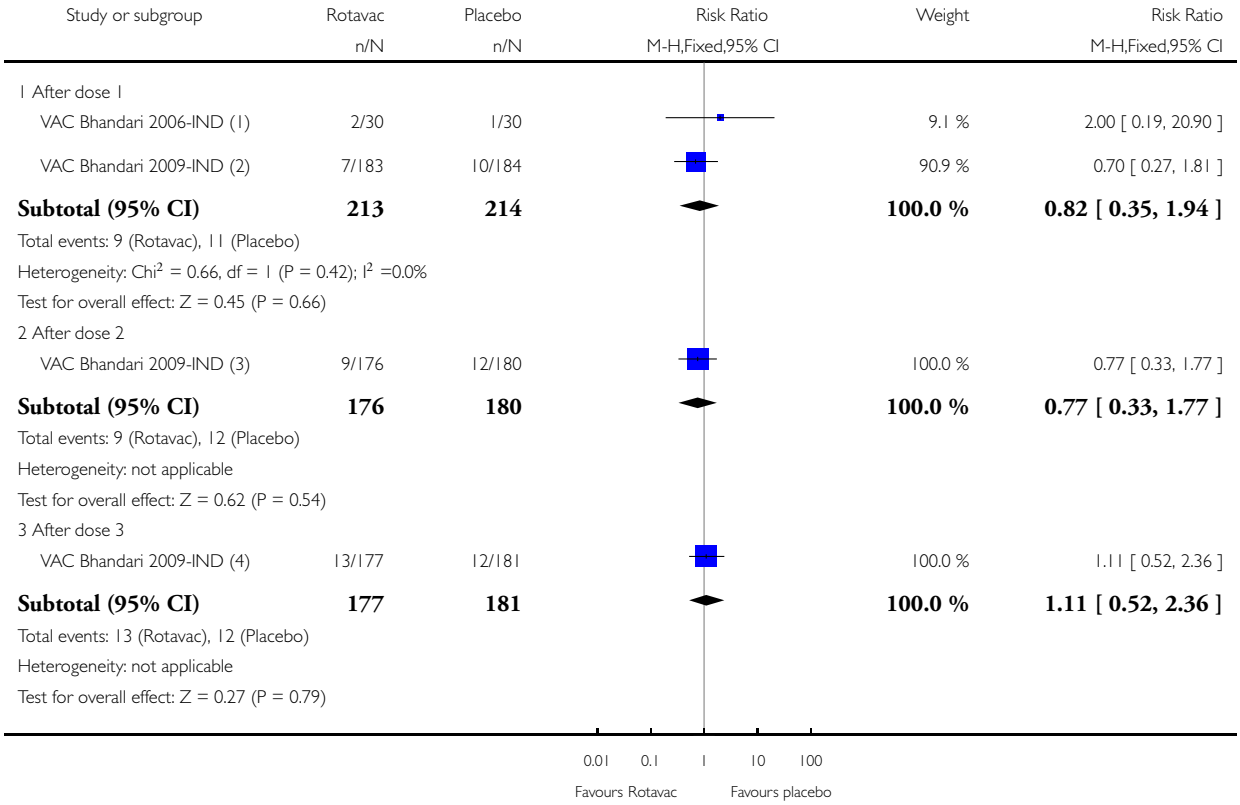


Analysis 3.10. Comparison 3 Rotavac versus placebo, Outcome 10 Reactogenicity: fever.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 10 Reactogenicity: fever



(1) intervention: 1 dose only

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

(3) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

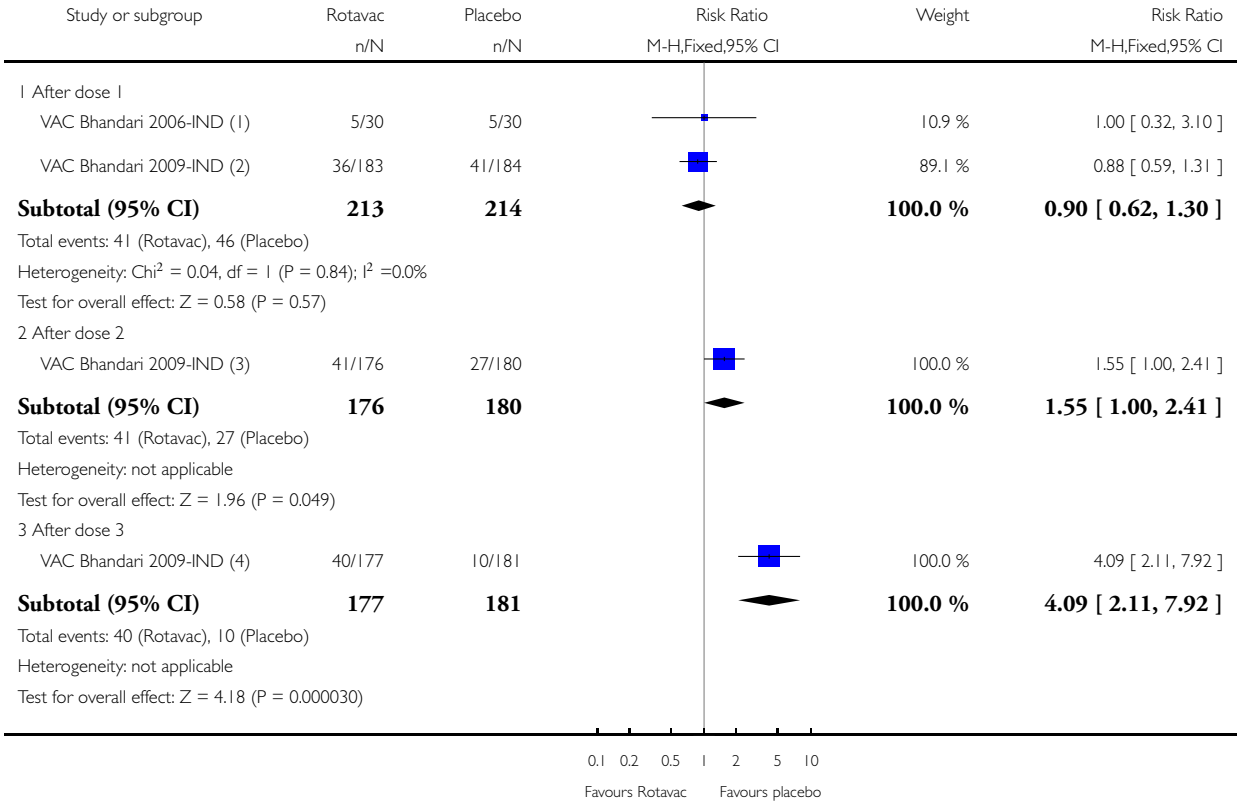
(4) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

Analysis 3.11. Comparison 3 Rotavac versus placebo, Outcome 11 Reactogenicity: diarrhoea.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 11 Reactogenicity: diarrhoea



(1) intervention: 1 dose only

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

(3) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

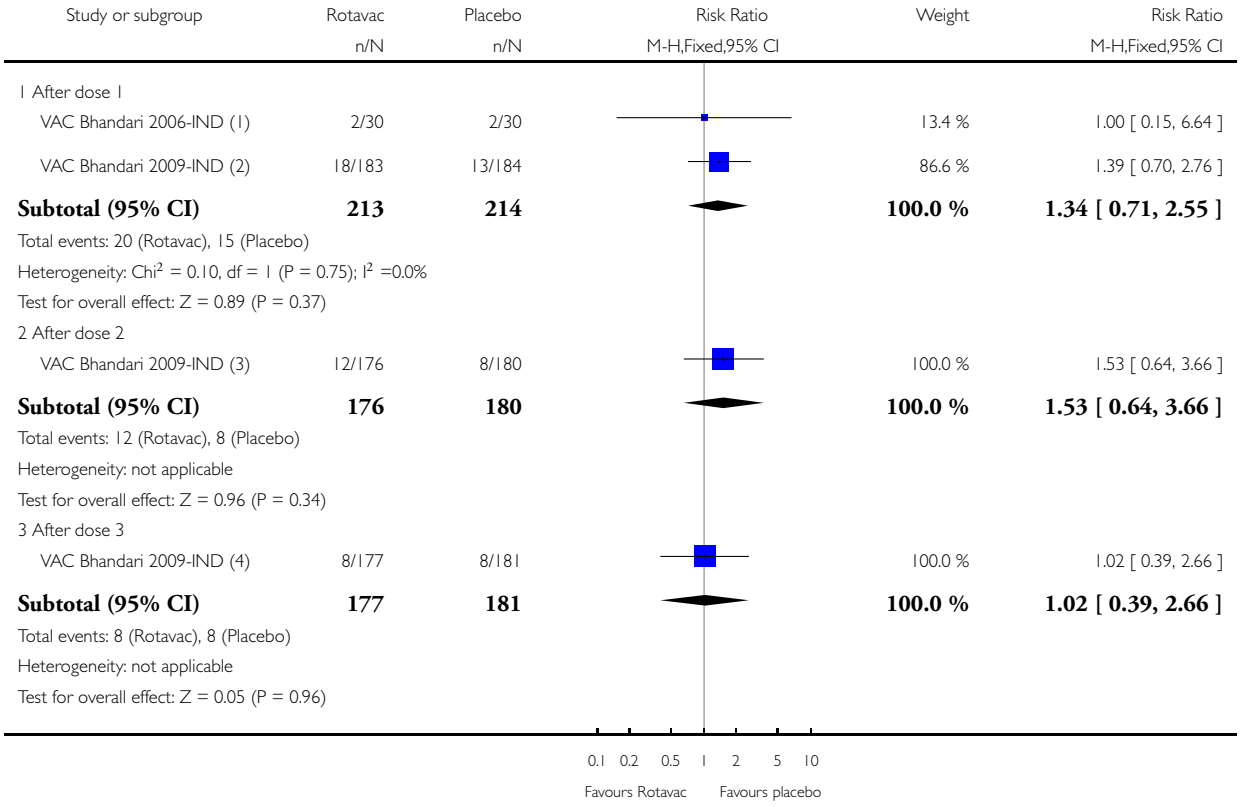
(4) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

Analysis 3.12. Comparison 3 Rotavac versus placebo, Outcome 12 Reactogenicity: vomiting.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 12 Reactogenicity: vomiting



(1) intervention: 1 dose only

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

(3) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

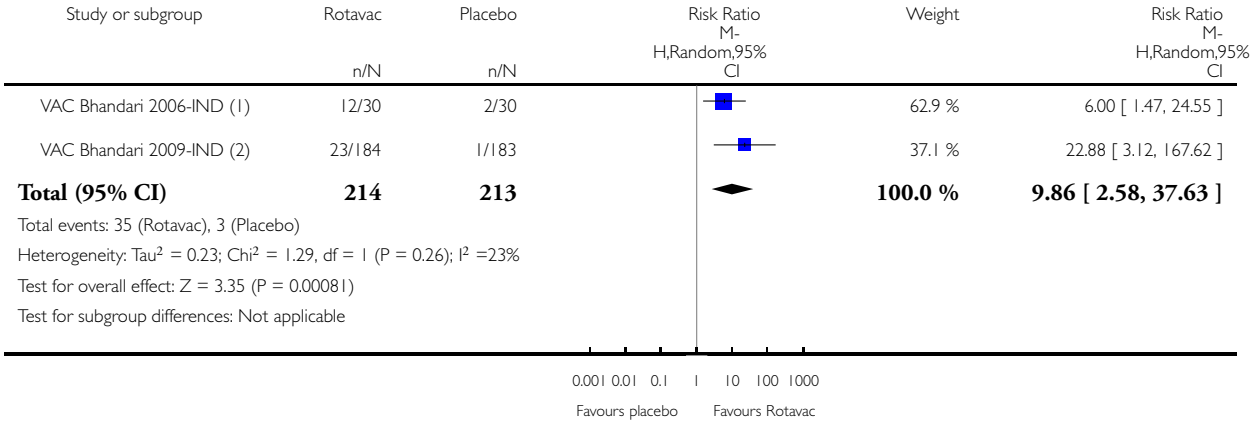
(4) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

Analysis 3.13. Comparison 3 Rotavac versus placebo, Outcome 13 Immunogenicity: rotavirus vaccine shedding (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 13 Immunogenicity: rotavirus vaccine shedding (end of follow-up)



(1) intervention: 1 dose only

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

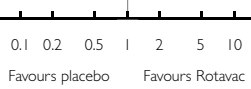
Analysis 3.14. Comparison 3 Rotavac versus placebo, Outcome 14 Immunogenicity: seroconversion.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 14 Immunogenicity: seroconversion

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 After dose 1					
VAC Bhandari 2009-IND (1)	40/61	11/60		100.0 %	3.58 [2.03, 6.29]
Subtotal (95% CI)	**61**	**60**		**100.0 %**	**3.58 [2.03, 6.29]**
Total events: 40 (Rotavac), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.43 (P < 0.00001)					
2 After dose 2					
VAC Bhandari 2009-IND (2)	38/58	13/59		100.0 %	2.97 [1.78, 4.98]
Subtotal (95% CI)	**58**	**59**		**100.0 %**	**2.97 [1.78, 4.98]**
Total events: 38 (Rotavac), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.15 (P = 0.000034)					
3 After dose 3					
VAC Bhandari 2009-IND (3)	44/58	16/63		15.1 %	2.99 [1.91, 4.67]
VAC Bhandari 2014-IND	115/288	25/136		33.4 %	2.17 [1.48, 3.18]
VAC Chandola 2017-IND	335/866	35/288		51.6 %	3.18 [2.31, 4.39]
Subtotal (95% CI)	**1212**	**487**		**100.0 %**	**2.82 [2.26, 3.51]**
Total events: 494 (Rotavac), 76 (Placebo)					
Heterogeneity: Chi^2 = 2.40, df = 2 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 9.22 (P < 0.00001)					



(1) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

(2) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

(3) vaccine: 3 doses of either 1x10^4 or 1x10^5 FFUs

Analysis 3.15. Comparison 3 Rotavac versus placebo, Outcome 15 Dropouts before the end of the trial.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 15 Dropouts before the end of the trial

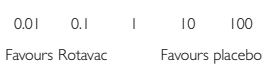
Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VAC Bhandari 2006-IND (1)	2/30	2/30		1.8 %	1.00 [0.15, 6.64]
VAC Bhandari 2014-IND	113/4532	76/2267		91.4 %	0.74 [0.56, 0.99]
VAC Chandola 2017-IND	24/1017	5/339		6.8 %	1.60 [0.62, 4.16]
Total (95% CI)	**5579**	**2636**		**100.0 %**	**0.81 [0.62, 1.06]**

Total events: 139 (Rotavac), 83 (Placebo)

Heterogeneity: $Chi^2 = 2.33$, df = 2 (P = 0.31); $I^2 = 14\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable



(1) intervention: 1 dose only

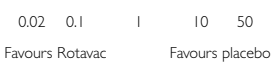
Analysis 3.16. Comparison 3 Rotavac versus placebo, Outcome 16 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 16 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 1 year follow-up)

Study or subgroup	Rotavac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 G1P[8]					
VAC Bhandari 2014-IND	25/4354	19/2187		100.0 %	0.66 [0.36, 1.20]
Subtotal (95% CI)	**4354**	**2187**		**100.0 %**	**0.66 [0.36, 1.20]**
Total events: 25 (Rotavac), 19 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 G2P[4]					
VAC Bhandari 2014-IND	21/4354	27/2187		100.0 %	0.39 [0.22, 0.69]
Subtotal (95% CI)	**4354**	**2187**		**100.0 %**	**0.39 [0.22, 0.69]**
Total events: 21 (Rotavac), 27 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.24 (P = 0.0012)					
3 G12P[6]					
VAC Bhandari 2014-IND	8/4354	13/2187		100.0 %	0.31 [0.13, 0.74]
Subtotal (95% CI)	**4354**	**2187**		**100.0 %**	**0.31 [0.13, 0.74]**
Total events: 8 (Rotavac), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.62 (P = 0.0089)					
4 G12P[8]					
VAC Bhandari 2014-IND	3/4354	5/2187		100.0 %	0.30 [0.07, 1.26]
Subtotal (95% CI)	**4354**	**2187**		**100.0 %**	**0.30 [0.07, 1.26]**
Total events: 3 (Rotavac), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					

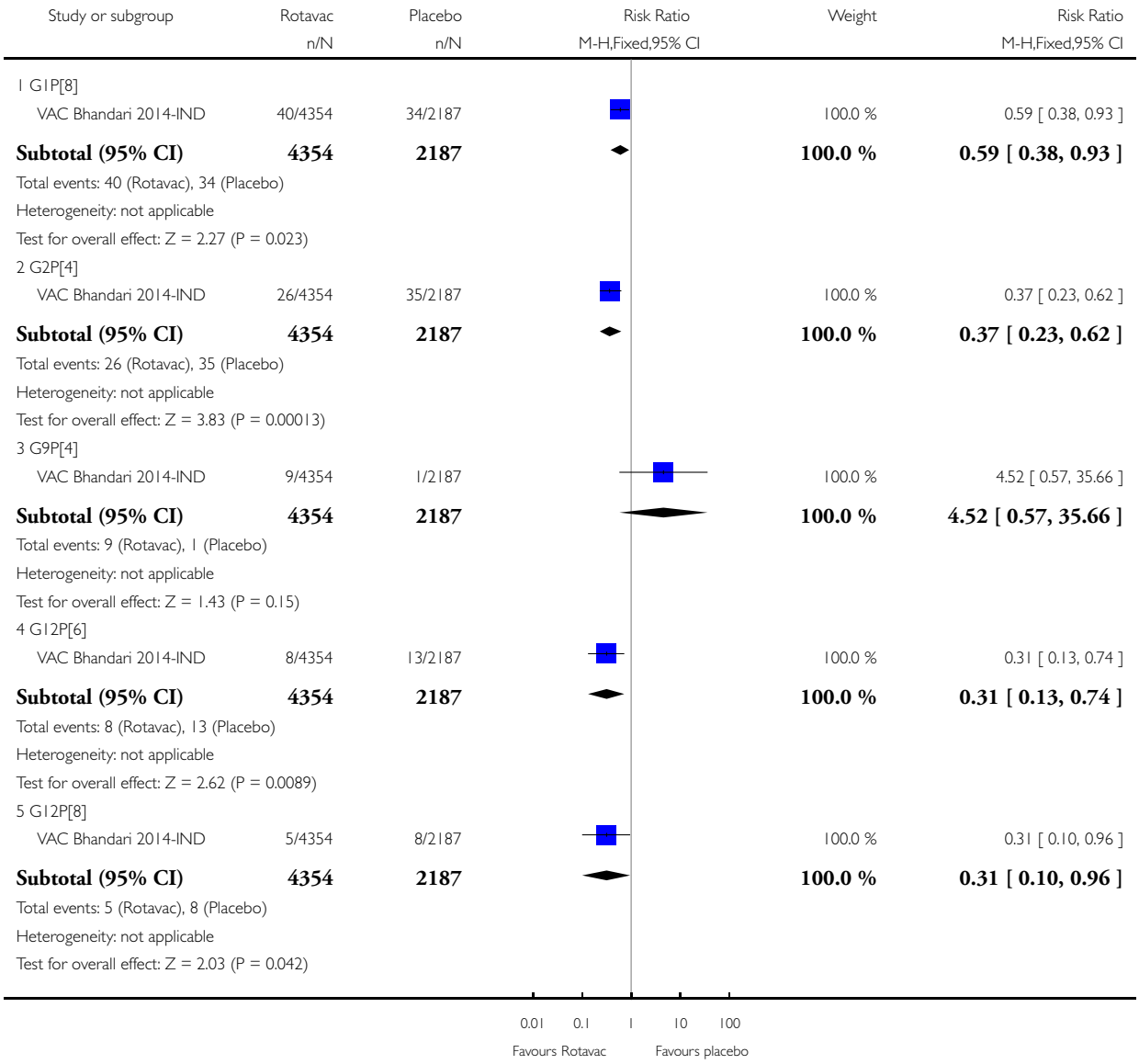


Analysis 3.17. Comparison 3 Rotavac versus placebo, Outcome 17 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 3 Rotavac versus placebo

Outcome: 17 Subgroup analysis: severe cases of rotavirus diarrhoea by G and P types (up to 2 years follow-up)



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]	BIOSIS
1	rotavirus	rotavirus	rotavirus	rotavirus	rotavirus	rotavirus
2	diarrhoea	diarrhoea	ROTAVIRUS INFECTIONS	ROTAVIRUS	diarrhoea	diarrhoea
3	diarrhoea	diarrhoea	1 or 2	1 or 2	diarrhea	diarrhoea
4	gastroenteritis	gastroenteritis	diarrhoea	diarrhoea	gastroenteritis	gastroenteritis
5	2 or 3 or 4	2 or 3 or 4	gastroenteritis	gastroenteritis	2 or 3 or 4	2 or 3 or 4
6	1 and 5	1 and 5	4 or 5	4 or 5	1 and 5	1 and 5

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011); upper case: MeSH or EMTREE heading; lower case: free-text term.

Appendix 2. Trial type (efficacy or safety) and length of follow-up

Trial	Type: efficacy or safety	Follow-up time
RV1 Anh 2011-PHL	Safety	1 month after last dose
RV1 Anh 2011-VNM	Safety	1 month after last dose
RV1 Bernstein 1998-USA	Safety	1 month
RV1 Bernstein 1999-USA	Efficacy/Safety	2 years
RV1 Colgate 2016-BGD	Efficacy	1 year
RV1 Dennehy 2005-NA	Safety	10 to 12 months
RV1 GSK[021] 2007-PAN	Safety	1 month after dose 3
RV1 GSK[033] 2007-LA	Safety	1 month
RV1 GSK[041] 2007-KOR	Safety	2 months
RV1 GSK[101555] 2008-PHL	Safety	1 month

(*Continued*)

RV1 Kawamura 2011-JPN	Efficacy/Safety	Up to the age of 2 years
RV1 Kerdpanich 2010-THA	Safety	2 months after last dose
RV1 Kim 2012-KOR	Safety	1 month after last dose
RV1 Li 2013a-CHN	Safety	1 month
RV1 Li 2013b-CHN	Safety	1 month
RV1 Li 2014-CHN	Efficacy/Safety	2 years
RV1 Madhi 2010-AF	Efficacy/Safety	2 years
RV1 Narang 2009-IND	Safety	1 month
RV1 NCT00158756-RUS	Safety	1 year
RV1 Omenaca 2012-EU	Safety	At least 1 month after dose 2
RV1 Phua 2005-SGP	Efficacy/Safety	Until infant aged 18 months (ie 13 to 15 months)
RV1 Phua 2009-AS	Efficacy/Safety	3 years
RV1 Rivera 2011-DOM	Safety	17 weeks after each dose
RV1 Ruiz-Palac 06-LA/EU	Efficacy/Safety	9 to 10 months
RV1 Salinas 2005-LA	Efficacy/Safety	Up to 2 years
RV1 Steele 2008-ZAF	Safety	Up to 6 months
RV1 Steele 2010a-ZAF	Safety	31 days after each dose, 42 days after the last dose
RV1 Steele 2010b-ZAF	Safety	Up to 6 months
RV1 Tregnaghi 2011-LA	Efficacy/Safety	Up to age 1 year
RV1 Vesikari 2004a-FIN	Safety	8 to 30 days after each dose
RV1 Vesikari 2004b-FIN	Efficacy/Safety	1 and 2 years (both reported)
RV1 Vesikari 2007a-EU	Efficacy/Safety	1 and 2 years (plus 3 years in Finland)
RV1 Vesikari 2011-FIN	Safety	2 months

(*Continued*)

RV1 Ward 2006-USA	Safety	7 days after each vaccination; 3 to 5 weeks after dose 2
RV1 Zaman 2009-BGD	Safety	31 days
RV1 Zaman 2017-BGD	Effectiveness	2 years
RV5 Armah 2010-AF	Efficacy/Safety	Up to 43 days for safety outcomes, up to 21 months for efficacy outcomes
RV5 Block 2007-EU/USA	Efficacy/Safety	42 days for safety/immunogenicity; 1 year for efficacy
RV5 Ciarlet 2009-EU	Safety	42 days
RV5 Clark 2003-USA	Efficacy/Safety	1 year
RV5 Clark 2004-USA	Efficacy/Safety	1 year
RV5 Dhingra 2014-IND	Safety	1 month
RV5 Iwata 2013-JPN	Efficacy/Safety	25 months
RV5 Kim 2008-KOR	Safety	42 days
RV5 Lawrence 2012-CHN	Safety	2 weeks after last dose
RV5 Levin 2017-AF	Safety	1 month
RV5 Merck[009] 2005-USA	Safety	42 days
RV5 Mo 2017-CHN	Efficacy/Safety	2 years
RV5 Vesikari 2006a-FIN	Efficacy/Safety	1 to 3 years
RV5 Vesikari 2006b-INT	Efficacy/Safety	43 days for safety; 2 years for efficacy
RV5 Zaman 2010-AS	Efficacy/Safety	Up to 43 days for safety outcomes, up to 2 years for efficacy outcomes
VAC Bhandari 2006-IND	Safety	1 month
VAC Bhandari 2009-IND	Safety	12 weeks
VAC Bhandari 2014-IND	Efficacy/Safety	up to 2 years of age
VAC Chandola 2017-IND	Safety	1 year

Appendix 3. Efficacy outcome measures by trial

Trial	Rotavirus diarrhoea (any severity)			All-cause diarrhoea		ED visit	Hospitalization (all-cause)	All-cause death	Dropouts
	All	Severe	Hospital	All	Severe				
RV1 Anh 2011-PHL	X	-	-	X	-	-	-	X	X
RV1 Anh 2011-VNM	X	-	-	X	-	-	-	X	X
RV1 Bernstein 1998-USA	-	-	-	-	-	-	-	-	-
RV1 Bernstein 1999-USA	X	X	X	X[a]	-	X[a]	-	X	-
RV1 Colgate 2016-BGD	X	X	-	X	X	-	-	X	X
RV1 Dennehy 2005-NA	-	-	-	-	-	-	-	-	-
RV1 GSK[021] 2007-PAN	-	-	-	-	-	-	-	X	X
RV1 GSK[033] 2007-LA	-	-	-	-	-	-	-	X	X
RV1 GSK[041] 2007-KOR	X	-	-	-	-	-	-	X	X

(*Continued*)

RV1 GSK[10155 2008-PHL	X	-	-	-	-	-	-	X	X
RV1 Kawa-mura 2011-JPN	-	X	X	-	-	-	-	X	X
RV1 Kerd-panich 2010-THA	X	-	-	X	-	-	-	X	X
RV1 Kim 2012-KOR	X	-	-	X	-	-	-	X	X
RV1 Li 2013a-CHN	-	-	-	-	-	-	-	X	X
RV1 Li 2013b-CHN	-	-	-	-	-	-	-	-	-
RV1 Li 2014-CHN	X	X	X	X	X	-	-	X	X
RV1 Madhi 2010-AF	X	X	X	-	X	-	-	X	X
RV1 Narang 2009-IND	X	-	-	-	-	-	-	X	X
RV1 NCT00158 RUS	-	-	-	-	-	-	-	X	X
RV1 Omenaca 2012-EU	X	-	-	X	-	-	-	-	X

(*Continued*)

RV1 Phua 2009-AS	X[a]	X	X	X[a]	X		X[a]	X	
RV1 Phua 2005-SGP	X	X	X	X	X	X	X	X	X
RV1 Rivera 2011-DOM	X	-	-	X	-	-	-	-	X
RV1 Ruiz-Palac 06-LA/EU	X[a]	X	X	X[a]	X	-	X[a]	X	X[a]
RV1 Salinas 2005-LA	X	X	X	X	X[a]	-	X[a]	X	
RV1 Steele 2008-ZAF	-	-	-	-	-	-	-	X	X
RV1 Steele 2010a-ZAF	X	-	-	X	-	-	-	X	X
RV1 Steele 2010b-ZAF	X	X	-	-	-	-	-	X	X
RV1 Tregnaghi 2011-LA	-	X	-	-	X[a]	-	-	X	X
RV1 Vesikari 2004a-FIN	-	-	-	-	-	-	-	X[a]	X
RV1 Vesikari 2004b-FIN	X	X	X	X	-	-	-	X	X
RV1 Vesikari 2007a-EU	X	X	X	X[a]	X	X[a]	X[a]	-	-

(*Continued*)

RV1 Vesikari 2011-FIN	X	-	-	X	-	-	-	X	X
RV1 Ward 2006-USA	-	-	-	-	-	-	-	-	-
RV1 Zaman 2009-BGD	X	-	-	-	-	-	-	X	
RV1 Zaman 2017-BGD	-	X	-	-	-	-	-	-	-
RV5 Armah 2010-AF	X	X	-	X	X	-	-	X	X
RV5 Block 2007-EU/USA	X	X	-	-	-	-	-	X	X
RV5 Ciarlet 2009-EU	-	-	-	-	-	-	-	X	-
RV5 Clark 2003-USA	X	X[a]	-	-	-	-	-	-	X
RV5 Clark 2004-USA	X	X	-	-	-	-	-	-	X
RV5 Dhingra 2014-IND	-	-	-	-	-	-	-	-	X
RV5 Iwata 2013-JPN	X	X	-	-	-	-	-	X	X
RV5 Kim 2008-KOR	-	-	-	-	-	-	-	-	-

(*Continued*)

RV5 Lawrence 2012-CHN	-	-	-	-	-	-	-	X	X
RV5 Levin 2017-AF	-	-	-	-	-	-	-	X	X
RV5 Merck[009] 2005-USA	-	-	-	-	-	-	-	X	X
RV5 Mo 2017-CHN	-	-	-	-	-	-	-	X	X
RV5 Vesikari 2006a-FIN	X	X	-	-	-	-	-	X	X
RV5 Vesikari 2006b-INT	X	X	X	-	-	X[a]	X[a]	X	X
RV5 Zaman 2010-AS	X	X	-	-	X	-	-	X	X
VAC Bhandari 2006-IND	-	-	-	-	-	-	-	-	X
VAC Bhandari 2009-IND	-	-	-	-	-	-	-	-	-
VAC Bhandari 2014-IND	X	X	X	-	X	-	-	X	X
VAC Chandola 2017-	-	-	-	-	-	-	-	X	X

(*Continued*)

IND									

[a] Reported as an outcome measure in trial, but no data available for analysis.

Appendix 4. Safety and immunogenicity outcomes measures by trial

Trial	Safety			Immunogenicity	
	Serious AE	Reactogenicity	AE to discontinuation	Vaccine virus shedding	Seroconversion
RV1 Anh 2011-PHL	X	X	X	-	X
RV1 Anh 2011-VNM	X	X	X	-	X
RV1 Bernstein 1998-USA	X	X	X	X	X
RV1 Bernstein 1999-USA	-	X	-	X	X
RV1 Colgate 2016-BGD	-	-	-	-	-
RV1 Dennehy 2005-NA	X	X	X	X	X
RV1 GSK[021] 2007-PAN	X	X	X	X	X
RV1 GSK[033] 2007-LA	X	X	X	X	X
RV1 GSK[041] 2007-KOR	X	X	X	-	X
RV1 GSK[101555] 2008-PHL	X	X	X	X	X
RV1 Kawamura 2011-JPN	X	X	X	-	X
RV1 Kerdpanich 2010-THA	X	X	X	X	X
RV1 Kim 2012-KOR	X	X	X	-	X

(*Continued*)

RV1 Li 2013a-CHN	X	X	X	X	X
RV1 Li 2013b-CHN	-	-	-	-	-
RV1 Li 2014-CHN	X	X	X	-	X
RV1 Madhi 2010-AF	X	-	-	-	-
RV1 Narang 2009-IND	X	X	X	-	X
RV1 NCT00158756-RUS	X	-	X	-	X
RV1 Omenaca 2012-EU	X	X	-	-	X
RV1 Phua 2005-SGP	X	X	X[a]	X[a]	X
RV1 Phua 2009-AS	X	-	X	-	-
RV1 Rivera 2011-DOM	X	X	-	-	X
RV1 Ruiz-Palac 06-LA/EU	X	X	X	-	X[a]
RV1 Salinas 2005-LA	X	X	-	X	X
RV1 Steele 2008-ZAF	X	X	X	X	X
RV1 Steele 2010a-ZAF	X	X[a]	-	X	X
RV1 Steele 2010b-ZAF	X	X	X	X	X
RV1 Tregnaghi 2011-LA	X	-	X	-	X
RV1 Vesikari 2004a-FIN	X	X	X	X	X

(*Continued*)

RV1 Vesikari 2004b-FIN	X	X	X	-	X
RV1 Vesikari 2007a-EU	X	X	-	-	X
RV1 Vesikari 2011-FIN	X	X	X	X	X
RV1 Ward 2006-USA		X[a]	-	X	X[a]
RV1 Zaman 2009-BGD	X	X	-	X	X
RV1 Zaman 2017-BGD	X	-	-	-	-
RV5 Armah 2010-AF	X	X[a]	X	-	X
RV5 Block 2007-EU/USA	X	X	X	-	X
RV5 Ciarlet 2009-EU	X	X	-	-	X
RV5 Clark 2003-USA	X	X	X	X	X
RV5 Clark 2004-USA	X[a]	X	X	X	X
RV5 Dhingra 2014-IND	X	X	X	X	X
RV5 Iwata 2013-JPN	X[a]	X	X	-	-
RV5 Kim 2008-KOR	X	X[a]	-	-	X[a]
RV5 Lawrence 2012-CHN	X	X[a]	X	X	-
RV5 Levin 2017-AF	X	X	X	X	X
RV5 Merck[009] 2005-USA	X	X	X	-	-

(*Continued*)

RV5 Mo 2017-CHN	X	X	X	-	-
RV5 Vesikari 2006a-FIN	X	X	X	-	X
RV5 Vesikari 2006b-INT	X	X	X[a]	-	X
RV5 Zaman 2010-AS	X	X[a]	X	-	X[a]
VAC Bhandari 2006-IND	X	X	-	X	-
VAC Bhandari 2009-IND	X	X	-	X	X
VAC Bhandari 2014-IND	X	-	-	-	X
VAC Chandola 2017-IND	X	-	-	-	X

AE: adverse events.
[a] Reported as an outcome measure in trial, but no data available for analysis.

Appendix 5. Trial location

Trial	Year	Location	Sites	Country mortality rate	WHO mortality strata	Region
RV1 Anh 2011-PHL	2007	Philippines	1	Low-mortality	B	Asia
RV1 Anh 2011-VNM	2007	Vietnam	11	Low-mortality	B	Asia
RV1 Bernstein 1998-USA	1998	USA	1	Low-mortality	A	North America
RV1 Bernstein 1999-USA	1999	USA	2	Low-mortality	A	North America
RV1 Colgate 2016-BGD	2014	Bangladesh	1	High-mortality	D	Asia

(*Continued*)

RV1 Dennehy 2005-NA	2005	USA and Canada	41	Low-mortality	A	North America
RV1 GSK[021] 2007-PAN	2007	Panama	1	Low-mortality	B	Latin America
RV1 GSK[033] 2007-LA	2007	Colombia, Mexico, and Peru	(2 in Colombia, 1 in Mexico, and 4 in Peru)	High-mortality[a]	B, D	Latin America
RV1 GSK[041] 2007-KOR	2007	South Korea	6	Low-mortality	B	Asia
RV1 GSK[101555] 2008-PHL	2008	Philippines	1	Low-mortality	B	Asia
RV1 Kawamura 2011-JPN	2009	Japan	18	Low-mortality	A	Asia
RV1 Kerdpanich 2010-THA	2005	Thailand	2	Low-mortality	B	Asia
RV1 Kim 2012-KOR	2010	Republic of Korea	19	Low-mortality	B	Asia
RV1 Li 2013a-CHN	2010	China	1	Low-mortality	B	Asia
RV1 Li 2013b-CHN	2010	China	1	Low-mortality	B	Asia
RV1 Li 2014-CHN	2012	China	4	Low-mortality	B	Asia
RV1 Madhi 2010-AF	2010	South Africa and Malawi	2	High-mortality	E	Africa
RV1 Narang 2009-IND	2009	India	4	High-mortality	D	Asia
RV1 NCT00158756-RUS	2006	Russian Federation	9	Low-mortality	C	Europe
RV1 Omenaca 2012-EU	2008	France, Poland, Portugal,	Multiple sites in each country	Low-mortality	A, B	Europe

(*Continued*)

		and Spain				
RV1 Phua 2005-SGP	2005	Singapore	8	Low-mortality	A	Asia
RV1 Phua 2009-AS	2009	Hong Kong, Singapore, and Taiwan	3	Low-mortality	A	Asia
RV1 Rivera 2011-DOM	2008	Dominican Republic	1	Low-mortality	B	Latin America
RV1 Ruiz-Palac 06-LA/EU	2006	Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	Multiple	Low-mortality[b]	A, B, D	Latin America/ Europe
RV1 Salinas 2005-LA	2005	Brazil, Mexico, and Venezuela	3	Low-mortality	B	Latin America
RV1 Steele 2008-ZAF	2007	South Africa	1	High-mortality	E	Africa
RV1 Steele 2010a-ZAF	2008	South Africa	5	High-mortality	E	Africa
RV1 Steele 2010b-ZAF	2007	South Africa	7	High-mortality	E	Africa
RV1 Tregnaghi 2011-LA	2008	Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama	Multiple sites in each country	Low-mortality	B	Latin America
RV1 Vesikari 2004a-FIN	2004	Finland	2	Low-mortality	A	Europe
RV1 Vesikari 2004b-FIN	2004	Finland	6	Low-mortality	A	Europe
RV1 Vesikari 2007a-EU	2007	Czech Republic, Finland, France, Germany, Italy, and Spain	98	Low-mortality	A	Europe

(*Continued*)

RV1 Vesikari 2011-FIN	2005	Finland	5	Low-mortality	A	Europe
RV1 Ward 2006-USA	2006	USA	2	Low mortality	A	North America
RV1 Zaman 2009-BGD	2005	Bangladesh	1	High-mortality	D	Asia
RV1 Zaman 2017-BGD	2011	Bangladesh	142	High-mortality	D	Asia
RV5 Armah 2010-AF	2009	Ghana, Kenya, and Mali	3	High-mortality	D, E	Africa
RV5 Block 2007-EU/USA	2007	Finland and USA	30	Low-mortality	A	Europe and North America
RV5 Ciarlet 2009-EU	2008	Austria, Belgium, and Germany	26	Low-mortality	A	Europe
RV5 Clark 2003-USA	2003	USA	19	Low-mortality	A	North America
RV5 Clark 2004-USA	2004	USA	10	Low-mortality	A	North America
RV5 Dhingra 2014-IND	2012	India	2	High-mortality	D	Asia
RV5 Iwata 2013-JPN	2009	Japan	32	Low-mortality	A	Asia
RV5 Kim 2008-KOR	2008	South Korea	8	Low-mortality	B	Asia
RV5 Lawrence 2012-CHN	2010	China	Not reported	Low-mortality	B	Asia
RV5 Merck[009] 2005-USA	2005	USA	10	Low-mortality	A	North America
RV5 Mo 2017-CHN	2015	China	5	Low-mortality	B	Asia
RV5 Vesikari 2006a-FIN	2006	Finland	4	Low-mortality	A	Europe

(*Continued*)

RV5 Vesikari 2006b-INT	2006	Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and USA	356	Low-mortality[b]	A, B, D	Asia, Caribbean, Europe, Latin America, North America
RV5 Zaman 2010-AS	2009	Bangladesh and Vietnam	Multiple	High-mortality[a]	B, D	Asia
VAC Bhandari 2006-IND	2005	India	1	High-mortality	D	Asia
VAC Bhandari 2009-IND	2006-8	India	1	High-mortality	D	Asia
VAC Bhandari 2014-IND	2011-13	India	3	High-mortality	D	Asia
VAC Chandola 2017-IND	2014-15	India	1	High-mortality	D	Asia

[a]This study was conducted mainly in high-mortality countries, but also in low-mortality countries.
[b]This study was conducted mainly in low-mortality countries, but also in high-mortality countries.

Appendix 6. Vaccine schedules

Trial	Number of doses	Time between doses (weeks)	Number of arms: vaccine/placebo	Infant vaccination status	Note
RV1 Anh 2011-PHL	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of	Compares different schedules: (1) vaccine dose at month 1 and 2, and placebo at day 0; and (2) vaccine dose at day 0 and month 2, and placebo at month 1

(*Continued*)

				Immunization (EPI) in the Philippines	
RV1 Anh 2011-VNM	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in Vietnam	Compares different schedules: (1) vaccine dose at day 0 and month 1, and placebo at month 2; and (2) vaccine dose at day 0 and month 2, and placebo at month 1
RV1 Bernstein 1998-USA	2	6 to 10	1/1	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks	-
RV1 Bernstein 1999-USA	2	6 to 10	1/1	Other vaccines separated from the trial vaccines by at least 2 weeks	-
RV1 Colgate 2016-BGD	2	7	1/1 (no RV1)	Alongside Rotarix at 10 and 17 weeks of age the polio vaccine intervention was the administration of an injected, inactivated polio vaccine (IPV) dose replacing the 4th dose of tOPV at 39 weeks of age. Study children also received all standard EPI vaccines (BCG at birth; pentavalent vaccine (DPT, HepB, Hib) at 6, 10, and 14 weeks; bivalent	RV1 plus polio vaccine (IPV), observational control group only

(*Continued*)

				Measles-Rubella at 40 weeks; and monovalent Measles at 65 weeks)	
RV1 Dennehy 2005-NA	2	7	2/1	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular pertussis, inactivated poliovirus, *H influenzae* type b, and *S pneumoniae* conjugate vaccines for participants in USA or with a diphtheria-tetanus-acellular pertussis/inactivated poliovirus/*H influenza* type b combination vaccine for participants in Canada "Routine hepatitis B vaccinations were administered according to local practice."	2 different PFUs compared
RV1 GSK[021] 2007-PAN	3	8	2/2	Use of other vaccines not mentioned	Licensed formulation versus modified formulation
RV1 GSK[033] 2007-LA	2	8	3/1	Use of other vaccines not mentioned	3 'Lots' of RV1 vaccine compared
RV1 GSK[041] 2007-KOR	2	8	1/1	*H influenzae* type b vaccine administered concomitantly along with the 2 doses of vaccine/placebo and at 2 months after dose 2; other routine childhood vaccines were to be given at least 14 days before trial vaccine/placebo	-

(*Continued*)

RV1 GSK[101555] 2008-PHL	2	8	2/2	No mention of whether infants received other vaccines	Data from the lyophilized formulation, which is not yet approved or marketed, are not reported
RV1 Kawamura 2011-JPN	2	4	1/1	Combined diphtheria and tetanus toxoids and acellular pertussis (DTPa) and Hepatitis B (HBV) vaccines were allowed to be co-administered along with RV1 vaccine/placebo	-
RV1 Kerdpanich 2010-THA	2	8	3/2	Diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *H influenzae* type b combination vaccine (*Infanrix*™-IPV/Hib) at 2 and 4 months of age and diphtheria toxoid, tetanus toxoid, acellular pertussis, hepatitis B, inactivated polio and*H influenzae* type b combination vaccine (*Infanrix hexa*^{TM}) at 6 months of age	Compares: regular vaccine reconstituted in buffer; vaccine reconstituted in water; vaccine stored above recommended temperature; placebo reconstituted in water; placebo reconstituted in buffer
RV1 Kim 2012-KOR	2	4	1/1	Routine childhood vaccines as recommended by the local vaccination schedule were allowed to be administered concomitantly with RIX4414/placebo. These vaccines included the combined diphthe-	-

(*Continued*)

				ria-tetanus-acellular pertussis vaccine, *Hemophilus influenzae* type b vaccine, inactivated poliovirus vaccine and pneumococcal vaccine. The infants had received the BCG vaccine and 2 doses of hepatitis B vaccine prior to study enrolment	
RV1 Li 2013a-CHN	1	-	1/1	Children were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo	Child arm (2 - 6 years of age) of the same study as RV1 Li 2013b-CHN
RV1 Li 2013b-CHN	1	-	1/1	Infants were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 days between the administration of routine vaccines and the study vaccine or placebo	Infant arm (6-16 weeks of age) of the same study as RV1 Li 2013a-CHN
RV1 Li 2014-CHN	2	4	2/2	As part of the routine childhood vaccination according to the EPI	-

(*Continued*)

				recommendations in China, participants also received 3 doses of Infanrix™ vaccine and 3 doses of the oral poliovirus vaccine. The Infanrix™ and the OPV vaccines were administered independently of (Sub-cohort 1) or concomitantly with (Sub-cohort 2) the Rotarix™ vaccine. When administered concomitantly, participants received the 3 doses of Infanrix™ vaccine at months 1, 2 and 3, and the 3 doses of the OPV vaccine at Day 0, Month 1 and Month 2	
RV1 Madhi 2010-AF	2 or 3	5 to 10	2/1	All participants received routine infant vaccinations according to EPI recommendations	-
RV1 Narang 2009-IND	2	8	1/1	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *H influenzae* type b, and oral poliovirus vaccine) were administered at 6, 10, and 14 weeks of age (given with a 2-week separation from the first and subsequent dose of the RV1 vaccine or placebo)	-

(*Continued*)

RV1 NCT00158756-RUS	3	6	5	GlaxoSmithKline (GSK) Biologicals' Tritanrix™HepB and GSK Biologicals Kft's DTPwHBV vaccines as compared to concomitant administration of Commonwealth Serum Laboratory's (CSL's) DTPw (Triple Antigen™) and GSK Biologicals' HBV (Engerix™B), when coadministered With GSK Biologicals' Oral Live Attenuated Human Rotavirus (HRV) vaccine, to healthy infants at 3, 4½ and 6 months of age, after a birth dose of Hepatitis B vaccine	Hep B and DTPw-HBV vaccines in combination with other vaccines/ placebo were compared in the study arms
RV1 Omenaca 2012-EU	2	4 or 8	1/1	All participants received routine infant vaccinations in accordance with the local National Plan of Immunization schedule in each of the respective participating countries	-
RV1 Phua 2005-SGP	2	4	3/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *H influenzae* type b co-administered with interventions	3 different PFUs compared

(*Continued*)

RV1 Phua 2009-AS	2	6 to 10	1/1	Infants received other routine paediatric immunizations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis (DTPa) - inactivated poliovirus [IPV] and *H influenzae* type B (Hib) vaccine and hepatitis B vaccine (HBV)) during the study period according to local schedules. Almost all infants received BCG dose at birth. If oral polio vaccine (OPV) was given as part of the routine schedule in the participating countries, a time interval of 2 weeks was observed between the OPV doses and RIX4414 vaccine/placebo doses	-
RV1 Rivera 2011-DOM	2	7	1/1	All infants received 3 doses of combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and *H influenzae* vaccine.	1 complimentary dose of RV1 was administered to all infants enrolled in this study (both study groups) who were aged < 6 months at Visit 3 (Week 13) as a benefit to the placebo group for participation in the study
RV1 Ruiz-Palac 06-LA/EU	2	4 or 8	1/1	Routine immunizations according to local regulations; oral poliovirus vaccination at least 2 weeks before or after	-

(*Continued*)

				rotavirus vaccine	
RV1 Salinas 2005-LA	2	8	3/1	Oral polio vaccine given after 2 weeks, not together with RV1	3 different PFUs compared Main publication did not report that the trial included 2 subsets: 2 doses of human rotavirus or placebo subset: these participants received 2 oral doses of RV1 vaccine or placebo according to a 0, 2 months schedule, and routine vaccinations (DTPw- Hepatitis B vaccine (HBV) + Hib vaccine) at a 0, 2, and 4 months schedule 3 doses of RV1 or placebo subset: these participants received 3 oral doses of RV1 vaccine or placebo, and routine vaccinations (DTPw-HBV + Hib vaccine) concomitantly with each dose of human rotavirus vaccine and placebo at a 0, 2, and 4 months schedule
RV1 Steele 2008-ZAF	2	4	3/1	RV1 plus (1) oral polio vaccine (OPV) + diphtheria-tetanus-acellular pertussis/*H influenzae* type b (DTPA/HIB) vaccine; (2) OPV placebo + diphtheria-tetanus-acellular pertussis inactivated	Compares different co-administration combinations (see previous column)

(*Continued*)

				polio-*H influenzae* type b (DTPA-IPV/HIB) vaccine; or (3) OPV + DTPA/HIB vaccine	
RV1 Steele 2010a-ZAF	3	4	1/1	RV1 vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and *H influenzae* type b vaccine (TritanrixHepB-Hib) and OPV (PolioSabin)	For infants who developed clinical symptoms of HIV (WHO stages III or IV disease) any time after enrolment, access to antiretroviral therapy (cotrimoxazole) according to the South African national guidelines was facilitated. Infants who needed treatment were referred to antiretroviral therapy centres by the investigators
RV1 Steele 2010b-ZAF	2 or 3	4	2/1	Infants received routine vaccinations according to the local EPI schedule in South Africa. BCG and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, *H influenzae* type b, and OPV) were administered concomitantly with the study vaccine	Compares number of doses (2 or 3)
RV1 Tregnaghi 2011-LA	2	4 or 8	1/1	All participants received routine infant vaccinations (Hepatitis B vaccine), diphtheria-tetanus-acellular pertus-	-

(*Continued*)

				sis, poliovirus, and *H influenzae* type b) according to EPI recommendations in each country. First 2 doses of routine EPI vaccinations were co-administered with the RV1 vaccine or placebo doses; the 3ird routine EPI vaccination was administered 1 to 2 months later according to the national plan of immunization in each country	
RV1 Vesikari 2004a-FIN	2	8	3/1	Infant routine vaccinations were separated from the study vaccines by 2 weeks	3 different PFUs compared
RV1 Vesikari 2004b-FIN	2	8	1/1	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *H influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks	-
RV1 Vesikari 2007a-EU	2	4 or 8	1/1	Concomitant vaccines included 7 valent pneumococcal polysaccharide conjugate vaccine (Prevenar) and meningococcal group c conjugate vaccine (Meningitec); Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, po-	-

(*Continued*)

				lio virus, and *H influenzae* type b vaccines were co-administered	
RV1 Vesikari 2011-FIN	2	4	2/2	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine	Compares liquid and lyophilized vaccine formulations
RV1 Ward 2006-USA	2	4	2/1	Not specified	2 different PFUs compared
RV1 Zaman 2009-BGD	2	-	2/2	All children in the study received the standard EPI vaccines starting at 6 weeks of age. Oral polio vaccine (OPV) co-administered in trial: either concomitantly with RV1 or 15 days before RV1	Compared RV1 plus oral polio vaccine with RV1 alone
RV1 Zaman 2017-BGD	2	4	1/1 (no RV1 vaccine)	HRV was scheduled to be given along with other standard infant vaccines including OPV at the DTP1 and DTP2 immunization visits, recommended in Bangladesh to occur at 6 and 10 weeks of age	Cluster randomised trial
RV5 Armah 2010-AF	3	4	1/1	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age	-

(*Continued*)

RV5 Block 2007-EU/USA	3	4 to 10	1/1	Use of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo was an exclusion criterion; administration of other vaccines permitted	-
RV5 Ciarlet 2009-EU	3	4 to 6	1/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H influenzae* type b co-administered	-
RV5 Clark 2003-USA	3	6 to 8	1/1	Children that had recently received oral polio vaccine were excluded from the study	Breastfed; infants in the vaccine control group (Group 1) received the reassortants as administered in previous studies within 30 mins of feeding Enfamil formula (30 ml) or Mylanta Double Strength (0.5 ml/kg). Infants in a corresponding placebo group (Group 2) were prefed as in Group 1
RV5 Clark 2004-USA	3	6 to 8	1/1	Receipt of any other vaccines within 14 days was not allowed	-
RV5 Dhingra 2014-IND	3	4	4/1	Infants in Cohort 2 concomitantly received a combined DTPw-HB-Hib pentavalent vaccine and Trivalent Oral Polio Vaccine	BRV-TV at 3 different concentrations, compared to RV5 or placebo

(*Continued*)

RV5 Iwata 2013-JPN	3	4 to 10	1/1	No information about use of other vaccines	-
RV5 Kim 2008-KOR	3	4 to 10	1/1	Infants excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not restricted	-
RV5 Lawrence 2012-CHN	3	4-10	1/1	Other live vaccines 14 days before or after study vaccine were not allowed	-
RV5 Levin 2017-AF	3	4-10	1/1	Enrolment was closed in participating countries when RV1 was added to national vaccine schedules	-
RV5 Merck[009] 2005-USA	3	4 to 10	1/1	Infants were excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not reported	-
RV5 Mo 2017-CHN	3	4	2/2	The routine China EPI vaccines (oral poliovirus vaccine and diphtheria, tetanus, and acellu-	-

(*Continued*)

				lar pertussis vaccine) either staggered or concomitantly with RV5 or placebo	
RV5 Vesikari 2006a-FIN	3	4 to 8	3/1	Licensed vaccines could be administered throughout the study, but were not given on the same day as study vaccine; inactivated poliovirus vaccine was exclusively used in Finland at the time of the study	Compares different RV5 components: G1-4, P1A; G1-4; and P1A
RV5 Vesikari 2006b-INT	3	4 to 10	1/1	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of participants in the USA (U.A. concomitant use cohort), Merck also provided the licensed paediatric vaccines that were administered concomitantly (same day) with RV5 or placebo, which included Comvax, Infanrix, Ipol, and Prevnar	-
RV5 Zaman 2010-AS	3	4	1/1	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age	-
VAC Bhandari 2006-IND	1	-	1/1 (/1)	Infants were vaccinated with DPT,	Included an additional

(*Continued*)

				Hep B and OPV separately from rotavirus vaccine	vaccine arm for a rotavirus vaccine candidate (I321) that was not included for anaysis in this review
VAC Bhandari 2009-IND	3	4	2/2	Infants received 3 doses of DTP; OPV; and Hep B at 6, 10, and 14 weeks of age; Rotavac was administered at 8, 12, and 16 weeks of age	Randomized participants to high- (1×10^5 ffu) and low-dose (1×10^4 ffu) vaccine arms which were combined in this review
VAC Bhandari 2014-IND	3	4	1/1	Other childhood vaccines (DTPw, Hib, Hep B, and OPV) given concurrently	-
VAC Chandola 2017-IND	3	4-8	3/1	Co-administered with EPI vaccines: OPV and combined DPT, HepB and Hib	Randomized participants to 3 vaccine production lots as well as to placebo; we combined the different production lot arms in our analyses

BCG: Bacille Calmette Guérin; EPI: Extended Programme of Immunization; FFU: focus-forming unit;*H influenzae: Haemophilus influenzae*; PFU: plaque-forming unit.

Appendix 7. Methods to collect adverse event data

Trial	Passive or active
RV1 Anh 2011-PHL	Not reported
RV1 Anh 2011-VNM	Not reported
RV1 Bernstein 1998-USA	Passive
RV1 Bernstein 1999-USA	Passive and active
RV1 Colgate 2016-BGD	Passive

(*Continued*)

RV1 Dennehy 2005-NA	Passive and active
RV1 GSK[021] 2007-PAN	Not reported
RV1 GSK[033] 2007-LA	Not reported
RV1 GSK[041] 2007-KOR	Not reported
RV1 GSK[101555] 2008-PHL	Not reported
RV1 Kawamura 2011-JPN	Not reported
RV1 Kerdpanich 2010-THA	Passive
RV1 Kim 2012-KOR	Passive
RV1 Li 2013b-CHN	Passive
RV1 Li 2014-CHN	Not reported
RV1 Madhi 2010-AF	Active
RV1 Narang 2009-IND	Passive
RV1 NCT00158756-RUS	Not reported
RV1 Omenaca 2012-EU	Not reported
RV1 Phua 2005-SGP	Passive
RV1 Phua 2009-AS	Passive
RV1 Rivera 2011-DOM	Passive
RV1 Ruiz-Palac 06-LA/EU	Active
RV1 Salinas 2005-LA	Passive
RV1 Steele 2008-ZAF	Not reported
RV1 Steele 2010a-ZAF	Active and passive
RV1 Steele 2010b-ZAF	Not reported
RV1 Tregnaghi 2011-LA	Not reported
RV1 Vesikari 2004a-FIN	Passive

(*Continued*)

RV1 Vesikari 2004b-FIN	Passive
RV1 Vesikari 2007a-EU	Passive and active
RV1 Vesikari 2011-FIN	Passive
RV1 Ward 2006-USA	Not reported
RV1 Zaman 2009-BGD	Passive and active
RV1 Zaman 2017-BGD	Not reported
RV5 Armah 2010-AF	Active
RV5 Block 2007-EU/USA	Passive and active
RV5 Ciarlet 2009-EU	Passive and active
RV5 Clark 2003-USA	Passive and active
RV5 Clark 2004-USA	Passive and active
RV5 Dhingra 2014-IND	Passive and active
RV5 Iwata 2013-JPN	Passive
RV5 Kim 2008-KOR	Passive
RV5 Lawrence 2012-CHN	Not reported
RV5 Levin 2017-AF	Active
RV5 Merck[009] 2005-USA	Not reported
RV5 Mo 2017-CHN	Passive
RV5 Vesikari 2006a-FIN	Passive and active
RV5 Vesikari 2006b-INT	Active
RV5 Zaman 2010-AS	Active and passive
VAC Bhandari 2006-IND	Passive and active
VAC Bhandari 2009-IND	Passive and active
VAC Bhandari 2014-IND	Passive and active
VAC Chandola 2017-IND	Active

Appendix 8. Ongoing studies: vaccine and location

Trial	Rotavirus vaccine	Location	
		Region	Country
OTHER ACTRN12610000525088	RV3-BB	Oceania	Australia
OTHER CTRI/2015/07/006034	Rotasiil (Serum Institute of India Ltd.)	Asia	India
OTHER CTRI/2015/12/006428	RV1; Rotavac (Bharat)	Asia	India
OTHER NCT01061658	BRV-TV	Asia	India
OTHER NCT02153866	RV vaccine, type not reported	Asia	China
OTHER NCT02193061	RV1; RV5	America	Mexico
OTHER NCT02542462	RV1; RV5	America	USA
OTHER NCT02646891	Trivalent P2VP8	Africa	South Africa
OTHER NCT02847026	RV1; RV5	Asia	Bangladesh
OTHER NCT03462108	Rotavirus vaccine (Bio Farma)	Asia	Indonesia
OTHER NCT03483116	RV3-BB	Africa	Malawi
RV1 ISRCTN86632774	RV1	Africa	South Africa
RV1 NCT02941107	RV1	Oceania	Australia
RV1 Tatochenko 2008	RV1	Not reported	Not reported
RV5 NCT02728869	RV5	Asia	Bangladesh

Appendix 9. Deaths[a]: from published trials and from communication with trial authors

Vaccine	Trial	No. of deaths				Cause of death
		Vaccine	Placebo	Unclear	Total	
RV1	RV1 Anh 2011-PHL	1	0	0	1	*Salmonella* gastroenteritis

(*Continued*)

	RV1 Anh 2011-VNM	0	0	0	0	-
	RV1 Bernstein 1998-USA	0	0	0	0	-
	RV1 Bernstein 1999-USA	0	0	1 (1)	1	Pneumococcal sepsis
	RV1 Colgate 2016-BGD	1	1	0	2	Reasons not reported
	RV1 GSK[021] 2007-PAN	0	0	0	0	-
	RV1 Tregnaghi 2011-LA	10	2	0	12	Meningitis bacterial (1 vaccine, 1 placebo), pneumonia (3 vaccine), aortic valve stenosis (1 vaccine) , bronchiolitis (1 vaccine), dengue fever (1 vaccine), endocarditis bacterial (1 vaccine), intussusception (1 vaccine), multi-organ failure (1 placebo), respiratory failure (1 vaccine), sepsis (2 vaccine)
	RV1 GSK[033] 2007-LA	3	0	0	3	Gastroenteritis (1 vaccine), bronchopneumonia (1 vaccine), aspiration (1 vaccine)
	RV1 GSK[041] 2007-KOR	0	0	0	2	Not reported
	RV1 GSK[101555] 2008-PHL	0	0	0	0	-
	RV1 Kawamura 2011-JPN	0	0	0	0	-
	RV1 Kerdpanich 2010-THA	0	0	0	0	-
	RV1 Kim 2012-KOR	0	0	0	0	-
	RV1 Li 2013a-CHN	0	0	0	0	-
	RV1 Li 2013b-CHN	0	0	0	0	-
	RV1 Li 2014-CHN	6	7	0	13	Vaccine (6): Asphyxia, Drowning, Central nervous system infection, Bronchopneumonia, Cortical dys-

(*Continued*)

						plasia, Intracranial Haemorrhage, Asphyxia, Meningitis, Multi-organ failure, Hemotophagic histiocytosis, Acute lymphocytic leukemia, Multi-organ failure Placebo (7): Diarrhea, Multi-organ failure, Congenital heart disease, Respiratory failure, brain contusion, subarachnoid hemorrhage, skull fracture, cerebral hematoma, and brain herniation
	RV1 Madhi 2010-AF	83	43	0	126	Reasons not stated
	RV1 Narang 2009-IND	0	0	0	0	-
	RV1 NCT00158756-RUS	0	0	0	0	-
	RV1 Phua 2005-SGP	3	0	0	3	Leukaemia (1 vaccine); accident-induced subarachnoid haemorrhage (1 vaccine); cardiorespiratory failure after acute viral pneumonitis (1 vaccine)
	RV1 Phua 2009-AS	1	3	0	4	Aspiration and metabolic disorder, adenoviral pneumonia, interstitial pneumonia, and sudden infant death syndrome (not stated which group)
	RV1 Rivera 2011-DOM	0	0	0	0	-
	RV1 Ruiz-Palac 06-LA/EU	56	43	0	99	Diarrhoea (4 vaccine, 2 placebo); pneumonia (16 vaccine, 6 placebo); other causes not mentioned
	RV1 Salinas 2005-LA	2	1	0	3	Generalized visceral congestion (1 placebo); sepsis (1 vaccine); automobile accident (1 vaccine)
	RV1 Steele 2008-ZAF	3	5	0	8	Bronchopneumonia (1 placebo), pneumonia (2 vaccine, 2 placebo), hepatic steatosis (1 placebo), brain oedema (1 vaccine, 1 placebo)
	RV1 Steele 2010a-ZAF	6	9	0	15	Bronchopneumonia, sepsis, and gastroenteritis were the most common causes
	RV1 Steele 2010b-ZAF	3	0	0	3	Bronchopneumonia and gastroenteritis (3 vaccines)
	RV1 Vesikari 2004b-FIN	0	0	0	0	-

(*Continued*)

	RV1 Vesikari 2007a-EU	0	0	0	0	-
	RV1 Vesikari 2011-FIN	0	0	0	0	-
	RV1 Zaman 2009-BGD	1	0	0	1	-
RV5	RV5 Armah 2010-AF	76	82	0	158	Gastroenteritis (20 vaccine, 16 placebo); 11 deaths occurred in identified HIV-infected participants in Kenya; sudden infant death syndrome (1 placebo); other causes not mentioned
	RV5 Block 2007-EU/USA	1	0	0	1	Sudden infant death syndrome (1 vaccine)
	RV5 Ciarlet 2009-EU	0	0	0	0	-
	RV5 Iwata 2013-JPN	0	0	0	0	-
	RV5 Lawrence 2012-CHN	0	0	0	0	-
	RV5 Levin 2017-AF	1	2	0	3	Pneumonia
	RV5 Merck[009] 2005-USA	0	0	0	0	-
	RV5 Mo 2017-CHN	0	1	0	1	Reasons not reported
	RV5 Vesikari 2006a-FIN	0	0	0	0	-
	RV5 Vesikari 2006b-INT	24	20	0	44	Sudden infant death syndrome (7 vaccine and 7 placebo), other causes not mentioned
	RV5 Zaman 2010-AS	3	4	0	7	Not all causes reported, most common causes were drowning and sepsis
Rotavac	VAC Bhandari 2014-IND	30	18	0	48	The most common causes of death were infection and infestations followed by general disorders and administration site conditions. Days after vaccination not reported. None were considered to be vaccine-related

(*Continued*)

	VAC Chandola 2017-IND	5	0	0	5	Cause of death: sepsis and aspiration (79 - 141 days after Rotavac vaccination), unexplained sudden death (3 days after Rotavac vaccination). None were considered to be vaccine-related

[a] Numbers in brackets are the number of deaths reported by the trial authors following personal communication with them, i.e. they are not in the published trial reports.

Appendix 10. Other licensed rotavirus vaccines in use

Vaccine	Vaccination schedule	Vaccine antigens	Manufacturer	License information
Lanzhou lamb rotavirus (LLR)	1 dose annually for children 2 months to 3 years and one booster dose at 3 to 5 years	Monovalent, live-attenuated lamb G10 P[12] strain	Lanzhou Institute of Biological Products, China	2000 (China), nationally licenced
Rotasiil, Bovine rotavirus-pentavalent vaccine (BRV-PV)	3 doses at 6, 10 and 14 weeks	Pentavalent, bovine-human reassortant vaccine containing serotypes G1, G2, G3, G4 and G9	Serum Institute of India Ltd.	2017 (India), nationally licenced
Rotavin-M1	2 doses Minimum 6 weeks given at least 30 days apart	Monovalent, live-attenuated human G1 P[8] strain	Polyvac, Vietnam	2007 (Vietnam), nationally licenced

WHAT'S NEW

Date	Event	Description
19 March 2019	New search has been performed	We amended the protocol to include only vaccines prequalified for use by the World Health Organization (WHO). We included 14 new studies from the April 2018 search, including four studies on a new vaccine (Rotavac). Nicholas Henschke joined the author team
19 March 2019	New citation required but conclusions have not changed	This is the fourth update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines that have been prequalified for global use by the WHO (WHO 2018). In the previous versions of this review we included any rotavirus vaccine in use

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 5, 2010

Date	Event	Description
10 May 2012	New search has been performed	No new trials were identified from the updated May 2012 search
10 May 2012	New citation required but conclusions have not changed	Review updated to incorporate different country mortality strata and outcomes changed to reflect the different rotavirus vaccines' efficacy and safety in countries with different mortality rates
8 January 2012	New search has been performed	Review updated to include nine trials identified in a new literature search, which was conducted in October 2011 (MEDLINE via PubMed) and June 2011 (other databases)
11 November 2011	New citation required but conclusions have not changed	Hanna Bergman and Sukkrti Nagpal joined the author team.
10 May 2010	Amended	Minor typographical errors corrected.
2 February 2010	New citation required and conclusions have changed	A new search on 2 February 2010 identified 9 new potentially relevant studies. We independently assessed these studies and incorporated data from the eligible trials into the review
21 July 2009	New search has been performed	The original rotavirus vaccines review (Soares-Weiser 2004) was split into two reviews: rotavirus vaccines in use (this review); and other rotavirus vaccines, including those no longer in use or in development (Soares-Weiser 2004). This involved a new search, revised inclusion criteria, updated review methods. All data from those trials also included in the original review were re-extracted. New authors joined the review team for this review

CONTRIBUTIONS OF AUTHORS

Hanna Bergman: created 'Summary of findings' tables, screened references, extracted, input and analyzed data, including 'Risk of bias' assessments, and updated the review text for the 2012 update and this review update.

Nigel Cunliffe: provided guidance on inclusion criteria, review structure and content; and commented on 'Summary of findings' and review drafts. He updated the Background and Discussion sections, and commented on 'Summary of findings' and review drafts for this review update.

Femi Pitan: piloted data extraction form, provided guidance on inclusion criteria, and helped write the Background. He commented on review drafts for this review update.

Nicholas Henschke: screened abstracts and full texts, extracted and analyzed data, assessed risk of bias, and reviewed 'Summary of findings' tables and the manuscript for this review update.

Karla Soares-Weiser: updated review methods, designed data forms, took the lead in extracting and analyzing data, including 'Risk of bias' assessments; and wrote the review. She commented on review drafts for this review update.

DECLARATIONS OF INTEREST

Hanna Bergman: received payment for work on this review from Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response was contracted by the WHO to produce a systematic review upon which a part of this review update is based (see 'Sources of support').

Nigel Cunliffe: received research grant support and honoraria for participation in Data Safety Monitoring Boards from GlaxoSmithKline Biologicals.

Femi Pitan: none known.

Nicholas Henschke: received payment for work on this review from Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response was contracted by the WHO to produce a systematic review upon which a part of this review update is based (see 'Sources of support').

Karla Soares-Weiser: has received payment in the past (not for the current update) to conduct this review from the DFID UK via the Effective Health Care Research Programme Consortium (see 'Sources of support').

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.

Project number 300342-104

- Initiative for Vaccine Research (IVR), World Health Organization (WHO), Switzerland.

A large part of this review update is based on a systematic review of RCTs and observational studies that was funded by the IVR department, WHO

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is the fourth update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines that have been prequalified for global use by the WHO (WHO 2018). In the previous versions of this review we included any rotavirus vaccine in use (Soares-Weiser 2004; Soares-Weiser 2010; Soares-Weiser 2012a; Soares-Weiser 2012b).

INDEX TERMS

Medical Subject Headings (MeSH)

Diarrhea [*prevention & control; virology]; Diarrhea, Infantile [*prevention & control; virology]; Randomized Controlled Trials as Topic; Rotavirus Infections [*prevention & control]; Rotavirus Vaccines [*therapeutic use]; Vaccines, Attenuated [therapeutic use]

MeSH check words

Humans; Infant; Infant, Newborn

A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years

Laura M. Lamberti, PhD, MHS, Sania Ashraf, MPH, Christa L. Fischer Walker, PhD, MHS, and Robert E. Black, MD, MPH

Background: Rotavirus is the leading cause of vaccine-preventable diarrhea among children under 5 globally. Rotavirus vaccination has been shown to prevent severe rotavirus infections with varying efficacy and effectiveness by region.

Methods: We sought to generate updated region-specific estimates of rotavirus vaccine efficacy and effectiveness. We systematically reviewed published vaccine efficacy and effectiveness studies to assess the region-specific effect of rotavirus vaccination on select diarrheal morbidity and mortality outcomes in children under 5 years of age. We employed meta-analytic methods to generate pooled effect sizes by Millennium Development Goal region.

Results: Rotavirus vaccination was both efficacious and effective in preventing rotavirus diarrhea, severe rotavirus diarrhea and rotavirus hospitalizations among children under 5 across all regions represented by the 48 included studies. Efficacy against severe rotavirus diarrhea ranged from 90.6% [95% confidence interval (CI): 82.3–95.0] in the developed region to 88.4% (95% CI: 67.1–95.9) in Eastern/Southeastern Asia, 79.6% (95% CI: 71.3–85.5) in Latin America and the Caribbean, 50.0% (95% CI: 34.4–61.9) in Southern Asia and 46.1% (95% CI: 29.1–59.1) in sub-Saharan Africa. Region-specific effectiveness followed a similar pattern. There was also evidence of vaccine efficacy against severe diarrhea and diarrheal hospitalizations.

Conclusion: Our findings confirm the protective efficacy and effectiveness of rotavirus vaccination against rotavirus diarrheal outcomes among children under 5 globally.

Key Words: rotavirus, vaccine, children, global

(*Pediatr Infect Dis J* 2016;35:992–998)

Diarrheal disease is a leading cause of childhood morbidity and mortality globally, causing an estimated 0.578 million [95% confidence interval (CI): 0.448–0.750 million] deaths in children under 5 years of age in 2013.[1] Rotavirus is the leading cause of vaccine-preventable diarrhea among children under 5 and is associated with approximately 28% of diarrheal deaths.[2,3] The highest burden of severe disease and deaths due to rotavirus infections occurs in low-income countries, specifically India, Democratic Republic of Congo, Ethiopia, Nigeria and Pakistan.[2,4] In countries without rotavirus vaccination, nearly all children become infected with rotavirus during the first few years of life, regardless of hygiene or sanitation facilities or whether they live in high-income or resource-poor settings.[5]

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World Health Organization recommends the inclusion of rotavirus vaccination in all national immunization programs.[6] There are 2 licensed oral live attenuated rotavirus vaccines currently available globally: a monovalent human rotavirus vaccine [Rotarix (RV1) GlaxoSmithKline Biologicals, Rixensart, Belgium] and a pentavalent bovine–human reassortant rotavirus vaccine [RotaTeq (RV5), Merck Vaccines, Whitehouse Station, NJ].[6] RV1 is administered in 2 oral doses at 6 and 10 weeks of age, and RV5 is administered in 3 oral doses at ages 6, 10 and 14 weeks.[6] In addition, the Lanzhou lamb rotavirus vaccine was licensed in 2000 for prevention of group A rotavirus in China and is administered on a 2-dose schedule at ages 2 months to 3 years and 3–5 years.[7,8] More recently, a monovalent human–bovine vaccine was developed in India and evaluated for efficacy.[9]

In 2011, a systematic review of published vaccine efficacy trials and effectiveness studies estimated that rotavirus vaccines reduced severe rotavirus diarrhea by 91% in developed countries, 88% in low-mortality countries in Asia and North Africa, 81% in Latin America and 50% in sub-Saharan Africa.[10] A Cochrane review published in 2012 also found that the effect of rotavirus vaccination varied by region, with higher efficacy of both RV1 and RV5 among children <2 years of age in low-mortality compared with high-mortality countries.[11] Both studies cite various potential explanations for the reduced effect of rotavirus vaccination in high-mortality countries, including the prevalence of malnutrition, increased rates of severe infectious disease and comorbidities and differences in immune response resulting from the passive immunity conferred by breastfeeding.[10,11]

In this systematic review, we aimed to expand upon the existing evidence base for the efficacy and effectiveness of rotavirus vaccination against morbidity and mortality among children <5 years of age. Given the previously observed variation across regions,[10] we sought to generate updated estimates of the global effect sizes by Millennium Development Goal (MDG) region. To achieve this goal, we expanded upon a previous review of publications before 2011 using newly available data from efficacy and effectiveness studies published from 2011 to 2014.

METHODS

Search Strategy

We aimed to update our previously published systematic review of studies published before 2011,[10] which included data from 11 studies assessing the effect of rotavirus vaccination on diarrheal morbidity and mortality among children under 5.[12–22] We employed an identical search strategy to systematically screen literature published between January 2011 and October 2014, the period immediately following that of the original search. There was no overlap in the search dates of the 2 reviews. We searched PubMed, EMBASE, the Cochrane central register for controlled trials and the Global Health Library Global Index and Regional Index using combinations of key search terms: *rotavirus*, *rotavirus vaccine*, *randomized controlled trials*, *case-control*, *efficacy*, *phase III trials*, *vaccine effectiveness* and *impact and program evaluation*. In an effort to identify relevant studies that had not yet been published,

we also reviewed conference abstracts from the 11th International Rotavirus Symposium. All articles from both our previous and current searches were screened for inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

Two independent reviewers screened titles and subsequently reviewed abstracts for inclusion and exclusion criteria. All randomized controlled trials (RCTs) and observational studies reporting outcomes related to rotavirus diarrhea or diarrhea of unspecified etiology in children <5 years of age were eligible for inclusion. Outcomes of interest included episodes of any severity, severe episodes as indicated by a Vesikari score of ≥11 on a 20-point scale or a Clark score of >16 on a 24-point scale,[23,24] hospitalizations and deaths.

We excluded review articles, phase I and II trials, cost-effectiveness studies and editorials. We excluded efficacy trials that failed to report separate effect sizes for the intention-to-treat and per-protocol populations and observational studies only reporting the effectiveness of partial vaccine doses. We did not exclude studies on the basis of age at vaccination. Data from studies that solely focused on specific subpopulations, such as HIV-infected children, in which immune responses are likely to differ from those of the general population, were excluded to ensure the generalizability of the pooled estimates. For analytical purposes, we also excluded studies that did not report the inputs required for meta-analysis (eg, effect size and 95% CI) and did not provide sufficient raw data from which the required inputs could be calculated.

Data Abstraction

We categorized the included studies by study design and MDG region[25]; we combined data from Southeastern Asia and Eastern Asia but excluded studies that pooled outcomes across other MDG regions. For each outcome, we abstracted published effect sizes and 95% CIs for vaccine efficacy, vaccine effectiveness and percent reduction of relevant outcomes into standardized abstraction tables. We used Stata 12.0 to compute these figures for studies that did not publish effect estimates but provided adequate raw data to carry out such calculations.[26]

We recorded estimates of vaccine efficacy and effectiveness from RCTs and observational studies, respectively. Vaccine efficacy was defined as the proportionate reduction in an outcome comparing those randomized to rotavirus vaccination to those receiving placebo.[27] In abstracting data for efficacy trials, we used only the per-protocol estimate which assessed the efficacy of vaccination among children receiving all required vaccine/placebo doses. Vaccine effectiveness was defined as the vaccine-attributable reduction in an outcome in an uncontrolled or real-world setting and was assessed by several study designs, including case-control studies and cross-sectional studies using historical controls to compare the presence of an outcome in a population prevaccine and postvaccine implementation.[27] For case-control studies reporting stratified analyses of partial and complete doses, we used the estimate of vaccine effectiveness of the full recommended dose. We considered healthy neighborhood children, children with nondiarrheal illness and children with non-Rotavirus diarrhea appropriate control groups but utilized the estimate based on diarrhea-free controls if available. In addition to vaccine effectiveness, we abstracted the percent change in selected outcomes from observational studies utilizing historical controls. We recorded individual and population estimates of vaccine effectiveness from cluster randomized controlled trials (cRCTs), which were categorized separately of other study designs.

For studies reporting both separate and pooled effect sizes over various years and/or age strata, we abstracted the pooled estimate only. For studies reporting only separate effect sizes over various years and/or age strata, we conducted fixed-effects meta-analyses in Stata 12.0 to generate the pooled effect size.[26]

Data Analysis

From the abstracted estimates of vaccine efficacy and effectiveness, we calculated relative risk (RR) and odds ratios (OR) and used random effects meta-analysis to generate inverse-variance-weighted pooled estimates across studies. We subsequently converted the pooled effect sizes into vaccine efficacy [100%*(1−RR)] and vaccine effectiveness [100%*(1−OR)]. For observational studies reporting percent reduction, we combined estimates across studies by fitting logistic regression models weighted by inverse variance. All statistical analyses were conducted using Stata 12.0 statistical software.[26] We conducted Q-tests to assess heterogeneity across studies.

We assessed the quality of evidence for each pooled outcome using the standards for *Child Health Epidemiology Reference Group* reviews of child survival interventions.[28] Applying these guidelines, we graded the evidence for each effect estimate on a 4-point scale (ie, high, moderate, low, very low) based on an evaluation of the design, limitations, consistency and generalizability of contributing studies. RCTs were automatically granted a score of "high" and downgraded for lack of consistency or major limitations, including failure to blind or conceal allocation. Observational studies were given a score of low and upgraded to moderate if effect sizes were consistent across all studies and regions.

RESULTS

Systematic Literature Review

We screened 1221 titles and abstracts identified through literature searches (Fig. 1). After removing duplications and searching the resulting titles and abstracts, we reviewed 66 full manuscripts. In addition to the 11 studies included from our previous

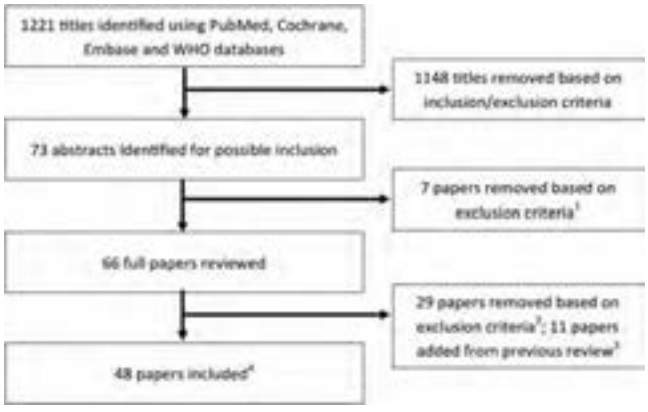

FIGURE 1. Flow chart diagram of the systematic review process. 1 = Main reason for exclusion: study design (n = 4); review article (n = 3). 2 = Main reason for exclusion: no outcome of interest (n = 10); insufficient data for meta-analysis (n = 14); population not generalizable (n = 2); partial vaccine doses (n = 3). 3 = *BMC Public Health*. 2011. 11(suppl 3): S16. 4 = Included papers: 22 RCT reporting vaccine efficacy; 19 observational reporting vaccine effectiveness; 6 observational reporting percent change; 1 cRCT reporting population effectiveness and total vaccine effectiveness.

TABLE 1. Region-specific Pooled Effect Estimates of Rotavirus Vaccination on Select Outcomes

Outcome	Study Design	MDG Region	Effect Size (95% CI)	References
Rotavirus diarrhea*	RCT (vaccine efficacy)†	Developed	75.9 (72.4, 78.9)	18, 19, 30–32, 62
		Southern Asia	34.6 (21.6, 45.3)	9
		Sub-Saharan Africa	55.4 (27.6, 72.6)	15, 33–35
	Observational (vaccine effectiveness)‡	Developed	86.8 (60.7, 95.6)	36, 37
		Latin America and Caribbean	29.6 (−53.5, 67.7)	38
	Observational (percent change)§	Developed	61.4 (60.2, 62.6)	39
Severe rotavirus diarrhea	RCT (vaccine efficacy)*	Developed	90.6 (82.3, 95.0)	18, 19, 30–32, 62
		Eastern Asia/SE Asia	88.4 (67.1, 95.9)	16, 17, 40–42
		Latin America and Caribbean	79.6 (71.3, 85.5)	13, 46, 57
		Southern Asia	50.0 (34.4, 61.9)	9, 16
		Sub-Saharan Africa	46.1 (29.1, 59.1)	14, 15, 33–35, 43, 44
	Observational (vaccine effectiveness)‡	Latin America and Caribbean	68.8 (55.8, 77.9)	12, 20, 38, 45, 47, 63
Rotavirus hospitalizations	RCT (vaccine efficacy)*	Developed	94.3 (72.8, 98.8)	19, 32
		Eastern Asia/SE Asia	93.8 (81.5, 97.9)	40, 42
		Latin America and Caribbean	83.8 (74.6, 89.6)	13, 57
		Sub-Saharan Africa	57.5 (7.2, 80.8)	14
	Observational (vaccine effectiveness)‡	Developed	88.9 (80.9, 93.5)	21, 36, 37, 48–53, 60, 61
		Latin America and Caribbean	67.6 (54.8, 76.7)	12, 20, 38, 45, 54, 63
		Sub-Saharan Africa	57.0 (40.0, 68.0)	55
	Observational (percent change)§	Latin America and Caribbean	76.7 (75.6, 77.7)	56
Diarrhea	RCT (vaccine efficacy)*	Sub-Saharan Africa	10.0 (−22.3, 33.9)	33
Severe diarrhea	RCT (vaccine efficacy)*	Developed	49.6 (39.8, 57.8)	19
		Eastern Asia/SE Asia	30.3 (13.1, 44.2)	17
		Latin America and Caribbean	35.8 (24.1, 45.7)	13, 57
		Southern Asia	18.6 (1.9, 32.3)	9
		Sub-Saharan Africa	15.3 (2.9, 26.1)	15, 33, 34, 43
	Observational (vaccine effectiveness)‡	Developed	83.2 (41.7, 95.1)	21
Diarrhea hospitalizations	RCT (vaccine efficacy)*	Developed	71.5 (53.4, 82.9)	19
		Eastern Asia/SE Asia	28.9 (16.3, 39.6)	40, 42
		Latin America and Caribbean	38.5 (29.0, 46.7)	13, 57
	Observational (vaccine effectiveness)‡	Developed	77.7 (40.2, 91.7)	21
	Observational (percent change)§	Latin America and Caribbean	41.5 (32.5, 50.5)	56, 58, 59
Diarrhea mortality	Observational (percent change)§	Latin America and Caribbean	41.2 (39.9, 42.4)	22, 29, 58

*A cRCT reported population effectiveness 28.4% (95% CI: 11.0–42.4) and total vaccine effectiveness 39.0% (95% CI: 22.0–52.3) against RV diarrhea of any severity.[64]
†Effect size is vaccine efficacy, defined as 100%*(1–RR).
‡Effect size is vaccine effectiveness, defined as 100%*(1–OR) or 100%*(1–Hazard Ratio).
§Effect size is percentage reduction in specified outcome (ie, number cases, hospitalization or mortality rate).

review,[12–22] we identified 37 papers meeting our inclusion/exclusion criteria.[9,29–64] Of the 48 studies, there were 22 RCTs reporting vaccine efficacy,[9,13–19,30–35,40–44,46,57,62] 19 observational studies reporting vaccine effectiveness,[12,20,21,36–38,45,47–55,60,61,63] 6 observational studies reporting percent reductions[22,29,39,56,58,59] and 1 cRCT[64] (Fig. 1 and Table 1). By outcome, 44 studies reported rotavirus diarrheal morbidity outcomes, 15 studies reported diarrheal morbidity outcomes and 3 studies reported diarrhea-attributable mortality (Table 1). The majority of included studies were conducted in the MDG developed region (n = 18) and Latin America and the Caribbean (n = 15), followed by sub-Saharan Africa (n = 8), Eastern/Southeastern Asia (n = 5) and Southern Asia (n = 3). Additional data on included studies are provided in the Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C503.

The Effect of Rotavirus Vaccination on Rotavirus Diarrhea of Any Severity Among Children Under 5

The efficacy of rotavirus vaccination in preventing rotavirus diarrhea was highest in developed countries (75.9%; 95% CI: 72.4–78.9) followed by sub-Saharan Africa (55.4%; 95% CI: 27.6–72.6) and Southern Asia (34.6%; 95% CI: 21.6–45.3; Table 1; Appendix: Figs. 1, 2, Supplemental Digital Content 1, http://links.lww.com/INF/C503). Rotavirus vaccine effectiveness was 86.8% (95% CI: 60.7–95.6) in developed countries and 29.6% (95% CI: −53.5–67.7) in Latin America and the Caribbean (Table 1; Appendix: Fig. 3, Supplemental Digital Content 1, http://links.lww.com/INF/C503). In one study from the developed region, rotavirus vaccination was attributed with a 61.4% (95% CI: 60.2–62.6) reduction in rotavirus cases (Table 1). A cRCT conducted in Bangladesh reported population effectiveness of 28.4% (95% CI: 11.0–42.4) and total vaccine effectiveness of 39.0% (95% CI: 22.0–52.3) against rotavirus diarrhea of any severity.[64]

The Effect of Rotavirus Vaccination on Severe Rotavirus Diarrhea Among Children Under 5

Rotavirus vaccination was most efficacious against severe rotavirus diarrhea in the developed region (90.6%; 95% CI: 82.3–95.0) followed by Eastern/Southeastern Asia (88.4%; 95% CI: 67.1–95.9), Latin America and the Caribbean (79.6%; 95% CI: 71.3–85.5), Southern Asia (50.0%; 95% CI: 34.4–61.9) and sub-Saharan Africa (46.1%; 95% CI: 29.1–59.1; Table 1; Appendix: Figs. 4–8, Supplemental Digital Content 1, http://links.lww.com/INF/C503). In Latin America and the Caribbean, vaccine effectiveness against

TABLE 2. Quality Assessment of Included Studies

Outcome	No. of Studies	Design	Major Limitations	Consistency	Generalizability to Population of Interest*	Generalizability to Intervention of Interest
Rotavirus diarrhea†‡§	11	RCT	None	Consistent across all studies and regions	Representative of DEV, SA, SSA	Generalizable
	3	Observational	None	DEV: positive effect; LAC: positive, not statistically significant	Representative of DEV, LAC	Generalizable
	1	Observational	None	1 study; unable to gauge consistency	Representative of DEV	Generalizable
Severe rotavirus diarrhea†‡	23	RCT	None	Consistent across all studies and regions	Representative of DEV, EA, LAC, SA, SSA	Generalizable
	6	Observational	None	1 region; mostly consistent across studies	Representative of LAC	Generalizable
Rotavirus hospitalizations†‡§	7	RCT	None	Consistent across all studies and regions	Representative of DEV, EA, LAC, SSA	Generalizable
	17	Observational	None	Consistent across all studies and regions	Representative of DEV, LAC, SSA	Generalizable
	1	Observational	None	1 study; unable to gauge consistency	Representative of LAC	Generalizable
Diarrhea¶	1	RCT	None	1 study; unable to gauge consistency	Representative of SSA	Generalizable
Severe diarrhea†‖	9	RCT	None	Consistent across regions; mostly consistent across all studies	Representative of DEV, EA, LAC, SA, SSA	Generalizable
	1	Observational	None	1 study; unable to gauge consistency	Representative of DEV	Generalizable
Diarrhea hospitalizations†‖**	5	RCT	None	Consistent across all studies and regions	Representative of DEV, EA, LAC	Generalizable
	1	Observational	None	1 study; unable to gauge consistency	Representative of LAC	Generalizable
	3	Observational	None	1 region; consistent across all studies	Representative of LAC	Generalizable
Diarrhea mortality**	3	Observational	None	1 region; consistent across all studies	Representative of LAC	Generalizable

*MDG regions: Developed (DEV); Central Asia (CA); North Africa (NA); Sub Saharan Africa (SSA); Latin America & Caribbean (LAC); East/Southeastern Asia (EA); South Asia (SA); West Asia (WA); Oceania (OC).

†Vaccine Efficacy: high outcome-specific quality.

‡Vaccine Effectiveness: moderate outcome-specific quality.

§Percentage Reduction: low outcome-specific quality.

¶Vaccine Efficacy: moderate outcome-specific quality.

‖Vaccine Effectiveness: low outcome-specific quality.

**Percentage Reduction: moderate outcome-specific quality.

severe rotavirus was 68.8% (95% CI: 55.8–77.9; Table 1; Appendix: Fig. 9, Supplemental Digital Content 1, http://links.lww.com/INF/C503).

The Effect of Rotavirus Vaccination on Rotavirus Diarrhea Hospitalizations Among Children Under 5

Vaccine efficacy against rotavirus hospitalizations ranged from 94.3% (95% CI: 72.8–98.8) in the developed region to 57.5% (95% CI: 7.2–80.8) in sub-Saharan Africa, and vaccine effectiveness followed a similar regional pattern (Table 1; Appendix: Figs. 10–14, Supplemental Digital Content 1, http://links.lww.com/INF/C503). In Latin America and the Caribbean, rotavirus vaccination led to a 76.7% (95% CI: 75.6–77.7) decrease in rotavirus hospitalizations.

The Effect of Rotavirus Vaccination on Diarrhea and Severe Diarrhea Among Children Under 5

In one study conducted in sub-Saharan Africa, the efficacy of rotavirus vaccination was 10.0% (95% CI: −22.3–33.9) against diarrhea. Efficacy against severe diarrhea ranged from 49.6% (95% CI: 39.8–57.8) in the developed region to 15.3% (95% CI: 2.9–26.1) in sub-Saharan Africa (Table 1; Appendix: Figs. 15–16, Supplemental Digital Content 1, http://links.lww.com/INF/C503). In the developed region, vaccine effectiveness was 83.2% (95% CI: 41.7–95.1) against severe diarrhea.

The Effect of Rotavirus Vaccination on Diarrheal Hospitalizations Among Children Under 5

Rotavirus vaccination was 71.5% (95% CI: 53.4–82.9), 28.9% (95% CI: 16.3–39.6) and 38.5% (95% CI: 29.0–46.7) efficacious against hospitalization for diarrhea in the developed, Eastern/Southeastern Asia and Latin America and Caribbean regions, respectively (Table 1; Appendix: Figs. 17–18, Supplemental Digital Content 1, http://links.lww.com/INF/C503). In the developed region, rotavirus vaccination was 77.7% (95% CI: 40.2–91.7) effective against diarrheal hospitalizations among children under 5 and in Latin America and the Caribbean, rotavirus vaccination resulted in a 41.5% (95% CI: 32.5–50.5) reduction in such hospitalizations (Table 1).

The Effect of Rotavirus Vaccination on Diarrhea-attributable Mortality Among Children Under 5

In Latin America and the Caribbean, rotavirus vaccination resulted in a 41.2% (95% CI: 39.9–42.4) reduction in the diarrhea mortality rate.

Quality Assessment

In general, outcome-specific quality was high or moderate for most outcomes (Table 2). Pooled effect estimates were consistent across studies and regions. In terms of directness, included studies assessed interventions generalizable to the intervention of

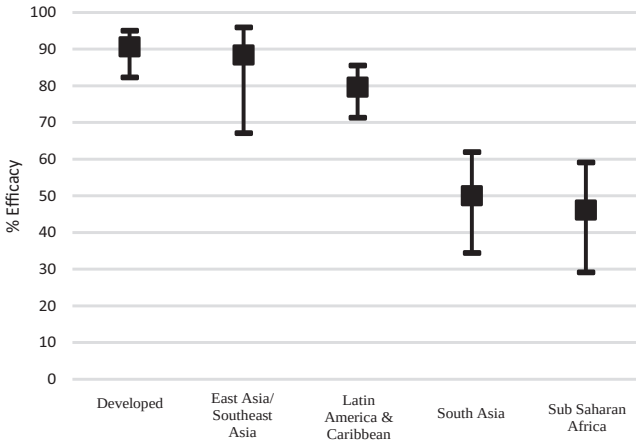

FIGURE 2. Efficacy of rotavirus vaccination on severe rotavirus diarrhea by MDG region. Box represents percent efficacy; whiskers represent upper and lower bounds for the 95% confidence interval.

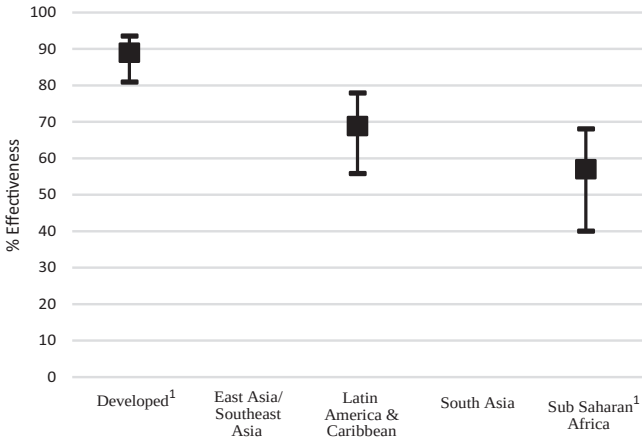

FIGURE 3. Effectiveness of rotavirus vaccination on severe rotavirus diarrhea by MDG region. Due to a dearth of studies reporting the effectiveness of rotavirus vaccination on severe rotavirus diarrhea, the effectiveness on rotavirus hospitalizations was used as a proxy for the Developed and Sub Saharan Africa regions; no comparable estimates were available for the East/Southeastern Asia and South Asia regions. Box represents percent effectiveness; whiskers represent upper and lower bounds for the 95% confidence interval.

interest but were not representative of all MDG regions because of a dearth of available studies reporting certain outcomes for each region.

DISCUSSION

The results of our systematic review confirm the protective efficacy and effectiveness of rotavirus vaccination against rotavirus and all diarrheal outcomes among children under 5 globally. Rotavirus vaccination was efficacious against severe rotavirus infection in all MDG regions, but efficacy was highest in the developed region followed by East/Southeastern Asia, Latin America and the Caribbean, South Asia and sub-Saharan Africa (Fig. 2), and effectiveness estimates followed a similar regional pattern (Fig. 3). Possible explanations for varying levels of protection include regional differences in gut microbiome, environmental enteropathy, inhibitory maternal antibodies and/or interactions with other viruses in the gut.[5] Though the protective effects conferred by rotavirus vaccines are greater in higher income settings, rotavirus vaccination has the potential to avert more severe childhood diarrhea cases and deaths in low-income regions where the incidence of severe rotavirus is highest and adequate diarrhea management is less accessible.[6] In Latin America and the Caribbean, the region with the most data from different types of evaluations, the efficacy and effectiveness against severe rotavirus diarrhea were 79.6% and 68.8%, respectively, but there was a 41.2% reduction in the diarrhea-attributable mortality rate, reflecting the predominance of this etiologic agent as a cause of death in the region, which is also true in developed countries. Both the lower etiologic fraction of severe diarrhea for rotavirus in less developed regions[3] and the lower efficacy of the vaccine in these areas suggest that a smaller percentage of all severe diarrhea and diarrheal deaths would be prevented by routine vaccination.

The results of this systematic review are strengthened by consistency across all studies, which contributed to a quality assessment of high or moderate for most outcomes (Table 2). However, there was a dearth of studies reporting the region-specific effectiveness of rotavirus vaccine against severe rotavirus diarrhea and hospitalizations. In addition, the regions of Eastern/Southeastern Asia and Southern Asia were less represented by included studies, and there were only 3 studies reporting an effect on diarrhea-attributable mortality—all of which were conducted in Latin America and the Caribbean where the vaccine is highly efficacious (Tables 1 and 2). Further research assessing the mortality effect of rotavirus vaccination, as well as the overall protective effects in Asia, is thus warranted.

The lack of studies meeting our inclusion criteria also precluded further stratification of our analysis by characteristics of the national immunization program, such as coverage level or vaccine type. All included studies used either RV1 or RV5 with the exception of one Indian study assessing the efficacy of a newly introduced monovalent human-bovine reassortant vaccine (116E) and one Ghanaian study of a rhesus/rhesus-human reassortant tetravalent vaccine (RotaShield, RRV-TV).[9,35] As countries increasingly adopt rotavirus vaccine recommendations into their national immunization programs, mounting data should enable future analysis of the relative efficacy and effectiveness of the available vaccine types by region.

As of October 2015, 79 countries have introduced rotavirus vaccines, and this number is expected to grow because of the global recommendation and cofinancing by the World Health Organization for eligible countries through the Gavi Alliance.[65] The public health benefits of rotavirus vaccination, which are already being realized in early adopter countries, could have considerable impact in low-income, high-burden countries yet to include the vaccine in their immunization programs. Global efforts should continue to push for the introduction of rotavirus vaccines into every national immunization strategy. These efforts should especially focus on the 2 regions with the highest rotavirus mortality—sub-Saharan Africa, where 22 of 51 countries have yet to begin national rotavirus vaccination programs, and Asia, where there are no early adopters.[65]

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