DESCRIPTION OF STUDIES AND RISK OF BIAS ASSESSMENT FOR RCTS

ROTAVIRUS VACCINES SCHEDULES:

A SYSTEMATIC REVIEW OF SAFETY AND EFFICACY FROM RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES OF CHILDHOOD SCHEDULES USING RV1 AND RV5 VACCINES

REPORT TO WHO/IVR

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DESCRIPTION OF STUDIES AND RISK OF BIAS ASSESSMENT FOR RCTS

Study characteristics and risk of bias assessments for the included RCTs are described below, with the main reference for each trial. Data is taken from the recently published Cochrane review[1], except for two trials (*Latin America RV5* and *Finland2 RV5*) comparing schedules of co-administration of different childhood vaccines with RV5 without a placebo group.

Philippines2 RV1 RV1 Anh 2011a-AS[2]

Methods	Randomized controlled trial **Length of follow-up:** 1 month after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** 375 enrolled; ATP safety cohort: 345; ATP immunogenicity cohort: 292 **Inclusion criteria:** Healthy infants aged 5–10 weeks at the time of the first study vaccination dose with a birth weight of >2 kg. **Exclusion criteria:** Use of any investigational drug or vaccine other than the study vaccine or confirmed immunosuppression/immunodeficient conditions or allergy to RIX4414 vaccine/placebo components.
Interventions	1. Two doses of RIX4414* plus one dose of placebo according to a PL-V-V schedule 2. Two doses of RIX4414* plus one dose of placebo according to a V-PL-V schedule 3. Three placebo doses * HRV [RV1] liquid vaccine, oral suspension (GSK Biologicals, Belgium), containing at least $10^{6.0}$ median Cell Culture Infective Dose 50 percent ($CCID_{50}$) of live attenuated RIX4414 human rotavirus strain (G1P[8]) **Schedule:** 3 doses according to a 0, 1, and 2 month schedule
Immunization status	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 the Philippines.
Location	Philippines (single centre)
Notes	Study known as *RIX GSK[063] 2008-AS* in previously published versions of this review. **Date:** March – September 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** “This study will provide data on the immune response and safety of GSK Biologicals' HRV liquid vaccine when given along with the routine infant immunizations in Philippines.” "The study also[...]explored the potential effect of scheduling of the HRV vaccine doses with respect to the existing routine vaccination schedules"

Risk of bias table

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	Low risk	Computer generated “Block randomization scheme (2:2:1 ratio) with standard SAS program was used”
Allocation concealment (selection bias)	Low risk	Central allocation “Based on the block size, the vaccine doses were distributed to each of the study centers.”
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel were blinded. “The study was double-blind with respect to the RIX4414 oral suspension (liquid formulation), placebo and scheduling of doses. The parents/guardians of infants, investigators and study personnel were unaware of the study vaccine/ placebo administered.” “The placebo was identical to the vaccine in composition”
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced across groups with reasons for drop-out/exclusion reported.
Selective reporting (reporting bias)	Low risk	All pre-published outcomes included.
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals.

Vietnam RV1 ***RV1 Anh 2011b-AS[2]***

Methods	Randomized controlled trial **Length of follow-up:** 1 month after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** 375 enrolled; ATP safety cohort: 352; ATP immunogenicity cohort: 330. **Inclusion criteria:** Healthy infants aged 6–10 weeks at the time of the first study vaccination dose with a birth weight of >2 kg **Exclusion criteria:** Use of any investigational drug or vaccine other than the study vaccine or confirmed immunosuppression/immunodeficient conditions or allergy to RIX4414 vaccine/placebo components.
Interventions	1. Two doses of RIX4414* plus one dose of placebo according to a V-V-PL schedule 2. Two doses of RIX4414* plus one dose of placebo according to a V-PL-V schedule 3. Three placebo doses * HRV [RV1] liquid vaccine, oral suspension (GSK Biologicals, Belgium), containing at least 10^6 median Cell Culture Infective Dose 50 percent ($CCID_{50}$) of live attenuated RIX4414 human rotavirus strain (G1P[8]) **Schedule:** 3 doses according to a 0, 1, and 2 month schedule
Immunization status	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.
Location	Vietnam (11 satellite centers)

Notes	Study known as *RIX GSK[051] 2008-AS* in previously published versions of this review. **Date:** September 2006 – March 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale: "**To provide specific data on immunogenicity of GSK Biologicals' HRV liquid vaccine, when co-administered with the routine Expanded Program of Immunization (EPI) in Vietnam. The study will also assess reactogenicity and safety of the HRV liquid vaccine relative to the placebo."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated "Block randomization scheme (2:2:1 ratio) with standard SAS program was used"
Allocation concealment (selection bias)	Low risk	Central allocation "Based on the block size, the vaccine doses were distributed to each of the study centers."
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel were blinded. "The study was double-blind with respect to the RIX4414 oral suspension (liquid formulation), placebo and scheduling of doses. The parents/guardians of infants, investigators and study personnel were unaware of the study vaccine/ placebo administered." "The placebo was identical to the vaccine in composition"
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced across groups with reasons for drop-out/exclusion reported.
Selective reporting (reporting bias)	Unclear risk	One outcome (Rotavirus diarrhoea) not included in the pre-published protocol.
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals.

USA1 RV1 RV1 Bernstein 1998-NA [3]

Methods	Randomized controlled trial **Length of follow-up:** outcomes measured up to 1 month after the second dose **Adverse event data collection methods:** participants or their parents filled out a diary card for 7 days after each dose (passive method)
Participants	**Number:** 42 enrolled; 42 evaluable **Inclusion criteria:** all infants aged 6 to 26 weeks recruited from private practice offices in Cincinnati **Exclusion criteria:** not stated
Interventions	RV1 1. RIX4414 (RV1): 10^5 PFU; 21 participants 2. Placebo: 20 participants **Schedule:** 2 doses given 6 to 10 weeks apart

Immunization status	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks
Location	Cincinnati, USA
Notes	**Date:** August to November 1995 **Source of funding:** Virus Research Institute, Inc. (now Avant Immunotherapeutics Inc.) 1 participant in the placebo group did not complete the study because of persistent otitis media

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Trial report does not provide enough details

USA2 RV1 RV1 Bernstein 1999-NA[4]

Methods	Randomized controlled trial **Length of follow-up:** outcomes measured at 2 years **Adverse event data collection methods:** "diary card for 7 days after vaccine. All moderate to severe side effects were reported by the investigator to an independent study monitor on a continuous basis during the study" (passive method); "telephoned parents every 2 weeks after the first immunisation, and then weekly during the expected rotavirus season (Jan 1-May 31) as a reminder and to collect data on any adverse events" (active method)
Participants	**Number:** 215 randomized; 214 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** healthy children aged 10 to 16 weeks at the time of the first dose **Exclusion criteria:** fever; premature labour; an immunosuppressed or pregnant individual in the same household; birth at < 36 weeks of gestation; participation in any other investigational clinical trial; or no telephone in the household

Interventions	89-12 (a precursor of RIX4414 (RV1) 1. 89-12 (a precursor of RIX4414 (RV1)): 10^5 PFU; 2 doses given 6 to 10 weeks apart; 108 participants 2. Placebo: 10^5 PFU; 2 doses given 6 to 10 weeks apart; 107 participants "Infants received an oral dose of 1.0 mL vaccine (10^5 PFU) or placebo immediately after 2.0 mL of an antacid containing 160 mg aluminium hydroxide and 160 mg magnesium hydroxide to buffer stomach acid. The infant was not fed for 1 h before or after the immunisation"
Immunization status	Other vaccines separated from the trial vaccines by at least 2 weeks
Location	Cincinnati, Baltimore, and Sellersviller, USA
Notes	**Date:** August 1997 to June 1998 **Source of funding:** Virus Research Institute, Inc. (now Avant Immunotherapeutics Inc.)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Infants were assigned to receive either 89-12 or placebo according to a computer-generated randomisation schedule (one/one) in blocks of ten provided by the sponsor. The intention-to-treat analysis included all participants who received at least one dose of study vaccine. Before the code was broken, all cases of rotavirus gastroenteritis and the severity of each episode were verified."
Allocation concealment (selection bias)	Low risk	As above
Blinding (performance bias and detection bias)	Unclear risk	Double-blind, no details
Incomplete outcome data (attrition bias)	Low risk	No impact on intervention effect estimate "Of the 215 children enrolled, 213 received both doses of vaccine or placebo, and 214 were followed up for gastrointestinal disease. One child in the vaccine group did not receive the vaccine because of persistent fever at the time of the scheduled revaccination, and one child in the placebo group was found to have a congenital tracheal malformation while in the trial and was not revaccinated."
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Insufficient information

USA and Canada RV1 RV1 Dennehy 2005-NA[5]

Methods	Randomized controlled trial **Length of follow-up:** 10 to 12 months

	Adverse event data collection methods: "For the 15 days after each dose of vaccine, the parent or guardian maintained a daily record that included fever, irritability/fussiness, diarrhoea, vomiting, loss of appetite and cough/runny nose. In addition, the parent or guardian was asked to record any gastroenteritis episode occurring in the period from the first dose until 2 months after the second dose of vaccine." (passive method); "Subjects were also monitored for any serious adverse events occurring throughout participation in the study (10–12 months in total) and for unsolicited adverse events occurring within 43 days after each dose of vaccine or placebo." (active method)
Participants	**Number:** 529 enrolled; 479 evaluable **Age range:** 1 to 3 months (beginning) **Inclusion criteria:** healthy infants aged 5 to 15 weeks at the time of the first dose. Vaccine administration delayed if acute illness present (fever > 38 °C/gastroenteritis/antibiotics within 7 days before scheduled vaccination) **Exclusion criteria:** premature labour (< 36 weeks); chronic condition; (chronic gastrointestinal disease, immunosuppressive diseases); household contact with immunosuppressed individuals/pregnant women
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{5.2}$; 212 participants 1.2. $10^{6.4}$; 209 participants 2. Placebo: 108 participants **Schedule:** 2 doses given 7 weeks apart
Immunization status	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b, and*Streptococcus 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."
Location	41 centres in USA and Canada
Notes	**Date:** 13 December 2000 to 2 August 2002 **Source of funding:** GlaxoSmithKline Biologicals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Low risk	Central allocation; "double blind randomized unbalanced allocation scheme (2:2:1 ratio)"
Blinding (performance bias	Low risk	Participants and key personnel; "Study personnel and families were blinded to group assignment until study completion"

and detection bias)		
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups; "Fifty-nine subjects, who were proportionately distributed among vaccine groups, did not complete the entire 10- to 12-month study."
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

Panama1 RV1 RV1 GSK[021] 2007-LA[6]

Methods	Randomized controlled trial **Length of follow-up:** 1 month after dose 3 **Adverse event data collection methods:** not reported
Participants	**Number:** 228 enrolled; 203 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into study **Exclusion criteria**: any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator and previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU*; 177 participants (randomized) 1.1. Received modified vaccine formulation 1.2. Received a licensed RV1 vaccine *Dose unclear; in the same study, some use $10^{6.5}$ PFU and some 10^{5} PFU 2. Placebo: 51 participants (randomized) 2.1. Received a placebo of the modified vaccine formulation 2.2. Received a placebo of the licensed RV1 vaccine **Schedule:** 3 doses at 2, 4, and 6 months of age
Immunization status	Use of other vaccines not mentioned
Location	1 centre in Panama
Notes	**Date:** 23 August 2002 to 9 May 2003 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to compare the immunogenicity and safety of a modified vaccine formulation to the licensed HRV [Rotarix] vaccine"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details; "treatment allocation of 7:7:1:1"
Blinding (performance bias and detection bias)	Unclear risk	No details; "Double blind with respect to HRV [Rotarix] vaccine and its placebo"
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

Latin America3 RV1 RV1 GSK[024] 2008-LA[7]

Methods	Randomized controlled trial **Length of follow-up:** up to 1 year of age **Adverse event data collection methods:** not reported
Participants	**Number:** 6568 enrolled; 6349 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** males or females between, and including 6 and 12 weeks (42 to 90 days) of age at the time of the first vaccination according to the country recommendations for the routine vaccination schedules; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 2 doses at 1 or 2 months; 4376 participants (randomized) 2. Placebo: 2 doses at 1 or 2 months; 2192 participants (randomized) **Schedule:** both groups received RV1 vaccine or placebo vaccine orally; first dose at month 0 then second dose at month 1 or month 2 **2 cohorts:** there were two periods of enrolment, each with its own visit schedule: Cohort enrolled in 2003 to 2004: visits 1, 2, 3, 4 (for a subset only) and 5 corresponded to month 0 (vaccine dose 1), month 1 to 2 (vaccine dose 2), month 2 to 4, month 3

	to 6, and month 10 in the schedule Cohort enrolled in 2005: visits 1, 2 (for a subset only), 3, 4 (for a subset only), 5, 6 (for a subset only), and 7 corresponded to month 0 (vaccine dose 1), month 1, month 2 (vaccine dose 2), month 3, month 4, month 5, and month 10 in the schedule
Immunization status	All participants received routine infant vaccinations (Hepatitis B vaccine), diphtheria-tetanus-acellular pertussis, poliovirus, and *Haemophilus influenzae* type b) according to Expanded Programme of Immunization (EPI) recommendations in each country First 2 doses of routine EPI vaccinations were co-administered with the RV1 vaccine or placebo doses; the third routine EPI vaccination was administered 1 to 2 months later according to the national plan of immunization in each country
Location	Multiple sites in 6 countries in Latin America (Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama)
Notes	**Date:** 3 December 2003 to 20 March 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to evaluate the efficacy, immunogenicity and safety of 2 doses of oral live attenuated HRV [Rotarix] vaccine given concomitantly with routine EPI vaccinations (including DTPw [licensed combined diphtheria and tetanus toxoids and whole-cell pertussis vaccine], HBV [licensed hepatitis type B vaccine], Hib [licensed *Haemophilus influenzae* type b vaccine] and OPV [oral polio vaccine]) in healthy infants"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: – who had received at least one dose of study vaccine/control according to their random assignment, – for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias)	Unclear risk	No details; "Double blind, randomized (2:1) and placebo controlled study with 2 parallel groups."
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

Latin America2 RV1 RV1 GSK[033] 2007-LA[8]

Methods	Randomized controlled trial **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 228 enrolled; 203 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course, free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator and previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU*; 730 participants (randomized) 1.1. Received RV1 vaccine Lot A 1.2. Received RV1 vaccine Lot B 1.3. Received RV1 vaccine Lot C *Dose unclear, some use $10^{6.5}$ PFU and some 10^{5} PFU 2. Placebo: 124 participants (randomized) **Schedule:** 2 oral doses given at 2 and 4 months; visits 1, 2, and 3 correspond to months 0, 2, and 4 in the schedule
Immunization status	Use of other vaccines not mentioned
Location	7 study centres (2 in Colombia, 1 in Mexico, and 4 in Peru)
Notes	**Date:** 8 August 2003 to 29 January 2004 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess the clinical consistency of 3 production lots of human rotavirus (HRV) vaccine in terms of immunogenicity and safety when given to healthy infants at 2 and 4 months of age"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details; "treatment allocation of 2:2:2:1"
Blinding (performance bias	Unclear risk	No details

and detection bias)		
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

South Korea RV1 RV1 GSK[041] 2007-AS[9]

Methods	Randomized controlled trial **Length of follow-up:** 2 months after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 400 enrolled; 391 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** full-term infants; healthy infants aged between 6 and 12 weeks (42 to 90 days) at the time of the first vaccination for whom the vaccination history was available **Exclusion criteria:** previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 103 participants (randomized) 2. Placebo: 52 participants (randomized) **Schedule:** 2 oral doses starting at about 2 months of age; second dose at 4 months of age
Immunization status	*Haemophilus 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
Location	6 centres in Korea
Notes	**Date:** 15 July 2005 to 11 May 2006 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess immunogenicity and safety of 2 doses of the HRV vaccine in Korean infants aged approximately 2 months at the time of the first dose"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: – who had received at least one dose of study vaccine/control according to their random assignment, – for whom the randomization code had not been broken"
Allocation concealment	Unclear risk	No details

(selection bias)		
Blinding (performance bias and detection bias)	Unclear risk	No details; "Randomized (2:1), double-blind, placebo-controlled study with 2 parallel groups"
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

India RV1 RV1 GSK[044] 2007-AS[10]

Methods	Randomized controlled trial **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 363 enrolled; 344 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy male or female infant between and including, 8 to 10 weeks of age at the time of first vaccination; free of obvious health problems as established by medical history and clinical examination before entering into the study; subjects had been administered the first dose of diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b, oral poliovirus vaccine as per the local universal immunization programme at age 6 weeks (given with a 2-week separation from the first and subsequent dose of the RV1 vaccine or placebo) **Exclusion criteria**: history of confirmed rotavirus gastroenteritis or with prior administration of experimental rotavirus vaccine
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 182 participants (randomized) 2. Placebo: 181 participants (randomized) **Schedule:** 2 oral doses given at age 2 and 4 months
Immunization status	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *Haemophilus 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)
Location	4 centres in India
Notes	**Date:** 10 February 2006 to 8 September 2006 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess the immunogenicity and safety of 2 doses of oral live attenuated HRV vaccine in healthy infants in India"

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: – who had received at least one dose of study vaccine/control according to their random assignment, – for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias)	Unclear risk	No details; "Double-blind, randomised (1:1), placebo-controlled study with 2 parallel groups"
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

Philippines1 RV1 RV1 GSK[101555] 2008-AS[11]

Methods	Randomized controlled trial **Length of follow-up:** outcomes measured 1 month after last dose of vaccine/placebo **Adverse event data collection methods:** not reported
Participants	**Number:** 150 enrolled; 145 evaluable **Age range:** 6 to 12 weeks **Inclusion criteria:** healthy, full-term infants aged 6 to 12 weeks; male or female infants between, and including, 6 and 12 weeks of age at the time of the first vaccination, free of obvious health problems, born after a normal gestation period (between 36 and 42 weeks) or with a birth weight > 2000 g **Exclusion criteria:** infants with previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$; 100 participants* 1.1. Licensed formulation 1.2. Lyophilized formulation 2. Placebo: 50 participants* 2.1. Normal placebo 2.2. Lyophilized formulation **Schedule:** 2 doses given 2 months **Data from the lyophilized formulation, which is not yet approved or marketed, are not reported in review*
Immunization status	Use of other vaccines not mentioned
Location	1 study centre in the Philippines

Notes	**Date:** 11 May 2004 to 13 September 2004 **Source of funding:** GlaxoSmithKline Biologicals **Trial objective:** "To assess the immunogenicity and safety of 2 different formulations of live attenuated HRV vaccine given as a two-dose primary vaccination in healthy infants previously uninfected with HRV."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: – who had received at least one dose of study vaccine/control according to their random assignment, – for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias)	Unclear risk	No details; "Double-blind with respect to each HRV [Rotarix] vaccine formulation and its respective placebo"
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

Japan RV1 RV1 Kawamura 2010-AS[12]

Methods	Randomized controlled trial **Length of follow-up:** up to the age of 2 years **Adverse event data collection methods:** not reported
Participants	**Number:** 765 **Age range:** 6 to 14 weeks **Inclusion criteria:** full-term healthy infants aged 6 to 14 weeks at the time of the first dose **Exclusion criteria:** use of any other investigational or non-registered product (drug or vaccine) within 30 days preceding the first dose of HRV vaccine; history of use of experimental rotavirus vaccine; chronic administration of immunosuppressants or other immune-modifying drugs since birth; concurrently participating in another clinical study; any clinically significant history of a serious medical condition; previous confirmed occurrence of RV GE
Interventions	1. RV1, 508 participants 2. Placebo, 257 participants. **Schedule:** 2 doses according to a 0, 1 month schedule

Immunization status	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.
Location	Japan
Notes	**Date:** June 2007 - November 2009 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00480324

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, no further information given.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias)	Unclear risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", no further details.
Incomplete outcome data (attrition bias)	Low risk	Attrition/exclusions balanced between groups.
Selective reporting (reporting bias)	Low risk	Protocol published a priori, all pre-published outcomes reported.
Other bias	Unclear risk	Study sponsor and collaborator: GlaxoSmithKline

Thailand RV1 RV1 Kerdpanich 2010-AS[13]

Methods	Randomized controlled trial **Length of follow-up:** 2 months post dose 2 **Adverse event data collection methods:** Passive. “Diary cards were provided to the parents/guardians of infants to record the solicited general symptoms occurring during the 15 day follow up period after each vaccine dose. The solicited general symptoms were loss of appetite, fussiness/irritability, fever, diarrhoea, vomiting and cough/runny nose. The intensity of each of these symptoms was graded on a 3-point scale where “0” indicates normal and “3” indicates severe.”
Participants	**Number:** 450 enrolled; ATP safety cohort: 447; ATP immunogenicity cohort: 339. **Inclusion criteria:** Healthy infants aged 6–12 weeks at the time of the first vaccination **Exclusion criteria:** Any other investigational drug or vaccine; a history of gastrointestinal disease or rotavirus gastroenteritis; allergy to any of the vaccine components; a history of immunosuppressive or immunodeficient condition.
Interventions	1. RIX4414* vaccine reconstituted in buffer stored at 2°C–8°C, n=174.

	2. RIX4414* vaccine reconstituted in water stored at 2°C–8°C, n=174. 3. RIX4414* vaccine reconstituted in buffer stored at 37°C for seven days, n=50. 4. Placebo reconstituted in buffer, n=26. 5. Placebo reconstituted in water, n=26. * Lyophilized formulation containing at least $10^{6.0}$ Cell Culture Infective Dose 50 ($CCID_{50}$) of the RIX4414 strain. **Schedule:** Two doses at month 0 and 2
Immunization status	"During the study period, participating infants were offered commercially available GSK Biologicals' diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and H. influenzae type b combination vaccine (*Infanrix*^{TM}-IPV/Hib) at two and four 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 six months of age."
Location	Two centres in Thailand
Notes	Study known as *RIX GSK[039] 2007-AS* in previously published versions of this review. **Date:** March - December 2005 **Source of funding:** GSK Biologicals **Study rationale:** This study evaluated the stability of lyophilized RIX4414 vaccine in terms of immunogenicity when reconstituted in water instead of regular buffer, and when stored at tropical room temperature (37°C) for 7 days before reconstitution.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding (performance bias and detection bias)	High risk	Partially blind study "Single blind", not reported whether personnel or participants were blinded. "The placebo was identical in appearance and composition to the active vaccine"
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced across groups with reasons for withdrawal reported.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Unclear risk	Funded by GSK Biologicals.

South Africa and Malawi RV1 RV1 Madhi 2010-AF[14]

Methods	Randomized controlled trial

	Length of follow-up: outcomes measured 2 weeks after last dose to 1 year of age **Adverse event data collection methods:** Active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations
Participants	**Number:** 4939 enrolled; 4417 evaluable **Age range:** 1 to 6 months **Inclusion criteria:** healthy infants aged 6 to 10 weeks for the group receiving 3 doses and 10 to 14 weeks for the group receiving 2 doses of RV1 **Exclusion criteria:** children HIV positive that were immunosupressed at <6 weeks before vaccination
Interventions	RV1 1. RIX4414 (RV1): dose same as commercial; 3298 participants 1.1. 2 doses 1.2. 3 doses 2. Placebo: 1641 participants 2.1. Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo
Location	South Africa and Malawi
Notes	**Date:** October 2005 to February 2007 (South Africa); October 2006 to July 2007 (Malawi) **Source of funding:** PATH Rotavirus Vaccine Program and GlaxoSmithKline **Other notes:** none

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomization list was generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and this was used to number the vaccines
Allocation concealment (selection bias)	Low risk	The vaccine doses were distributed to each study centre while respecting the randomization block size
Blinding (performance bias and detection bias)	Low risk	The site investigator, who was unaware of the group assignments of the children
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting	Low risk	All expected outcomes reported

(reporting bias)		
Other bias	Unclear risk	Sponsored by industry

***Dominican Republic RV1 RV1 NCT00396630 2009-LA*[15]**

Methods	Randomized controlled trial **Length of follow-up:** 17 weeks **Adverse events data collection methods:** not reported
Participants	**Number:** 200 **Age range:** 6-14 weeks of age at the time of the first study vaccination **Inclusion criteria:** healthy infants with a live twin living in the same household who is also enrolled in this study, born after a gestation period of over 32 weeks. **Exclusion criteria:** use of any investigational or non-registered product other than the study vaccine(s); any confirmed or suspected immunosuppressive or immunodeficient condition; any clinically significant history of chronic gastrointestinal disease; history of allergic disease; acute disease at time of enrolment; gastroenteritis within 7 days preceding the first study vaccine administration; documented HIV-positive subject
Interventions	1. RV1 (RIX 4414) Vaccine, 100 participants 2. Placebo, 100 participants **Schedule:** both vaccine and placebo 2 doses at Day 0 (Visit 1) and Week 7 (Visit 2) **Notes:** One complimentary dose of RV1 was administered to all infants enrolled in this study (both study groups) who are aged less than 6 months at Visit 3 (Week 13) as a benefit to the placebo group for participation in the study.
Immunization status	3 doses of Infanrix hexa administered to all participants at investigator's discretion
Location	Dominican Republic
Notes	**Date:** Jan 2007-February 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00396630 **Aim:** "to explore horizontal transmission of the HRV vaccine strain within a family from the twin vaccinated with Rotarix to the twin receiving placebo"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized", no further information given.
Allocation concealment (selection bias)	Unclear risk	No information given.

Blinding (performance bias and detection bias)	Unclear risk	"Double Blind (Subject, Investigator, Outcomes Assessor)" no further information given.
Incomplete outcome data (attrition bias)	Low risk	Attrition/exclusions balanced between groups.
Selective reporting (reporting bias)	Unclear risk	Trial report does not provide enough details.
Other bias	Unclear risk	Study sponsor: GlaxoSmithKline.

Europe2 RV1 RV1 NCT00420745 2009-EU[16]

Methods	Randomized controlled trial **Length of follow-up:** at least one month after dose two, not specified further **Adverse events data collection methods:** not reported
Participants	**Number:** 1009 **Age range:** 6-12 weeks of age at the time of the first study vaccination **Inclusion criteria:** medically stable pre-term infants, born within a gestational period of 27-36 weeks, planned to be discharged from hospital's neonatal stay on or before the day of the first HRV vaccine/Placebo administration **Exclusion criteria:** use of any investigational or non-registered product (drug or vaccine) other than the HRV vaccine within 30 days preceding the first dose of HRV vaccine; any clinically significant history of chronic gastrointestinal disease; any confirmed or suspected immunosuppressive or immunodeficient condition; history of allergic disease; major congenital defects or serious chronic illness. **Notes:** Each study group is further stratified into two subgroups depending on the gestational age at birth of the subject: Stratum I: very pre-term infants, born after a gestational period of 27-30 weeks (189-216 days) (20% of enrolment); Stratum II: mild pre-term infants born after a gestational period of 31-36 weeks (217-258 days) (80% of enrolment).
Interventions	1. RV1, 670 participants 2. Placebo, 339 participants **Schedule:** 2 oral doses of vaccine or placebo, 1 dose at Day 0 and 1 dose at Month 1 or 2 depending on the country
Immunization status	In accordance with the local National Plan of Immunisation schedule in each of the respective participating countries, GSK Biologicals' Infanrix Hexa® (DTPa-HBV-IPV/Hib), Infanrix Quinta® (DTPa-IPV-Hib), Infanrix®+IPV+Hib (DTPa+IPV+Hib) and/or Engerix-B® (HBV) will be co-administered (at a maximum interval of two days from each other) with each HRV vaccine or placebo dose. Hepatitis B and Bacille Calmette-Guérin vaccines (BCG) at birth are allowed if included in the local National Plan of Immunisation schedule in participating countries. At the discretion of the investigator the following vaccines may be administered during each subject's study participation: Vaccine against Streptococcus pneumoniae (Prevenar®) in France and Spain (concomitantly with HRV vaccine/Placebo). Vaccine against Neisseria meningitidis (Neis Vacc C®) is allowed if there is at least 14-days interval with respect to the administration of the HRV vaccine/Placebo.

Location	France, Poland, Portugal, Spain
Notes	**Date:** January 2007 - March 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00420745

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, no further information given.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding (performance bias and detection bias)	Unclear risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", no further information.
Incomplete outcome data (attrition bias)	High risk	Missing data unbalanced across groups, loss to follow-up higher in RV1 group.
Selective reporting (reporting bias)	High risk	Incomplete reporting on key expected outcome (rotavirus diarrhoea)
Other bias	Unclear risk	Sponsor: GlaxoSmithKline

Singapore RV1 RV1 Phua 2005-AS[17]

Methods	Randomized controlled trial **Length of follow-up:** until infants aged 18 months (i.e. about 13 to 15 months of follow-up) **Adverse events data collection methods:** "diary cards during a 15-day follow-up period after each vaccine dose was administered, and the symptoms were graded according to severity. AEs occurring up to 42 days after administration of each study vaccine was recorded" (passive method)
Participants	**Number:** 2464 enrolled; 2365 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** male or female infants, born after a normal gestation period of 36 to 42 weeks; aged 11 to 17 weeks at time of first dose of study vaccine; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria:** "Subjects with previous confirmed occurrence of rotavirus gastroenteritis, previous vaccination against or history of diphtheria, tetanus, pertussis, polio and/or Hib, had a history of allergic reaction to any vaccine component, were immunocompromised or had contact with immunosuppressed individual or pregnant women in their household, had any clinically significant history of chronic gastrointestinal (GI) disease including any uncorrected congenital malformation of GI tract or subjects with use of antibiotics within 7 days preceding Dose 1"

Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.7}$ focus forming units (FFU); 510 participants 1.2. $10^{5.2}$ FFU; 648 participants 1.3. $10^{6.1}$ FFU; 653 participants 2. Placebo; 653 participants All vaccines given in 2 doses with a 1-month interval *Outcomes measured at ~15 months (efficacy data from 2 weeks after second dose to 18 months of age)*
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *Haemophilus influenzae* type b co-administered with interventions
Location	8 centres in Singapore
Notes	**Date:** 4 January 2001 to 15 April 2003 **Funding:** GlaxoSmithKline Biologicals **Other:** 93% of population were Asian

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details: "Infants were randomly assigned (on a 1:1:1 basis)"; "randomized, double-blind, placebo-controlled study"
Allocation concealment (selection bias)	Unclear risk	No details: "randomized, double-blind, placebo-controlled study"
Blinding (performance bias and detection bias)	Unclear risk	No details: "double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias)	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Unclear risk	Reasons for low number of rotavirus gastroenteritis; "A smaller number of rotavirus-related gastroenteritis cases than expected were documented during the study. For 41% (160/387) of the reported gastroenteritis episodes, stool samples were not available for determination of the etiology of the gastroenteritis. No results were available for 6% (24/387) of the gastroenteritis episodes because of an insufficient quantity of stool samples collected or because of invalid results"
Other bias	Unclear risk	See above

East Asia RV1 RV1 Phua 2009-AS[18]

Methods	Randomized controlled trial **Length of follow-up:** 2 weeks post dose 2 to 2 years **Adverse events data collection methods:** passive method, using diary cards
Participants	**Number:** 10708 enrolled; 10519 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** Healthy infants 6 to 12 weeks of age in Hong Kong and Taiwan, or 11 to 17 weeks of age in Singapore at the time of the first dose **Exclusion criteria:** "they did not have a history of chronic administration of immunosuppressants since birth, any confirmed or suspected immunosuppressive or immunodeficient condition, history of allergic disease or reaction likely to be exacerbated by any vaccine component, had not received any investigational drugs/vaccines from 30 days before Dose 1 or planned use during the study, had not received immunoglobulins and/or blood products since birth or planned administration during the study period, did not have any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator, and did not have first or second degree of consanguinity of parents"
Interventions	RV1 1. RIX4414 (RV1) 10^6 FFU; 5359 participants 2. Placebo; 5349 participants All vaccines given in 2 doses with a 1-2 month interval
Immunization status	Infants received other routine paediatric immunisations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis [DTPa] inactivated poliovirus [IPV] and Haemophilus 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. One dose of oral polio vaccine (OPV) was given at birth in Hong Kong (99.8% subjects) and Taiwan (0.7% subjects). However, during the study period, >95% of infants in the three countries received DTPa-IPV-HiB concomitantly with both doses of RIX4414 vaccine/placebo as per local schedules 50.9% of subjects were male and the study population was predominantly Chinese (76.3%).
Location	Hong Kong, Singapore, Taiwan
Notes	**Date:** Dec 8, 2003 to Aug 31, 2005 **Funding:** GlaxoSmithKline **Other:** All enrolled infants received the first dose of RIX4414 vaccine or placebo, and 10,551 (98.5%) received both doses

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated at GSK Biologicals, Rixensart, using a standard SAS® program and was used to number the vaccines
Allocation concealment (selection bias)	Low risk	A randomisation blocking scheme was used to ensure that the balance between treatments was maintained. Treatment allocation at the investigator sites was performed using a central randomisation system on the Internet
Blinding (performance bias	Low risk	Data analysis was performed at GSK Biologicals. The treatment code remains masked, except for statisticians and the database

and detection bias)		administrator, to continue double-blinded follow-up of the children during the ongoing third year follow-up
Incomplete outcome data (attrition bias)	Low risk	Primary analysis of efficacy was performed from 2 weeks post dose 2 until 2 years of age on the "according-to-protocol" (ATP) cohort that included participants who completed the full two-dose vaccination course and complied with the protocol. The total vaccinated cohort was used to calculate vaccine efficacy starting from the first dose onwards.
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Study sponsored by GlaxoSmithKline Biologicals

Latin America and Finland RV1 RV1 Ruiz-Palac 06-LA/EU[19]

Methods	Randomized controlled trial **Length of follow-up:** 9 to 10 months **Adverse events data collection methods:** active surveillance system established at hospital and medical facilities in study areas to capture intussusceptions and severe gastroenteritis episodes (active method)
Participants	**Number:** 63,225 enrolled for safety and 20,169 enrolled for efficacy; 59,308 evaluable for safety, and 17,882 evaluable for first year efficacy and 14,615 for second year efficacy **Age range:** 1 to 3 months (start) and 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 12 weeks (in all countries except Chile) or 6 to 13 weeks (in Chile) at time of first dose of RV1 or placebo; "healthy infants 6-13 weeks of age at the time of the first study vaccination whose parent/guardian sign a written informed consent and whose parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits)" **Exclusion criteria (from NCT00140673):** use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine or placebo, or planned use during the study period; chronic administration (defined as > 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed); child unlikely to remain in the study area for the duration of the study; any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection; history of allergic disease or reaction likely to be exacerbated by any component of the vaccine; administration of immunoglobulins and/or blood products since birth or planned administration during the study period; any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 31,673 participants (safety), 10,159 participants (efficacy) 2. Placebo; 31,552 participants (safety), 10,010 participants (efficacy) Both vaccine and placebo given in 2 doses with 4 to 8 weeks interval Both vaccine and placebo reconstituted in 1.3 mL of liquid calcium carbonate buffer
Immunization status	Routine immunizations according to local regulations; oral poliovirus vaccination at least 2 weeks before or after rotavirus vaccine
Location	Latin America and Europe (Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela); second year

	follow-up in all locations except Finland and Peru
Notes	**Date:** 5 August 2003 to 20 October 2005 **Source of funding:** GlaxoSmithKline Biologicals Data extracted from appendix accompanying main report and GlaxoSmithKline companion reports

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"GlaxoSmithKline Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list. We used a blocking scheme randomisation. GSK did the masking and concealment."
Allocation concealment (selection bias)	Low risk	"Randomisation was done by a central internet randomisation system."
Blinding (performance bias and detection bias)	Low risk	"Treatment allocation remained concealed from investigators and parents of participating infants throughout the study. GSK did the masking and concealment."
Incomplete outcome data (attrition bias)	Low risk	"full GSK report account for all withdrawals regardless of reason"
Selective reporting (reporting bias)	High risk	The trial reported only on severe episodes of rotavirus diarrhoea and all-cause diarrhoea, and not on diarrhoea of any severity, which is unusual in these trials
Other bias	Unclear risk	Study sponsored by GlaxoSmithKline Biologicals

Latin America1 RV1 RV1 Salinas 2005-LA[20]

Methods	Randomized controlled trial **Length of follow-up:** up to 2 years (stated in GlaxoSmithKline report) **Adverse event data collection methods:** diary cards were supplied to the parents to record occurrence of specific solicited symptoms for 15 days after each vaccination (passive method); any other unsolicited symptoms were recorded during 43 days after each vaccination (passive method); serious adverse events were recorded throughout the study
Participants	**Number:** 2155 enrolled; 2004 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks or with a birth weight > 2000 g; aged 6 to 12 weeks at the time of the first vaccination; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria:** previous confirmed occurrence of rotavirus gastroenteritis; previous vaccination against or history of diphtheria, tetanus, pertussis, polio and/or *Haemophilus influenzae* type b vaccine (HiB)*;* any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of gastrointestinal tract; use of antibiotics within 7 days preceding dose 1; immunocompromised or were in household contact with an immunosuppressed individual or pregnant woman

Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.7}$ PFU; 538 participants (randomized) 1.2. $10^{5.2}$ PFU; 540 participants (randomized) 1.3. $10^{5.8}$ PFU; 540 participants (randomized) 2. Placebo: 537 participants (randomized) **Schedule:** 2 doses given every 2 months *An additional 200 participants were randomized to* RV1 *x placebo to receive 3 doses. This is not mentioned on the main publication, only in the GlaxoSmithKline report (no data available)*
Immunization status	Oral polio vaccine given after 2 weeks, not together with RV1
Location	Belem (Brazil), Mexico City (Mexico), Valencia (Venezuela)
Notes	**Date:** 25 May 2001 to 8 November 2003 **Source of funding:** GlaxoSmithKline Biologicals **Malnutrition:** reported in "J Infect Dis, 2007, 196(4): 537-40" **Other:** main publication did not report that the trial included 2 subsets: 2 doses of HRV 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 HRV vaccine and placebo at a 0, 2, and 4 months schedule **Immunogenicity sampling:** "A subset of infants (N 800) provided blood samples 2 months after the first dose (serology for antirotavirus IgA antibodies) and 2 months after the second dose (serology for antirotavirus IgA antibodies and antibodies against antigens of routine infant vaccines). The first 200 enrolled infants in each participating country constituted this subset, and the remaining 200 infants were included according to the order of enrolment irrespective of country."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated; "The participating infants were randomly assigned to one of the 4 study groups (3 vaccine groups and a placebo group) following a 1:1:1:1 allocation ratio according to a computer-generated randomization list."
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding (performance bias and detection bias)	Low risk	"Double blinding was maintained during the entire study period."
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported
Other bias	Unclear risk	GlaxoSmithKline final report stated that part of the population received 3 doses of rotavirus vaccine. This was not mentioned on the original published report

South Africa1 RV1 RV1 Steele 2008-AF[21]

Methods	Randomized controlled trial **Length of follow-up:** up to six months after last vaccine given **Adverse event data collection methods:** "The infants were monitored for at least 30 min after each vaccination. Parents received a diary card to record information daily about solicited general symptoms (fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite or cough/runny nose) for 15 days after each dose of RIX4414 or placebo, and any other adverse events occurring until the next study visit. Weekly supervision was done by Health Care Workers from Madibeng District Health Centre. The study physician or his staff questioned the parents on their child's health and verified the completed diary card at each visit.
Participants	**Number:** 450 enrolled; 406 evaluable Two cohorts were vaccinated: 1st cohort before the rotavirus season (271 participants); 2nd cohort after the rotavirus season (179) participants **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 5 to 10 weeks of age at the time of the first study visit; free of obvious health problems as established by medical history and clinical examination before entering into the study. There were no restrictions on feeding the infants before or after vaccination. **Exclusion criteria**: Infants were excluded if they had a clinically significant history of gastrointestinal disease or malformation, had received vaccines or treatment prohibited by the protocol, were immuno-compromised or were in household contact with an immuno-suppressed individual or pregnant woman. Bacillus Calmette-Guerin (BCG) and OPV vaccinations at birth were allowed according to the local EPI schedule. Vaccination was postponed if the infant had fever (≥37.5 C axillary or ≥38 C rectal) or gastroenteritis within the previous 7 days.
Interventions	RV1 1. RIX4414 (RV1): 10^5 FFU; 2 doses given 1 month apart; 300 participants (randomized) 1.1. RV1 vaccine + oral polio vaccine + diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b vaccine 1.2. RV1 vaccine + oral polio vaccine placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*Haemophilus influenzae* type b vaccine 1.3. RV1 placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*Haemophilus influenzae* type b vaccine 2. Placebo: 2 doses given 1 month apart; 150 participants (randomized)
Immunization status	Diphtheria-tetanus-acellular pertussis, polio virus, and *Haemophilus influenzae* type b co-administered in trial

Location	Madibeng District, North West Province, South Africa
Notes	**Date:** 1st cohort started from 22 November 2001; 2nd cohort from 23 October 2002 to 15 October 2003 **Source of funding:** The study (e-Track 444563-014/NCT00346892) was sponsored by a public-private partnership RAPID and GSK Biologicals. The RAPID partnership consists of public sector partners (including the World Health Organization, US Agency for International Development, National Institutes of Health, Children's Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely. "This study was conducted under the WHO RAPID (Rotavirus Action Partnership for Immunization and Development) programme that facilitates conduct of rotavirus vaccine trials in developing countries, specifically in Africa and Asia, to address specific developing country needs. The RAPID partnership consists of public sector partners (including the World Health Organization, US Agency for International Development, National Institutes of Health, Children's Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals."
Allocation concealment (selection bias)	Unclear risk	No details; "balanced allocation (1:1:1)"
Blinding (performance bias and detection bias)	Unclear risk	Blinding of oral polio vaccine co-administration not completely blinded. "OPV and its placebo used in the first cohort were identical in appearance allowing for double blinding while this was not possible in the second cohort due to differences in appearance of OPV and its placebo."
Incomplete outcome data (attrition bias)	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Funded by RAPID partnership and GlaxoSmithKline Biologicals. Protocol published a prior with ClinicalTrials.gov, number NCT00346892. "The public sector partners provided co-funding and technical expertise for clinical evaluation. GSK Biologicals supplied all vaccine doses, handled the study design, the collection and analysis of data, the monitoring and implementation of the study in collaboration with the study centres, which are WHO reference centres. In addition, GSK Biologicals also coordinated the report writing and took part in the decision to submit the paper for publication."

South Africa2 RV1 RV1 Steele 2010a-AF[22]

Methods	Randomized controlled trial **Length of follow-up:** up to 31 days after each vaccine dose and 42 days after the last vaccine dose **Adverse event data collection methods:** All solicited general symptoms (fever, fussiness /irritability, diarrhoea, vomiting, loss of appetite, cough/runny nose) and unsolicited

	symptoms were recorded during the 15-day and 31-day postvaccination follow-up period after each RIX4414/placebo dose, respectively. The intensity of adverse events was assessed on a 4-point scale, where “0” indicated no symptoms; “1,” mild; “2,” moderate; and “3” severe symptoms. Symptoms of Grade 3 intensity were defined as follows: rectal temperature ≥39.5°C (fever), ≥6 looser than normal stools per day (diarrhoea), ≥3 episodes of vomiting per day (vomiting), refusing food intake (loss of appetite), and preventing normal activity (cough/runny nose, fussiness/irritability). Grade 2 symptoms were defined as rectal temperature of 38.5°C to 39.5°C (fever), 4 to 5 looser than normal stools/d (diarrhoea), 2 episodes of vomiting/d (vomiting), eating lesser than usual, which interfered with normal activity (loss of appetite), and interfering with normal activity (cough/runny nose, fussiness /irritability). Occurrence of SAEs was recorded throughout the study period.
Participants	**Number:** 100 enrolled; 100 evaluable for safety, 50 for immunogenicity **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** Only HIV-positive infants (confirmed at screening) who were clinically asymptomatic or mildly symptomatic (clinical stages I and II according to WHO classification) and aged 6 to 10 weeks at the time of Dose 1 of RIX4414/placebo were enrolled. There were no restrictions on feeding the infants before or after vaccination. **Exclusion criteria**: Infants were not included in the study if they were confirmed HIV negative, had received any other investigational drug or vaccine 30 days before receiving the first dose of study vaccine, or had a history of chronic GE or previous documented rotavirus GE.
Interventions	1. RV1: 3 doses at least $10^{6.0}$ CCID50 viral concentration 2. Placebo
Immunization status	RV1 vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and Haemophilus influenzae type b vaccine (TritanrixHepBHib) and OPV (PolioSabin)
Location	Pretoria, South Africa
Notes	**Registration number:** ISRCTN11877362/NCT00263666 **Source of funding:** RAPID trials (USA); World Health Organization (WHO) (Switzerland) and GlaxoSmithKline Biologicals. For infants who developed clinical symptoms of HIV (WHO stages III or IV disease) anytime 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.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely. "This study was conducted under the WHO RAPID (Rotavirus Action Partnership for Immunization and Development) programme that facilitates conduct of rotavirus vaccine trials in developing countries, specifically in Africa and Asia, to address specific developing country needs. The RAPID partnership consists of public sector partners (including the World Health Organization, US Agency for International Development, National Institutes of Health, Children’s Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals."
Allocation concealment (selection bias)	Unclear risk	1:1 randomisation, no further details
Blinding (performance bias	Low risk	"The placebo was similar to RIX4414 in appearance and contained the same constituents as the active vaccine except that it did not contain

and detection bias)		the vaccine virus."
Incomplete outcome data (attrition bias)	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Supported by research grants from the World Health Organization (V27/181/173), the Program for Appropriate Technology in Health (PATH Grant GAV.1142–01–07211-SPS), the Norwegian Program for Development, Research and Higher Education research grant (PRO 48/2002), and the South African Medical Research Council. GlaxoSmithKline Biologicals was also the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also took in charge all costs associated with the development and the publishing of the present manuscript. Protocol published a priori with ClinicalTrials.gov, number NCT00263666.

South Africa3 RV1 RV1 Steele 2010b-AF[23]

Methods	Randomized controlled trial **Length of follow-up:** up to six months after last dose of vaccine or placebo **Adverse event data collection methods:** "The infants were monitored for at least 30 min after each vaccination. Parents received a diary card to record information daily about solicited general symptoms (fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite or cough/runny nose) for 15 days after each dose of RIX4414 or placebo, and any other adverse events occurring until the next study visit. Weekly supervision was done by Health Care Workers from Madibeng District Health Centre. The study physician or his staff questioned the parents on their child's health and verified the completed diary card at each visit.
Participants	**Number:** 475 participants enrolled; 420 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 6 to 10 weeks of age at the time of the first study visit; free of obvious health problems as established by medical history and clinical examination before entering into the study, and mothers had confirmed negative HIV status **Exclusion criteria**: Infants were excluded if they had a clinically significant history of gastrointestinal disease or malformation, had received vaccines or treatment prohibited by the protocol, were immuno-compromised or were in household contact with an immuno-suppressed individual or pregnant woman. Bacillus Calmette-Guerin (BCG) and OPV vaccinations at birth were allowed according to the local EPI schedule. Infants with acute disease at the time of enrolment or gastroenteritis (diarrhoea) within 7 days before administration of the study vaccine were also excluded. In addition, vaccination was postponed if the infant had fever (≥37.5 C axillary or ≥38 C rectal) or gastroenteritis within the previous 7 days.
Interventions	RV1 1. RIX4414 (RV1): at least $10^{6.0}$ PFU CCID50 1.1. 2 doses, 1 month apart (at 10 and 14 weeks) *plus* 1 dose of placebo (at 6 weeks); 190 participants (randomized) 1.2. 3 doses, 1 month apart (at 6, 10, and 14 weeks of age); 189 participants (randomized) 2. Placebo: 3 doses, 1 month apart (at 6, 10, and 14 weeks of age); 96 participants (randomized) **Schedule:** Visits 1 (Dose 1), 2 (Dose 2), 3 (Dose 3), 4 and 5 correspond to months 0, 1, 2, 4, and 8 to 11 in the schedule
Immunization status	Infants received routine vaccinations according to the local EPI schedule in South Africa. Bacille Calmette-Guerin and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, Haemophilus influenzae type b, and OPV) were administered

	concomitantly with the study vaccine. All of the infants received a dose of OPV concomitantly with each dose of study vaccine or placebo at all administration times
Location	7 centres in South Africa
Notes	Study known as *RIX GSK[013] 2007-AF* in previously published versions of this review. **Date:** 5 September 2003 to 25 October 2004 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "The aim of this study was to determine if there was a difference in immune response between the two different schedules that were tested."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely. This study was conducted under the auspices of WHO (eTrack 444563/013/NCT00383903)
Allocation concealment (selection bias)	Unclear risk	2:2:1 randomisation, no further details
Blinding (performance bias and detection bias)	Low risk	"The placebo was similar to RIX4414 in appearance and contained the same constituents as the active vaccine except that it did not contain the vaccine virus."
Incomplete outcome data (attrition bias)	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Supported by research grants from the World Health Organization (V27/181/173), the Program for Appropriate Technology in Health (PATH Grant GAV.1142–01–07211-SPS), the Norwegian Program for Development, Research and Higher Education research grant (PRO 48/2002), and the South African Medical Research Council. GlaxoSmithKline Biologicals was also the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also took in charge all costs associated with the development and the publishing of the present manuscript Protocol published a prior with ClinicalTrials.gov (eTrack 444563/013/NCT00383903).

***Finland1 RV1 RV1 Vesikari 2004a-EU*[24]**

Methods	Randomized controlled trial **Length of follow-up:** 8 to 30 days after each dose **Adverse event data collection methods:** diary cards provided to participants or participants' parents/guardians to record solicited general symptoms on the day of each vaccination and for 7 subsequent days (passive method)
Participants	**Number:** 192 enrolled; 178 evaluable

	Age range: 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: participating in any other clinical trial; acute disease; history of allergic reaction to any vaccine component; history of chronic gastrointestinal disease or other serious medical condition; undergone immunosuppressive therapy; received antibiotics within 14 days preceding the study vaccine administration and during the first 7 days after vaccine administration; any confirmed or suspected immunosuppressive or immunodeficient condition, had received any immunoglobulin therapy or blood products before start or during the trial; abnormal stool pattern or household contact with an immunosuppressed individual or pregnant woman; for the infants, previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.1}$ PFU; 32 participants (randomized) 1.2. $10^{4.7}$ PFU; 64 participants (randomized)* 1.3. $10^{5.8}$ PFU; 32 participants (randomized) 2. Placebo: 64 participants (randomized) **Schedule:** 2 doses given 2 months apart **Half of infants receiving $10^{4.7}$ PFU of* RV1 *were tested with prior administration of Mylanta as buffer; in the other half vaccine was diluted in a buffer containing calcium carbonate* Feeding was not allowed for an hour before and after study vaccine administration
Immunization status	Infant routine vaccinations were separated from the study vaccines by 2 weeks
Location	2 sites in Finland
Notes	**Date:** 29 May to 18 December 2000 **Source of funding:** GlaxoSmithKline Biologicals Trial report also includes results for a study in adults and in previously rotavirus infected children; neither included in this review

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	"The study was performed under double-blind with respect to the groups within each study part"
Incomplete outcome data	Unclear risk	"Fourteen subjects did not complete the study including one infant from 10*4.7 FFU with Mylanta® group who failed to complete the study

(attrition bias)		due to an unrelated SAE (allergic reaction to DTP vaccine)." "15 subjects were eliminated from ATP analysis for non-compliance with the protocol (nine subjects) or seropositivity before vaccination (six subjects)."
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Finland2 RV1 RV1 Vesikari 2004b-EU[25]

Methods	Randomized controlled trial Unbalanced randomization (2:1) **Length of follow-up:** 1 and 2 years of follow-up are reported **Adverse event data collection methods:** to assess reactogenicity, parents recorded daily on diary cards rectal temperature, any diarrhoea, vomiting, irritability, and loss of appetite for 15 days after each vaccination. Any other symptoms or signs occurring during a 43-day follow-up period after each vaccination were recorded as unsolicited symptoms (or signs) (passive method)
Participants	**Number:** 405 enrolled; 372 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: premature labour; vaccination was delayed if infant had fever (rectal temperature > 38 °C) or had had gastroenteritis within the previous 7 days
Interventions	RV1 1. RIX4414 (RV1): $10^{4.7}$ PFU; 2 doses given 2 months apart; 270 participants (randomized) 2. Placebo: 2 doses given 2 months apart; 135 participants (randomized) Feeding was not allowed for 1 h before administration of the study vaccine
Immunization status	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *Haemophilus influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks
Location	6 centres in Finland
Notes	**Date:** 21 August 2000 to 11 July 2002 **Source of funding:** GlaxoSmithKline Biologicals **Other:** GSK 444663/004 (rota-004annex) reports a second year extension of the study

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence	Low risk	"Eligible infants were randomly assigned (2:1 ratio) to 2 study groups according to a computer-generated randomization list to receive the

generation (selection bias)		vaccine or placebo by mouth."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Low risk	"The placebo had the same constituents and identical appearance as the active vaccine, but did not contain the vaccine virus."
Incomplete outcome data (attrition bias)	Unclear risk	44 subjects were eliminated from ATP analysis for non-compliance with the protocol (five subjects) or unknown rotavirus status (one subject) or reason not stated (38 subjects)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	No information

Europe1 RV1 RV1 Vesikari 2007a-EU[26]

Methods	Randomized controlled trial **Length of follow-up:** 1 and 2 years of follow-up in all countries, and a third year follow-up in Finland (GSK109810) **Adverse event data collection methods:** "active surveillance for gastroenteritis episodes and serious adverse events from the day of the first vaccine or placebo dose (8 September 2004) until the follow-up visit at the end of the second rotavirus epidemic season (10 August 2006) ... Study staff contacted parents every week" (active method); "During every episode, we asked parents to record in a daily diary card the number of looser than normal stools, axillary or rectal temperature, number of vomiting episodes, any rehydration or other medication administered, and any medical attention (defined as medical personnel contact, advice, or visit; emergency room contact or visit; or admission)." (passive method)
Participants	**Number:** 3994 enrolled; 3848 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 14 weeks who weighed > 2000 g at birth **Exclusion criteria**: acute disease at the time of enrolment; history of chronic administration of immunosuppressants since birth; received any vaccines or treatments prohibited by the protocol; or had any disorders or illnesses excluded by the protocol
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 2 doses given 1 or 2 months apart; 2646 participants (randomized) 2. Placebo: 2 doses given 1 or 2 months apart; 1348 participants (randomized)
Immunization status	Concomitant vaccines included 7 valent pneumococcal polysaccharide conjugate vaccine (Prevenar) and meningococcal group c conjugate vaccine (Meningitec); Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *Haemophilus influenzae* type b vaccines were co-administered
Location	98 centres in six European countries (Czech Republic, Finland, France, Germany, Italy, and Spain)
Notes	**Date:** 12 February 2007 to 08 August 2007 **Source of funding:** funded by GlaxoSmithKline Biologicals **Other:** vaccination postponed if baby either had a temperature of ≥ 37.5 °C (axillary) or of 38.0 °C (rectal) or had gastroenteritis within 7 days before planned vaccination

	Study aim: "to assess the efficacy and safety of HRV [Rotarix] vaccine during the 3rd year of age in subjects primed with a 2-dose schedule in study 102247, with the first dose administered at the age of 6 to 14 weeks"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"GSK Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	"Randomisation was done by a central internet randomisation system. Infants were randomly allocated in a 2/1 ratio two doses of either RIX4414 or placebo."
Blinding (performance bias and detection bias)	Low risk	"Treatment allocation remained concealed from investigators and the parents of participating infants throughout the study."
Incomplete outcome data (attrition bias)	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Unclear risk	Data are provided only rotavirus gastroenteritis and for severe gastroenteritis, not for all gastroenteritis episodes
Other bias	Unclear risk	No information

Finland3 RV1 RV1 Vesikari 2011-EU[27]

Methods	Randomized controlled trial **Length of follow-up:** Two months **Adverse event data collection methods:** Passive. "Parents/guardians of infants were provided diary cards to record solicited general symptoms (loss of appetite, fussiness/irritability, fever, diarrhoea, vomiting, and cough/runny nose) during a 15-day post-vaccination follow-up period. The intensity of each adverse event was assessed using a 4-point scale where "0" refers to 'absent' and "3" refers to 'severe'."
Participants	**Number:** 250 enrolled and randomized; ATP safety cohort: 240; ATP immunogenicity cohort: 237 **Inclusion criteria:** Healthy infants aged 6-10 weeks with a birth weight >2kg. **Exclusion criteria:** Any other investigational drug or vaccine 30 days prior to the administration of the first dose of the study vaccine; a history of allergy; rotavirus gastroenteritis; infants with acute illness at the time of enrolment could not receive the vaccine until the condition was resolved.
Interventions	1. Liquid formulation of RIX4414*/(RV1), 1.5 ml 2. Placebo corresponding to liquid vaccine formulation 3. Lyophilized formulation RIX4414*/(RV1), 1ml 4. Placebo corresponding to lyophilized vaccine formulation * vaccine containing at least 10^6 median cell culture infective dose ($CCID_{50}$) of live attenuated RIX4414 human rotavirus strain **Schedule:** Two oral doses at month 0 and 1 (minimum time interval between doses: 14 days)

Immunization status	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine.
Location	Five centers in Finland
Notes	Study known as *RIX GSK[048] 2007-EU* in previously published versions of this review. **Date:** August – November 2005 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** The immunogenicity, reactogenicity and safety of the RV1 liquid formulation were compared with lyophilized formulation and placebo.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated "A standard SAS® program was used for generating the randomization list and a block randomization was used in order to ensure that the balance between the treatment arms were maintained."
Allocation concealment (selection bias)	Unclear risk	Unique treatment number "A unique treatment number identified the vaccine/placebo doses that were to be administered to the infants." No details reported how allocation of treatment number was concealed.
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel were blinded as far as technically possible. "The study was double blind with respect to each of the vaccine formulation and their respective placebo; however, blinding between the two vaccine formulations was not technically possible because of the difference in appearance of the vaccines."
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced across study groups with reasons for drop-out/exclusion reported.
Selective reporting (reporting bias)	Low risk	All pre-published outcomes reported.
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals.

Bangladesh RV1 RV1 Zaman 2009-AS[28]

Methods	Randomized controlled trial **Length of follow-up:** 31 days after each vaccination (total of 14 weeks) **Adverse event data collection methods:** "active surveillance for reactogenicity and safety was conducted via daily home visits by study personnel for 8 days after each dose of vaccine or placebo dose and bi-weekly home visits thereafter until one month after last dose" (active method); "During every episode, parents were asked to record in a daily diary card the number of looser than normal stools, axillary or rectal temperature, number of vomiting episodes, any rehydration or other medication administered, and any medical attention (defined as medical personnel contact, advice, or visit; emergency room contact or visit; or admission)" (passive method); serious adverse events were reviewed periodically by an independent committee
Participants	**Number:** 300 enrolled; 290 evaluable

	Age range: 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 7 weeks **Exclusion criteria**: acute disease at the time of enrolment; malnourished children; history of chronic administration of immunosuppressants since birth; received any vaccines or treatments prohibited by the protocol; or had any disorders or illnesses excluded by the protocol
Interventions	RV1 1. RIX4414 (RV1) 1.1. 1 x $10^{6.5}$ dose + OPV; 100 participants (randomized) 1.2. 1 x $10^{6.5}$ dose; 100 participants (randomized) 2. Placebo: 2.1. Placebo + OPV; 50 participants (randomized) 2.2. Placebo; 50 participants (randomized) **Schedule:** 2 doses given at a 6- to 12-week interval
Immunization status	All children in the study received the standard EPI vaccines starting at 6 weeks of age
Location	Single site in urban Dhaka at Mirpur, Bangladesh
Notes	**Date:** June 2005 to January 2006 **Source of funding:** funded by GlaxoSmithKline Biologicals and the Rotavirus Vaccine Program (RVP) at the Program for Appropriate Technology in Health (PATH)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	"double-blinded, placebo-controlled study designed"
Blinding (performance bias and detection bias)	Unclear risk	"double-blinded, placebo-controlled study designed"
Incomplete outcome data (attrition bias)	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Africa RV5 RV5 Armah 2010-AF[29]

Methods	Randomized controlled trial **Length of follow-up:** up to 43 days for safety outcomes, and up to 21 months for efficacy outcomes **Adverse event data collection methods:** "Study physicians reported and documented all serious adverse events occurring within 14 days of any dose and deaths or vaccine-related serious adverse events occurring at any time during the study." A subset had active surveillance: "A subset of 300 participants enrolled in Kenya was followed up for 42 days for all adverse events, including vomiting, diarrhoea, and high temperature. Home visits were attempted on days 3, 5, 7, 14, 21, and 42 after all vaccinations."
Participants	**Number:** 5560 enrolled; 5468 randomized, 5225 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks; "no symptoms of active gastrointestinal disease and could be adequately followed up for safety by home visit or telephone contact (1 week and 2 weeks after any dose of vaccine or placebo)"; breastfeeding was not restricted; no enrolment restrictions based on HIV status - infants in Kenya were offered routine HIV testing, and a subset were followed up for safety All children exposed to or infected with HIV were referred for appropriate HIV care and treatment; voluntary counselling and testing were also offered to mothers of infants exposed to HIV **Exclusion criteria**: see above **Special group:** HIV-infected participants
Interventions	RV5 1. WC3 (RV5): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 2733 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 2735 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Kassena-Nankana district (Ghana), rural Karemo division, Siaya district (Kenya), and urban area of Bamako (Mali)
Notes	**Date:** 28 April 2007 to 31 March 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck **Registration number:** NCT00362648

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomisation, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled."
Blinding (performance bias	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial."

and detection bias)		Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. "The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication."

Finland and USA RV5 RV5 Block 2007-EU/USA[30]

Methods	Randomized controlled trial **Length of follow-up:** up to 42 days for safety/immunogenicity; up to 1 year for efficacy **Adverse event data collection methods:** parents or guardians contacted by the study site on day 7, day 14, and day 42 after each vaccination and asked about serious adverse events (active method); parents or guardians were provided diary cards and were instructed to record daily temperatures for the infant for 7 days after each vaccination (passive method)
Participants	**Number:** 1312 enrolled; 1200 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives **Exclusion criteria:** see above
Interventions	RV5 1. WC3 (RV5): 1.1 x 10^7 PFU; 651 participants (randomized) 2. Placebo: 661 participants (randomized) **Schedule:** 3 doses given 4 to 10 weeks apart
Immunization status	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

Location	30 sites; 27 in USA, and 3 in Finland
Notes	**Date:** 24 September 2002 (first patient in) to 11 February 2004 **Source of funding:** Merck & Co., Inc.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Enrolled infants were randomly assigned 1:1 by using computer-generated allocation schedules to receive either vaccine or visibly indistinguishable placebo in a sucrose citrate buffer administered orally as three 2-mL doses 4 to 10 weeks apart."
Allocation concealment (selection bias)	Low risk	Sequential identical containers (see quote above)
Blinding (performance bias and detection bias)	Low risk	"This randomized, clinical trial blinded to investigator, parent or guardian, and sponsor." "The placebo was identical to the vaccine except that it did not contain the rotavirus reassortants or trace trypsin."
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	High risk	Key expected outcome (episodes of gastroenteritis) not included
Other bias	Unclear risk	Relevant information needed for assessment not provided

Europe RV5 RV5 Ciarlet 2009-EU[31]

Methods	Randomized controlled trial **Length of follow-up:** up to 42 days after last dose **Adverse event data collection methods:** see outcome measures; passive method used for reactogenicity, and active method used for serious adverse events
Participants	**Number:** 403 enrolled; 403 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, aged 6 to 12 weeks; mothers negative for hepatitis B surface antigen; no known history of congenital abdominal disorders; intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no history of seizure with or without fever; no known hypersensitivity to any component of rotavirus vaccine or INFANRIX hexa; no prior receipt of any rotavirus, DTaP, DTP, *Haemophilus influenzae* type b, Hepatitis B, injectable poliovirus vaccine, or oral polio vaccine during the course of the study, within 42 days before first dose of RV5 or before final blood draw (42 days after dose 3); no fever, with a rectal temperature < 38.1 °C (< 100.5 °F) at the time of immunization; no history of known rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no prior receipt of intramuscular, oral, or intravenous corticosteroids treatment within 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no receipt of a blood transfusion or blood products, including immunoglobulin; did not participate in another clinical study within 42 days before or during current study; could be adequately followed for safety **Exclusion criteria:** as above

Interventions	RV5 1. WC3 (RV5) plus Infanrix hexa: RV5 (2 mL; 3 doses given 4 to 6 weeks apart); 201 participants (randomized) 2. Placebo plus Infanrix hexa: placebo (2 mL; 3 doses given 4 to 6 weeks apart); 202 participants (randomized) **Infanrix hexa:** comes in 2 parts; first part is a white, milky liquid (0.5 mL) in a pre-filled syringe that consists of the combined diphtheria, tetanus, pertussis, hepatitis b, and inactivated poliovirus vaccine; second part is the *Haemophilus influenzae* type b vaccine and is a white pellet in a separate glass vial; both parts mixed together before being injected intramuscularly
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *Haemophilus influenzae* type b co-administered
Location	26 study sites in Austria, Belgium, and Germany
Notes	**Date:** 22 February 2006 to 13 November 2006 **Source of funding:** Merck & Co., Inc. **Other:** only data about serious adverse events and adverse events leading to discontinuation are provided

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported
Other bias	Unclear risk	No details

USA1 RV5 RV5 Clark 2003-NA[32]

Methods	Randomized controlled trial **Length of follow-up:** up to 1 year **Adverse event data collection methods:** parents/guardians recorded temperatures 4 to 6 h after each dose and then daily thereafter for 7 days and the number of episodes of vomiting and diarrhoea daily for 7 days (passive method); also recorded any behavioral or systemic adverse experience on a vaccination report card and was

	asked to report any serious adverse experience immediately to the study site; telephone call made to each parent/guardian 14 days after each dose to verify that no serious adverse experiences had occurred (active)
Participants	**Number:** 731 enrolled; 681 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Special groups:** breastfed; infants in the vaccine control group (Group 1) received the reassortants as administered in previous studies within 30 min of feeding Enfamil formula (30 ml) or Mylanta Double Strength (0.5 ml/kg). Infants in a corresponding placebo group (Group 2) were pre-fed as in Group 1 **Inclusion criteria:** healthy infants 2 to 4 months of age **Exclusion criteria:** known hypersensitivity to any component of the rotavirus vaccine; known or suspected immunologic impairment; prior administration of any rotavirus vaccine; fever at the time of vaccination; history of chronic diarrhoea; failure to thrive or gastrointestinal illness; recent receipt of oral polio vaccine or blood products; residence in the household with an immunocompromised person; and failure to fast for 1 h before vaccination
Interventions	RV5 1. WC3 (RV5): 10^7 PFU; 581 participants (randomized) 2. Placebo: 581 participants (randomized) **Schedule:** 3 doses given 42 to 56 days apart
Immunization status	Not stated
Location	19 centres in the USA
Notes	**Date:** September 1997 through September 1998 **Source of funding:** Merck & Co., Inc. **Other:** active surveillance for cases of rotavirus gastroenteritis at each study site began when the local laboratory confirmed at least 3 cases of rotavirus gastroenteritis or on 31 January 1998, whichever came first

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details; "Children who met all eligibility criteria were randomized to one of eight treatment groups"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel; "Parents of participating infants and study personnel were blinded to receipt of vaccine/placebo but not to the volume administered or to the prefeeding requirement."
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting	High risk	Not all pre-specified outcomes reported; "Because there were relatively few confirmed cases of RV [rotavirus] caused by serotypes G1 and

(reporting bias)		G2, the evidence is insufficient to declare that the efficacy of any buffered formulation is >0.0%"
Other bias	High risk	Poor reporting of efficacy data

USA2 RV5 RV5 Clark 2004-NA[33]

Methods	Randomized controlled trial **Length of follow-up:** up to 1 year (season) **Adverse event data collection methods:** episodes of fever (subjective assessment of fever), vomiting, diarrhoea, behavioural changes, and any other adverse experiences during the 14 days after each dose also were reported on the diary card (passive method); parents were asked to report any serious adverse experience immediately to the study site (passive method); telephone call made to each participant 14 days after each vaccination to ask about serious adverse experiences (active method)
Participants	**Number:** 439 enrolled; 416 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants approximately 2 to 6 months of age were enrolled and followed for episodes of acute gastroenteritis **Exclusion criteria:** known hypersensitivity to any component of the rotavirus vaccine; known or suspected immunologic impairment; prior administration of any rotavirus vaccine; fever at time of vaccination (> 38.1 °C rectal); history of chronic diarrhoea or failure to thrive; clinical evidence of gastrointestinal illness; receipt of any other vaccines within 14 days; immunocompromised resident in the home; or any condition, which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
Interventions	RV5 1. WC3 (RV5): 10^7 PFU; 3 doses at 6 to 8 week intervals; 218 participants (randomized) 2. Placebo: 3 doses at 6 to 8 week intervals; 221 participants (randomized)
Immunization status	No mention of the use of other child vaccines
Location	10 study sites in the USA
Notes	**Date:** August 1993 to June 1994 **Source of funding:** Merck & Co., Inc.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Infants who met all eligibility criteria were randomly assigned in a 1:1 ratio."
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias	Low risk	"The vials of vaccine and placebo were visibly indistinguishable."

and detection bias)		"The placebo was identical to the vaccine except that it did not contain the rotavirus reassortants."
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	≥ 1 outcome of interest reported incompletely; "Only wild-type (ie, non-vaccine related) rotavirus cases were considered for the primary case definition."
Other bias	Unclear risk	Not enough detail to make a judgment

South Korea RV5 RV5 Kim 2008-AS[34]

Methods	Randomized controlled trial **Length of follow-up:** up to 42 days after last dose **Adverse event data collection methods:** diary cards (passive method)
Participants	**Number:** 178 enrolled; 171 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants; 6 to 12 weeks of age **Exclusion criteria:** history of congenital abdominal disorders, intussusception, or abdominal surgery; known or suspected impairment of immunological function; known hypersensitivity to any component of the rotavirus vaccine; prior receipt of any rotavirus vaccine; fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; clinical evidence of active gastrointestinal illness (infants with gastro-oesophageal reflux disease were permitted to participate in the study as long as the gastro-oesophageal reflux disease was well controlled with or without medication); receipt of intramuscular, oral, or intravenous corticosteroid treatment between the 2 weeks before first vaccination and 2 weeks after last vaccination; reside in a household with an immunocompromised person; prior receipt of a blood transfusion or blood products, including immunoglobulins; receipt of OPV during the course of the study or within 42 days before first dose of vaccine/placebo; and condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives
Interventions	RV5 1. WC3 (RV5): 6.9 to 8.6 x 10^7 PFU; 3 doses given 4 to 10 weeks apart; 115 participants (randomized) 2. Placebo: 3 doses given 4 to 10 weeks apart; 3 participants (randomized)
Immunization status	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
Location	8 study centres in South Korea
Notes	**Date:** 2 August 2005 (first patient in) to 25 May 2006 (last dose given); last participant completed follow-up on 5 July 2006 **Source of funding:** Merck & Co., Inc. **Other:** most of the outcome data is not provided in the reports

Risk of bias table

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	Unclear risk	"Infants were randomly assigned, in a 2:1ratio, to receive three 2-mL oral doses of vaccine or visibly indistinguishable placebo, 4–10 weeks apart."
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding (performance bias and detection bias)	Low risk	"Infants were randomly assigned, in a 2:1ratio, to receive three 2-mL oral doses of vaccine or visibly indistinguishable placebo, 4–10 weeks apart."
Incomplete outcome data (attrition bias)	High risk	Reason related to outcome
Selective reporting (reporting bias)	High risk	Key expected outcome not included
Other bias	Unclear risk	Information not provided

Japan RV5 RV5 NCT00718237 2010-AS[35]

Methods	Randomized controlled trial **Length of follow-up:** 25 months **Adverse event data collection methods:** Any death, Vaccine related SAE and Intussusception were collected during the study period. Parents/guardians were asked to record AEs on a standardized Vaccine Report Card during 14 days after each vaccination.
Participants	**Number:** 762 **Age range:** 6 to 12 weeks **Inclusion Criteria:** Healthy Japanese Infants **Exclusion Criteria:** history of known prior RV Gastroenteritis; subjects who are concurrently participating in or are anticipated to participate in other studies of investigational products at any time during the study period.
Interventions	1. Rotavirus vaccine, live, oral, pentavalent [RV5], 381 participants 2. Placebo (unspecified), 381 participants **Schedule:** 3 doses, 28 to 70 days apart, with 14 days of safety follow-up after each vaccination, and follow-up for acute GE episodes until the end of the study
Immunization status	no information about other vaccines given
Location	32 sites in Japan
Notes	**Date:** August 2008 - September 2009 **Registration number:** NCT00718237 **Source of funding:** Merck Sharp & Dohme Corp

	Rationale: To evaluate whether V260 is effective and well tolerated in Japanese healthy infants.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, no further information.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding (performance bias and detection bias)	Unclear risk	"Double Blind (Subject, Investigator)", no further information.
Incomplete outcome data (attrition bias)	Low risk	Attrition/exclusions balanced across groups.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Sponsor: Merck

China RV5 RV5 NCT00953056 2010-AS[36]

Methods	Randomized controlled trial **Length of follow-up:** two weeks after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** Infant cohort: 48 enrolled and randomized **Inclusion criteria:** Healthy infants aged 6 – 12 weeks **Exclusion criteria:** Receiving other live vaccines 14 days before or after study vaccine; Prior administration of any rotavirus vaccine; Elevated temperature, with axillary temperature ≥37.1°C 24 hours before study vaccine; Prior or active gastrointestinal illnesses; Immunodeficiency.
Interventions	1. 2.0 mL doses of RV5 (V260) administered orally. The vaccine consists of an oral solution of 5 live human-bovine reassortant rotaviruses. 2. 2.0 mL doses of matching placebo to RV5 administered orally. **Schedule:** 3 doses of RV5/placebo at 3 separate visits scheduled 28 to 70 days apart. The third dose was administered by 32 weeks of age.
Immunization status	Other live vaccines 14 days before or after study vaccine were not allowed.
Location	China
Notes	**Date:** September 2009 – March 2010

	Source of funding: Merck Sharp & Dohme Corp **Study rationale:** "This study will assess the safety and tolerability of RV5 (V260) in the healthy Chinese populations. Approximately 144 participants will be enrolled and equally stratified into three age cohorts, Cohort I ages 19-47 years, Cohort II ages 2-6 years, and Cohort III ages 6-12 weeks."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding (performance bias and detection bias)	Unclear risk	"Double-blind (Subject, Investigator)" no further details reported.
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced across groups with reasons reported for withdrawal.
Selective reporting (reporting bias)	Unclear risk	Trial report does not provide enough information.
Other bias	Unclear risk	Funded by Merck Sharp & Dohme Corp.

Finland1 RV5 RV5 Vesikari 2006a-EU[37]

Methods	Randomized controlled trial **Length of follow-up:** 1 to 3 rotavirus seasons (1 to 3 years) **Adverse event data collection methods:** diary cards (passive method); telephone calls to parents/legal guardians to ask about serious adverse events (active method) **Note:** the per-protocol population used for the primary efficacy analysis included 1496 participants after exclusion of 450 participants (23.1%). The modified intention-to-treat population used in a secondary efficacy analysis consisted of the 1647 participants, including protocol violators, who had any valid post-dose 3 efficacy data
Participants	**Number:** 1946 enrolled; 1496 evaluable (after 2 years) **Age range:** 3 to 6 months (beginning); > 6 months (end) **Inclusion criteria:** healthy infants between 2 and 8 months of age **Exclusion criteria:** not described
Interventions	RV5 1. WC3 (RV5) 1.1. G1-4, P1A (2.69×10^7, 7.92×10^6, 2.41×10^6); 3 doses given 4 to 8 weeks apart; 1027 participants (randomized) 1.2. G1-4 (2.9×10^7); 3 doses given 4 to 8 weeks apart; 270 participants (randomized) 1.3. P1A (9.24×10^7); 3 doses given 4 to 8 weeks apart; 327 participants (randomized) 2. Placebo: 3 doses given 4 to 8 weeks apart; 322 participants (randomized)

	We excluded the two arms dealing with different G or P serotypes and compared a single arm to placebo
Immunization status	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
Location	4 sites (Tampere, Espoo, Lahti, Pori) in Finland
Notes	**Date:** June 1998 and June 2001 **Source of funding:** Merck & Co., Inc. **Other:** in total, 1946 infants (1300 in the first year and 646 in the second year of the study) were enrolled in the study and received at least the first dose of 1 of the 5 active vaccines or placebo. Overall, 1813 (93.2%) participants received 3 three doses and were followed for ≥ 42 days after the final dose. 1800 participants (92.5%) were followed through the first rotavirus season after vaccination; 1740 participants (89.4%) were followed through a second rotavirus season. Of the 1300 participants enrolled in the first year, 880 (67.7%) were followed through a third rotavirus season

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Sequential identical containers; "The vials containing either vaccine or placebo were visibly indistinguishable."
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel; "This randomized clinical trial blinded to subject, investigator, parent/legal guardian, and sponsor. The placebo was identical to the vaccine except that it did not contain rotavirus reassortants or trace trypsin"
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	≥1 outcome of interest reported incompletely
Other bias	Unclear risk	Insufficient information to assess

Europe and the Americas RV5 RV5 Vesikari 2006b-INT[38]

Methods	Randomized controlled trial **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on days 7, 14, and 42 after each dose and every 6 weeks thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method)
Participants	**Number:** 70,301 enrolled and 69,274 randomized (efficacy study subpopulation of 5673); 57,134 evaluable for safety outcomes; for efficacy outcomes, 4512 evaluable in year 1 and 1569 evaluable in year 2

	Age range: 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants between 6 and 12 weeks of chronologic age were eligible regardless of gestational age; no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine during the course of the study or within 42 days prior to the first dose of vaccine/placebo **Exclusion criteria:** see above for details **Special group:** infants born at < 36 weeks of gestational age were considered premature and infants born at < 32 weeks of gestational age were considered extremely premature; no formal safety or efficacy hypotheses were prespecified for premature infants
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 to 10 weeks apart; 34,644 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 to 10 weeks apart; 34,630 participants (randomized)
Immunization status	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of subjects 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
Location	356 primary study sites in Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and the USA
Notes	**Date:** 12 January 2001 to 6 October 2004 **Source of funding:** Merck & Co., Inc. **Other:** there is a full report on premature babies that will be data extracted separately

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is likely that it was central computer randomisation, but no details are provided in none of the papers; "Infants were randomly assigned, in a 1:1 ratio, to receive three 2-ml oral doses of vaccine or visibly indistinguishable placebo"
Allocation concealment (selection bias)	Unclear risk	likely adequate, but not reported; "Infants were randomly assigned, in a 1:1 ratio, to receive three 2-ml oral doses of vaccine or visibly indistinguishable placebo"
Blinding (performance bias and detection bias)	Low risk	Participants and key personnel; "Randomized, multicenter, double blinded (operated under in-house blinding procedures), placebo controlled, safety and efficacy trial. The placebo was an exact match minus the virus"
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Unclear risk	Difficult to judge, as some important information about randomization/allocation concealment are not provided

South East Asia RV5 RV5 Zaman 2010-AS[39]

Methods	Randomized controlled trial **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on the first 14 days after each dose and every month thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method). "Serious adverse events were classified with the US regulatory definition, in line with ICH guidance, and identified by monthly query and parental reporting at any time or identification by study staff in hospitals or clinics. Intussusception at any time was assessed with an additional detailed protocol. All these events were monitored by an independent, unmasked, data and safety monitoring board that met about twice a year during the course of the investigation. The board also provided guidance about enrolment and severity scoring".
Participants	**Number:** 2,119 enrolled; 2036 randomized, 2016 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks. Breastfeeding was not restricted and there was no enrolment restrictions based on HIV status, although HIV testing was not done. **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 1,018 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 1,018 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Matlab (Bangladesh) and urban and peri-urban Nha Trang (Vietnam)
Notes	**Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomisation, with block sizes of six".
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled."
Blinding (performance bias and detection bias)	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial." Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment."
Incomplete outcome data	Low risk	Missing data balanced across groups

(attrition bias)		
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication.

Latin America RV5 RV5 Ciarlet 2008-LA[40]

Methods	Randomized, open-label trial, no placebo **Length of follow-up:** 42 days **Adverse event data collection methods:** active surveillance 14 days after each dose, spontaneously reports by parents thereafter throughout the study
Participants	**Number:** 735 randomized **Age range:** 6-12 weeks **Inclusion criteria:** healthy infants aged 6-12 weeks
Interventions	1. Concomitant group: RV5 and OPV co-administered 2. Sequential group: RV5, with OPV administered 2-4 weeks later **Schedule:** 3 doses given at a 8-10 week interval
Immunization status	No restrictions were placed on administration of other approved routine pediatric vaccines such as DTaP, hepatitis B, Hib conjugate, pneumococcal conjugate.
Location	Mexico, Costa Rica, Guatemala, Brazil
Notes	**Date:** September 2005 to July 2006 **Source of funding:** Merck & Co., Inc. **Study rationale:** The study evaluated the immunogenicity and safety of co-administering oral polio vaccine (OPV) with RV5 vaccine.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated" no further information provided.
Allocation concealment	Unclear risk	No information provided.

(selection bias)		
Blinding (performance bias and detection bias)	High risk	No blinding “open-label”.
Incomplete outcome data (attrition bias)	Low risk	95% completed the study
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Unclear risk	Funded by Merck & Co., Inc.

Finland2 RV5 RV5 Vesikari 2011[41]

Methods	Randomized, open-label trial, no placebo **Length of follow-up:** 42 days **Adverse event data collection methods:** active surveillance up to 6 days after each dose, spontaneously reports thereafter throughout the study.
Participants	**Number:** 249 enrolled; 247 randomized; 238 safety analysis **Age range:** 6-7 weeks **Inclusion criteria:** healthy infants aged 6 to 7 weeks.
Interventions	1. Concomitant group: First two doses of RotaTeq (RV5) co-administered with MenCC (Meningococcal serogroup C conjugate vaccine), a third dose of RV5 given 4 weeks later. 2. Sequential group: RotaTeq (RV5), with MenCC administered 4 weeks apart **Schedule:** 3 doses given at a 4-week interval
Immunization status	All children in the study received the standard EPI vaccines (including DTaP, IPV and Hib)
Location	Nine regional vaccination clinics in Finland.
Notes	**Date:** January to March 2007 **Source of funding:** Sanofi Pasteur MSD **Study rationale:** The study was designed to assess concomitant versus sequential administration of RV5 and MenCC on the immune response to both vaccines.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized” no further information provided.

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias)	High risk	No blinding “open-label”.
Incomplete outcome data (attrition bias)	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Unclear risk	Funded by Sanofi Pasteur MSD

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